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Review

Tumor cell malignancy: A complex trait built through reciprocal interactions between tumors and tissue-body system

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SUMMARY

Since the discovery of oncogenes and tumor suppressor genes in the late past century, cancer research has been overwhelmingly focused on the genetics and biology of tumor cells and hence has addressed mostly cell-autonomous processes with emphasis on traditional driver/passenger genetic models. Nevertheless, over that same period, multiple seminal observations have accumulated highlighting the role of non-cell autonomous effectors in tumor growth and metastasis. However, given that cell autonomous and non-autonomous events are observed together at the time of diagnosis, it is in fact impossible to know whether the malignant transformation is initiated by cell autonomous oncogenic events or by non-cell autonomous conditions generated by alterations of the tissue-body ecosystem. This review aims at addressing this issue by taking the option of defining malignancy as a complex genetic trait incorporating genetically determined reciprocal interactions between tumor cells and tissue-body ecosystem.

GLOSSARY

Cancer: A disease in which some of the body's cells grow uncontrollably and spread to other parts of the body(https://www.cancer.gov/about-cancer/understanding/what-is-cancer) and also "*Cancers consist of malignant cells which are served by a non-malignant stroma*" Cowdry, 1955 cited by Smithers (1962) and "*Cancer is a disease of organisation, not a disease of cells*" (Smithers, 1962).

Cell autonomy versus non-cell autonomy: Cell autonomy means that the cell phenotype is fully determined by its genotype. By contrast non-cell autonomy means that the cell phenotype is affected by the presence of other constituents of its habitat.

Cell competition: Cell competition occurs between cells of the same identity with different genotypes. It is qualified as homocellular. It is a form of cell-to-cell communication in which cells can compete in tissue for space and survival.

Driver mutation versus passenger mutation: In tumor cells the mutations burden includes mutations which impact on the phenotype (drivers) and mutations, which are neutral (passengers). Roughly, drivers affect gene coding or regulatory sequences whereas passengers affect non-coding region of the genome.

Ecosystem: Applied to living organisms, the concept of ecosystem defines a set of tissues and cells that live and interact with each other and with the external environment.

Epithelial Defense Against Cancer: Epithelial Defense Against Cancer (EDAC) is a competitive strategy implemented by normal epithelial cells which detects the presence of neighboring malignant cells, and actively eliminates them.

Hit and run: Literally fleeing the scene after a collision. Applied to biological processes, hit-and-run mechanisms involve events that activate a phenotype that persists even after the activator has disappeared.

Microenvironment versus macroenvironment: Two compartments within the tumor stroma. They differ physically by their respective proximity to the tumor and functionally by their role in tumorigenesis. The microenvironment is generated in immediate proximity ($\leq$~0.5cm) to the tumor as the results of crosstalks between stroma and tumor. In contrast, the macroenvironment is the constitutional structure of the tissue distant from the tumor by more than ~0.5–1 cm, presumably unaffected by the presence of the tumor.

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Microbiota: The microbiota represents the microorganisms population: bacteria, yeasts, fungi, protists… living in a specific environment called the microbiome. In humans, the intestinal microbiota plays an important and newly established role in essential physiological functions: immunity, weight control, etc.

Niche: Paget (1989) introduced the concept of niche in his "Seed and Soil" hypothesis to account for organotropism of cancer metastasis. Then the concept was introduced in hematology by Schofield (1983) and widely used in stem cell biology to designate *"the cellular environment which retains the stem cell, prevents it from maturation, and determines its behavior"*. It has been used since as a generic term for a tissue structure in which a cell or a group of cells finds a permissive environment for the expression of any physiological property such as survival, proliferation, differentiation Recently, the term « pre-metastatic niches » has also been used to describe microenvironments shaped by primary tumors in distant organs that are conducive to the survival and outgrowth of tumor cells before their arrival at these sites (Peinado et al., 2017).

Senescence: Senescence is a physiological process that alters the cell physiology leading to growth arrest. It is no longer considered a passive process since the demonstration that senescent cells secrete factors collectively called Senescence Associated Secretion Program (SASP) acting *in trans* on the tissue neighborhood. Observations of the accumulation of senescent cells in aged tissues have linked senescence *in vitro*, aging *in vivo* and pathological disorders such as diabetes and cancers.

System: A system is a set of elements (systemic components) interacting with each other according to certain principles or rules. A system is determined by (1) its border, that is to say the criterion of belonging to the system, (2) its interactions with its environment, (3) its function.

Tumor: An abnormal mass of tissue that forms when cells grow and divide more than they should or do not die when they should. Also called neoplasm.

(https://www.cancer.gov/abadultout-cancer/understanding/what-is-cancer).

INTRODUCTION: CELL AUTONOMOUS VERSUS NON-CELL AUTONOMOUS PROCESSES

The behavior of a cell population in a complex organism is governed by at least two programs. The first program is intrinsic to a given cell and qualified as cell autonomous. It defines the phenotype, driven by the expression of tissue-specific sets of genes. The second program is extrinsic to that cell and qualified as non-cell autonomous. It involves crosstalks between individual components of the population and the tissue ecosystem not limited to the host organ but extending to the whole organism. The crosstalks include multiple processes such as cross-feedings, secretomes, physical constraints in tissue structures, vascularization, and immunosurveillance. Applied to cancers, this model involves populations of neoplastic cells driven by autonomous oncogenic programs and exposed within the organ and body ecosystem to non-cell autonomous processes, which eventually determine permissiveness for survival, growth and ultimate dissemination. Since the discovery of oncogenes and tumor suppressor genes in the late past century, cancer research has been overwhelmingly focused on the genetics and biology of tumor cells and hence has addressed mostly cell-autonomous processes. However, over the past few decades, several seminal observations have highlighted the role of non-cell autonomous effectors in the transformation of neoplastic cells into tumors and ultimately into metastasis (Figure 1). The aim of this review is to update the role of these effectors and discuss how they pave the way for potential new therapeutic strategies. We will first define tumor-tissue-ecosystems and then describe several mechanisms of non-cell autonomous interventions that shape tissues into niches or cancerized fields conducive to tumor development. Intratumoral cell phenotypic heterogeneities are other manifestations of non-cell autonomous effects that shape the tumors via cell-to-cell communication. We will show how normal cells and tumor cells at different stage of tumor progression compete for space and survival leading to elimination of losers and prevalence of winners. Further examples of non-cell autonomous contributions will be presented illustrating the influences of the host system on tumors' fate. Finally the future of therapies targeting non-cell autonomous effectors will be discussed.

DEFINING A TUMOR-TISSUE-BODY ECOSYSTEM: MICROENVIRONMENT, MACROENVIRONMENT AND BEYOND

The constitution of functional tissues is specific to each organ. It determines the physiology of the organ and, if applicable, plays a role in the local growth and spread of tumors. For instance, the mammary gland is composed of epithelial cells, representing the functional compartment of the organ, embedded in a stroma consisting of fibroblasts, fat cells, inflammatory/immune cells, and endothelial cells, each

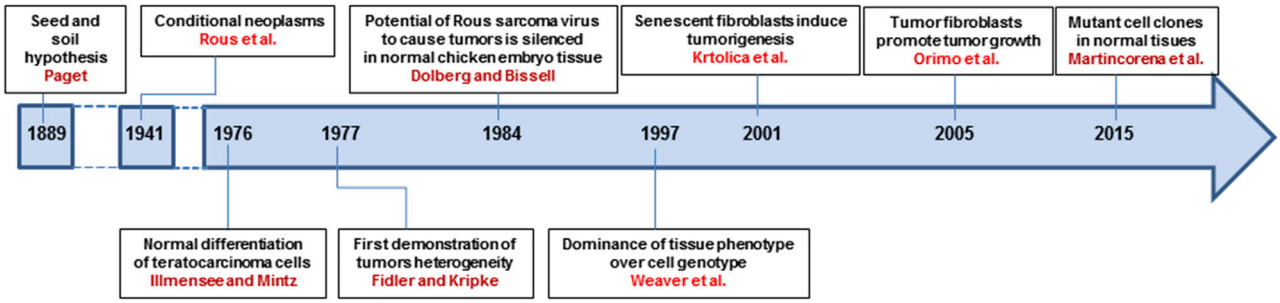

Figure 1. Timeline of seminal observations highlighting the role of non-cell autonomous effectors in tumor growth and metastasis

- 1889: original description by Paget of the concept of niche in his "Seed and Soil" hypothesis to account for organotropism of cancer metastasis (Paget, 1989).
- 1941: Rous et al. refer to « *conditional neoplasms or sub-threshold neoplastic states true tumors* » to describe tumors dependent for their continued existence upon encouraging local influences (Mackenzie and Rous, 1941; Rous and Kidd, 1941).
- 1976: Illmensee and Mintz demonstrate the totipotency and normal differentiation of single teratocarcinoma cells injected into blastocysts by (Illmensee and Mintz, 1976). This was an outstanding demonstration that « retention of euploidy in the tumor cells is a sufficient, and possibly a necessary condition for restoration of completely normal gene expression in an appropriate environment.»(Illmensee and Mintz, 1976).
- 1977: Fidler and Kripke show that metastatic cell variants preexist in tumors thus bringing the first experimental evidence for tumor heterogeneneity (Fidler and Kripke, 1977).
- 1984: Pioneering experiments by Bissell's group show that the potential of Rous sarcoma virus to cause sarcomas is silenced in the context of four days chicken embryo tissues and can be released in *in vitro* cultures (Dolberg and Bissell, 1984).
- 1997: Further contribution by Bissell's group illustrating the contribution of extracellular matrix to malignant phenotypes, thus bringing about the concept of dominance of tissue phenotype over cell genotype (Weaver et al., 1997).
- 2001: Krtolica et al. demonstrate that senescent fibroblasts promote epithelial cell growth and tumorigenesis thus bringing a link between cancer and aging (Krtolica et al., 2001).
- 2005: Orimo et al. show that tumor stromal fibroblasts promote tumor growth and angiogenesis (Orimo et al., 2005).
- 2015: Sequencing of human healthy tissues genomes highlights their colonization by mutant cells clones carrying driver mutations in cancer genes, hence demonstrating that cancer-prone genotypes can be silenced by tissue context (Martincorena and Campbell, 2015).
- Further experimental support to the role of non-cell autonomous contributions to tumorigenesis have been reviewed by Sieber et al. (Sieber et al., 2005) who appropriately introduced the concept of context by writing: "… *the effects of cancer associated mutations are dependent on the context — tissue and cell type, and the stage of development, differentiation and tumorigenesis — in which they arise, and that the observed changes are those that are selectively advantageous*".

playing a specific role in the organ functions. Over women's lifetime, the mammary gland undergoes profound structural and physiological changes governed by endocrine factors. Although some of these changes have lasting (puberty) or irreversible (menopause) effects, others are transient (menstruation, pregnancy, breast-feeding). A dramatic change potentially occurring in the mammary gland is the growth of a tumor and the central challenge of cancer research is to understand how this event happens. From a geneticist's perspective, the mammary tumors arise from the transformation of mammary epithelial cells initiated by cell autonomous oncogenic events and the emergence of a tumor *in situ* and the possible dissemination of metastases is determined by additional oncogenic events. However, as noted above, the role of non-cell autonomous effectors that shape neoplastic cells for tumor growth and metastasis can no longer be ignored. Given that both cell autonomous and non-autonomous events are present at diagnosis, it is indeed impossible to know if the malignant transformation is initiated by cell autonomous oncogenic events or by non-cell autonomous permissive conditions generated by alterations of the tissue-body ecosystem. Therefore, geneticists' short sightedness should be reset to incorporate the fact that malignancy of tumor cells should no longer be described as an exclusive property of cells carrying oncogenic events, but rather as a set of complex traits (in the genetic sense), describing ecosystems that include local components (tumor within tissue stroma) and systemic components (organ in whole body)

The local components of the ecosystem: Tumor within tissue stroma

The local components of a tumor ecosystem consist of a neoplastic cells compartment developing within an organ stroma.

The neoplastic cells compartment

It represents a complex ecosystem involving interactions within the tumor mass between distinct cell subpopulations, including minorities. Intratumoral heterogeneity is intrinsic to most tumors (McGranahan and Swanton, 2017). Indeed, differences in cell lineages within a neoplasm have been recognized for a long time (Heppner, 1984). More recently, single-cell RNA sequencing (scRNA-seq) has provided formal demonstrations of such heterogeneity (Ding et al., 2020) and the existence of active metabolic interactions between the heterogeneous components of neoplasms are well documented (Arnandis et al., 2018; Marusyk et al., 2014; Tabassum and Polyak, 2015). The complexity of this intra-tumor ecosystem will be discussed later.

The stroma

We distinguish two compartments within the stroma: the macroenvironment and the microenvironment. They differ physically by their respective distance to the neoplastic compartment and presumably functionally by their role in tumorigenesis. We arbitrarily define the microenvironment as the stroma proximal to the neoplastic compartment (<∼ 0.5-1cm), whereas the macroenvironment lies beyond this margin.

The macroenvironment. Governs the early life of a tumor. It is the tissue remote from the tumor (>0.5–1 cm) within which a cell, or a population of cells, having undergone potentially oncogenic events, finds a permissive homing for *in situ* proliferation. The definition applies to both primary tumors and metastases including « pre-metastatic niches »which describe microenvironments shaped by primary tumors in distant organs that are conducive to the survival and outgrowth of tumor cells before their arrival at these sites (Peinado et al., 2017). The macroenvironment does not have direct cross-relationships with the neoplastic compartment and could in fact be considered a systemic component. However, because the topography and because it represents the constitutional tissue that provides a permissive context for tumor growth, we consider it more as a component of the local ecosystem. It is noteworthy that the term "tumor macroenvironment" has been used in a different meaning to describe, "metabolites and other tumor-secreted factors (such as cytokines and chemokines) that circulate in the blood" (Al-Zoughbi et al., 2014; Masri and Sassone-Corsi, 2018).

The microenvironment. The microenvironment governs tumor's « adulthood ». It is generated in immediate proximity to the tumor as the results of crosstalks between stromal and neoplastic cells. These interactions are governed by mechanisms fundamentally unrelated to the physiology of the host organ; therefore, tumors should be considered as neo-organ with specific properties and metabolism (Bissell and Radisky, 2001) rather than organ diseases. The specific properties of major constituents of the tumor microenvironment such as cancer associated fibroblasts (CAFs) (Liao et al., 2019; Park et al., 2020; Pelon et al., 2020; Sahai et al., 2020), cancer-associated (Hammerl et al., 2018) are extensively reviewed and will not be considered here.

The systemic component of the ecosystem

Beyond the host organ, the tumor ecosystem extends to distant systemic components of the organism. Most studies on the role of the stroma, carried out in the context of tumor as neo-organ, have focused on crosstalks between tumor and microenvironment. More rarely, the roles of system organism have been considered to be part of the tumor ecosystem. Indeed, the tumor environment can be extended beyond the neo-organ itself to an integral part of the host organism. Functional interactions between tumors and their host organism are well highlighted for example by the effects of central circadian clock disruption on the incidence of specific cancers (Masri and Sassone-Corsi, 2018) or by the occurrence of paraneoplastic syndromes in which mediators secreted by tumors actively perturb host organs at distant anatomic sites. McAllister and Weinberg have described these host-tumor connections as "Far-Reaching Relationships" (McAllister and Weinberg, 2010). An interesting concept extending the tumor macroenvironment beyond the target tissue itself to the whole body ecosystem, dubbed as "Tumor Organismal Environment" (TOE), proposed by Laplane et al. (2019) will be discussed later.

THE TISSUE MACROENVIRONMENT: TUMOR NICHE AND FIELD CANCERIZATION

The permissiveness of tissues to tumor growth underlies fundamentally different processes depending on whether or not the tissue displays premalignant phenotype. We discriminate between tumor niche and

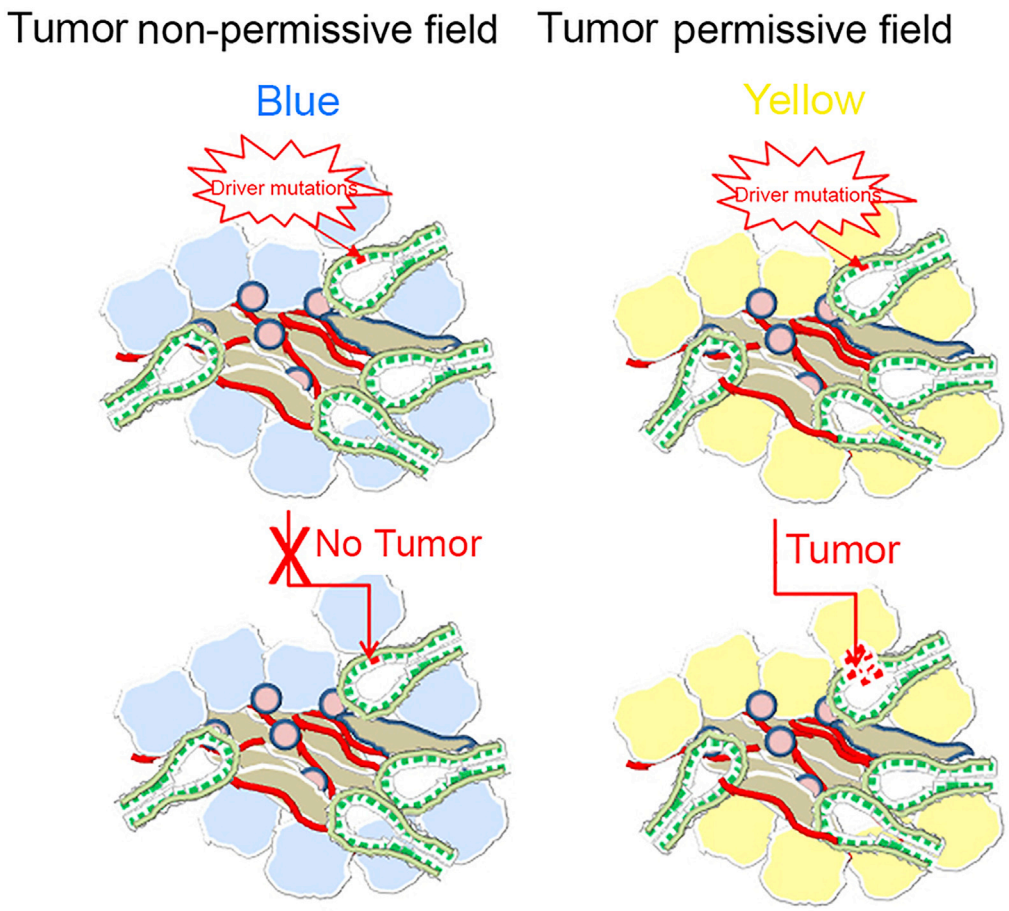

Figure 2. Tumor non-permissive field vs tumor permissive field

These schemes highlight the intrinsic behavior of tissues from different individual with respect to tumor proliferation. Left panel: in a non-permissive mammary tissue determined by fat cells of the blue type, a driver mutation in duct epithelial cells remains silent with regards to tumor growth. Right panel: the same mutation will initiate epithelial tumor growth in a permissive context determined by fat cells of the yellow type.

field cancerization. Both tissues represent permissive contexts for tumor growth, tumor niches being ostensibly normal constitutional tissues lacking any sign of malignancy whereas field cancerizations are shaped for cancer cell growth by exogenous interventions of different kinds (genetic or phenotypic). Tumor niches — a name borrowed from the nomenclature of the hematopoietic niche in the bone marrow — are predisposed to homing and development of tumors. These properties are intrinsic to the physiological status of tissues at a given time: organization, metabolism, immune competence … and do not imply exogenous intervention.

Tissues displaying early signs of malignancy at least dysplasia, whether or not they carry driver mutations, have undergone field cancerization. Field cancerizations are sporadic, resulting from exogenous events of various kinds: mutations from exposure to mutagens of exogenous or self-metabolism origin, altered epigenetic patterns, infection, senescence, inflammation, modification of the physical structure of the tissue (wound, surgery …). A simplified view of tissue permissiveness to tumor growth is presented on Figure 2.

Tumor niches are ostensibly normal tissues

The concept of niche, introduced by Schofield in hematology, is widely used in stem cell biology to designate *"the cellular environment which retains the stem cell, prevents it from maturation, and determines its behavior"* (Schofield, 1983). Applied to cancer, the concept of niche can be defined as a cellular environment ostensibly normal that exhibits constitutional or transient physiological properties predisposing to homing and development of tumors. Experiments by Sflomos et al. illustrate the best the concept of tumor

niche. These authors transplanted estrogen receptor positive (ER+) human breast tumor cells MCF7 either into the mouse cleared mammary fat pad or into the milk ducts and observed that different types of tumor developed in the two sites. Although basals tumor grew in the fat pad losing the ER + status, this status was retained in epithelial tumors growing in the milk ducts (Sflomos et al., 2016). These observations highlight the role of the tissue environment (fat pad versus milk duct epithelium) as a potent determinant of tumor phenotype, thus defining the tumor niche as constitutively determined by the intrinsic nature of the host tissue. The concept of niche applies to primary tumor and to metastases. Given that, by definition, niches have no premalignant or malignant-related phenotype, they are more difficult to document clinically than field cancerization. Hambardzumyan and Bergers (2015) have proposed that niches are « *communication centers in which tumor and host cell populations dynamically interact* via *direct cell contact or paracrine signaling cues*», a definition extended by Laplane et al. (2018) who incorporated a temporal dimension, the niche representing the initiation site of tumor expansion existing before tumor cell implantation. The properties of a tumor niche can be constitutive, intrinsically determined by the physiology of a tissue as exemplified by the mammary duct epithelia versus fat pad difference reported by Sflomos et al. or by the privileged-organ sites for metastases of various primary tumors. The niche status can also be acquired upon physiological modifications of the tissue such as aging, epithelial-mesenchymal transition, autophagy, inflammation, wound, surgery, hormone stimulation or other kind of metabolic stress. For instance, permissiveness of human breast to tumor development can be enhanced by estradiol (E2) exposure. The broad spectrum of physiological effects exerted by exposure to E2 may include some degree of permissiveness of the mammary gland stroma to tumor growth. Bendrik and Dabrosin (2009) have reported an increased secretion of interleukin 8 (IL-8) by epithelial cells upon E2 incubation of normal human breast tissue biopsies *in vitro* and a significant correlation of E2 and *in vivo* extracellular IL-8 in human breast cancer. IL-8 secretion being associated with onset of pro-inflammation, it is tempting to propose a model in which permissiveness of human breast stroma to cancer may result at least partly from exposure to IL-8 and other cytokines. Permissiveness can be transient or result from the accumulation of periodic exposures. This effect may contribute to the close correlation between the duration of exposure to ovarian hormones (between the onset of menarche and the onset of menopause) and the risk of breast cancer (Travis and Key, 2003). Furthermore, the correlation between the ER status of the tumor and the characteristics of the adipose environment observed by Miran et al. (2020) leads to the hypothesis that permissiveness for a specific type of tumor can be determined by a specific stroma status. Although this discussion has so far focused on a generic ''tumor niche'', Hambardzumyan and Bergers (Hambardzumyan and Bergers, 2015 240) introduced the concept of multiple functionally distinct tumor niches as microanatomic compartments already described in normal tissue like bone marrow (perivascular and osteoblastic niches). These authors have described three types of niches within a single glioblastoma tumor system: the perivascular, the hypoxic and the invasive glioblastoma niches. They suggest that each of these niches contributes with its specific properties to the needs of cancer stem cells and tumor cells. This level of complexity accounts, at least in part, for the intratumoral heterogeneity. Pronk and Raaijmakers (2019) have proposed an alternative definition of niche. They define ''niche-driven malignant transformation'', in which primary alterations in mesenchymal bone marrow generate niches, as the phenomenon, which induces hematopoiesis dysfunction leading to myelodysplastic syndrome. This phenomenon will be discussed below.

Field cancerization: Shaping tissues for cancer cell growth

Field cancerization is a property acquired by a tissue as a result of alterations in one of its components (Figure 3). Target tissues can be either the component that will eventually become malignant, *i.e.,* epithelial cells for carcinoma, or any component of the stroma. A cancerized field's hallmark is a predisposition to undergo malignant multifocal growth (Braakhuis et al., 2003). In their landmark 1953 paper, Slaughter et al. promoted the concept of field cancerization as a model to account for the high local recurrence of oral epidermoid carcinoma (Slaughter et al., 1953). The authors suggested that these tumors originate in an area of stratified squamous epithelium which has been « *preconditioned by an as-yet-unknown carcinogenic agent exposure*». Since this initial description, the concept has been enriched in an exponentially growing literature. More recently, Barcellos-Hoff et al. carried out a set of rigorous experiments designed as a formal demonstration of field cancerization. They transplanted mouse cells in hemibody irradiated cleared fat pad hosts and observed that tumors formed only in fat pads on the irradiated side (Barcellos-Hoff and Ravani, 2000). This result established that ionizing radiations elicit rapid and persistent changes in the mouse mammary stroma, which brings about permissiveness to cancer, and corroborated Slaughter et al.'s clinical observations of recurrent oral epidermoid carcinoma. In that case the acquisition of premalignant permissiveness to cancer was generated by exposure to alcohol and/or tobacco.

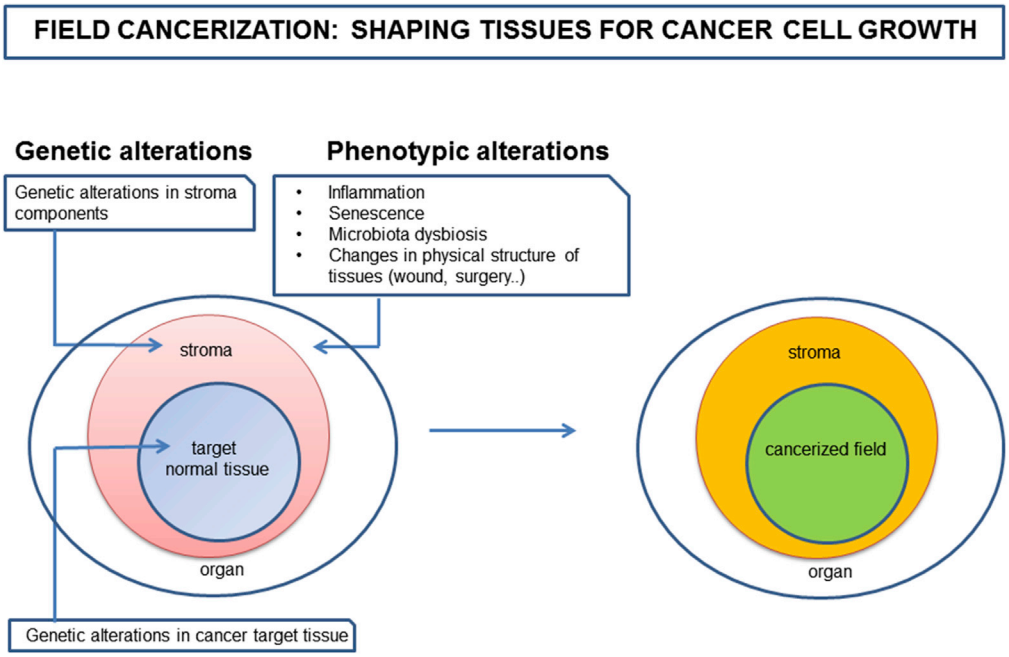

Figure 3. Pathways to the generation of cancerized fields

Field cancerization within the cancer target tissue

Field cancerization is often associated with early signs of malignancy, at least dysplasia. This phenotype results from either of the following conditions: (1) expression of somatic driver mutations, (2) transient genetic alterations by agents acting by hit-and-run mechanisms, (3) germline mutations conferring predisposition to cancer. The concept was further complicated by the discovery of high loads of driver mutations in ostensibly normal tissues.

Somatic mutations elicit a chronic "initiated" status. It is appropriate to give historical perspective to this chapter by citing Berenblum and Shubik pioneering observations (Berenblum and Shubik, 1947) who showed that "*painting a sub-threshold amount of a carcinogen such as 7,12-Dimethylbenz[a]anthracene (DMBA) on the skin of mice did not result in papilloma formation; however, papillomas developed if the carcinogen treatment was followed by repetitive application of croton oil* ». The concept of a " precarcinogenic " or " initiating "phase proposed by Berenblum and Shubik is indeed an early description of field cancerization generated by the mutagenic effects of the carcinogen DMBA. 12-0-tetradecanoyl phorbol 13-acetate (TPA), the active component of croton oil, promotes the hyperplasia-papilloma transition by activating protein kinase C (Castagna et al., 1982; Newton, 2018). In a recent review, Curtius et al. (2018) compiled a comprehensive list of field cancerization occurring in a broad spectrum of human tissues. Their definition of field cancerization is similar to that of Slaughter et al.: «*A collection of cells that have gained some but not all the phenotypic alterations required for malignancy; in general, the altered phenotype will have been caused by an underlying mutation*». Barrett's esophagus, inflammatory bowel disease (IBD) and *CDX2* mutations-associated colorectal cancers illustrate field cancerization associated with somatic mutations in the cancer target tissue.

(i) Barrett's esophagus (BE) is a stable metaplastic lesion that arises at the gastro-esophageal junction. Symptoms of gastroesophageal reflux disease are the primary risk factor for BE (Thrift et al., 2013). Interestingly, inverse correlation between colonization with *Helicobacter pylori* and presence of BE has been reported (<u>Thrift et al., 2013</u>). BE is the only known precursor lesion for esophageal adenocarcinoma although this progression is rare. As pointed by Jiang et al. (2017), «*in several organ systems, the transitional zone between different types of epithelium is a hotspot for pre-neoplastic metaplasia and malignancy*». The development of BE under the effects of gastro-esophageal reflux is the result of a complex interplay of events including profound alterations in tissue structure, mutations, activation of molecular pathways and contributions of the microbial

population (Badgery et al., 2020). In this metaplastic process, the normal stratified squamous epithelium is reprogrammed into an intestinal epithelium characterized by the frequent presence of goblet cells and evidenced by increased expression of CDX2, a marker of intestinal epithelial differentiation (<u>Jiang et al., 2017</u>; Moons et al., 2004). This metaplasia leads to breakdown of barrier functions aimed at protecting esophagus epithelium against mechanical, biological, and chemical insults thus giving rise to a tissue highly susceptible to environmental damage. Indeed, as demonstrated by whole-genome sequencing on paired BE and esophagus adenocarcinoma samples, the cells of Barrett's esophagus are polyclonal and highly mutated with frequent tumor suppressor genes alterations (Ross-Innes et al., 2015; Stachler et al., 2015). Differential expression patterns of long non-coding RNAs and of repeat elements are also detectable across different stages of Barrett's disease (Maag et al., 2017). As mentioned above, the progression of BE into adenocarcinoma is a rare event. The Barrett's metaplasia–dysplasia–neoplasia sequence is characterized by large-scale mutational events including loss of *CDKN2A* followed by *TP53* and *SMAD4* inactivation and aneuploidy (whole-genome doubling) (Stachler et al., 2015). «*Growth of a mutant clone to produce a field of cells predisposed to subsequent tumor growth* » has been proposed (Braakhuis et al., 2003). Several predictors of progression of BE into adenocarcinoma have been described. Progression is more frequent in BE cases with goblets cells (Bandla et al., 2014). Hypermethylation of both *p16INK4* and *APC* strongly predicts progression to high-grade dysplasia or cancer in patients with BE (Wang et al., 2009). Furthermore, alterations to the esophageal microbiota are associated with progression from BE to esophageal adenocarcinoma (Snider et al., 2019)

(ii) Inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the gastrointestinal tract. Repeated sequences of immune-related inflammatory damages, oxidative stress and tissue regeneration generate field cancerization. These inflammatory conditions are triggered, in part, by gut dysbiosis (Hansen and Sartor, 2015). IBD patients are at increased risk of developing carcinoma of the gastrointestinal tract, including colorectal carcinoma, small bowel adenocarcinoma, but also extra-intestinal malignancies such as lymphomas and skin cancers (Chang et al., 2018). A significant fraction of Crohn's disease patients develop synchronous and multifocal colorectal carcinoma. Remarkably the same point mutations in *KRAS, CDKN2A, or TP53* are observed in the tumors, the resection margins and even distant normal tissues, suggesting a sequence of transformation of normal cells into clonal tissue predisposed to malignant transformation (Galandiuk et al., 2012). The mutation signatures of these tumors are distinct from sporadic colorectal carcinoma (Hirsch et al., 2018).

(iii) CDX2 mutations-associated colorectal cancers. The homeobox *CDX2* gene plays an important role in embryonic development of the gut (Simmini et al., 2014). Its expression is frequently reduced in human colorectal cancers, particularly in the serrated subtype with the worst prognosis, and in animal models of intestinal cancers and thus is believed to function as a tumor suppressor (Hryniuk et al., 2014). Balbinot et al. (2018) have established a mouse model of mosaic *Cdx2* knockout of the adult intestinal epithelium, which develops imperfect gastric-type metaplastic lesions. In this mosaic setting, metaplastic knockout cells do not spontaneously become malignant. However, they induce changes in the tissue organization, which facilitate the malignant transformation of neighboring wild-type *Cdx2* cells through activation of NF-κB, induction of inducible nitric oxide synthase and stochastic loss of *Apc* gene. This model introduces a new paradigm in which field cancerization is promoted by mutations of a subfraction of the target tissue but the tumor grows from the non-mutated cell compartment of that tissue.

Transient effectors: hit-and-run mechanisms. Field cancerization can also be generated by hit-and-run mechanisms representing transient promoting events, which become dispensable for the maintenance of the malignant phenotype. Two illustrations of these mechanisms are presented below:

(i) Cutaneous infection with Human Papilloma Virus (HPV) of the *beta* types synergizes with UV radiations in the initial phase of squamous cell carcinogenesis. However, the presence of the virus is dispensable to maintain cells malignancy. The promoting activity of the virus relies on E6 and E7 oncoproteins, which facilitate genetic instability (Rollison et al., 2019).

(ii) A similar situation is observed in stomach cancers associated with *Helicobacter pilori* infection (Yakirevich and Resnick, 2013 203). Infection with *H. pilori* induces chronic inflammation and cell proliferation mediated by the bacterial *CagA* gene delivered into the gastric mucosa, causing a strong

NF-κB-mediated inflammatory response (Hatakeyama, 2017). Incidently, the structural polymorphisms of CagA explain the geographic difference in the incidence of gastric cancer. However, because the presence of the *CagA* gene is no longer necessary to maintain the established gastric malignant phenotype, the mode operating in this case is "hit and run" (Hatakeyama, 2017). In addition, inflammation triggered by *H. pylori* infection is associated with aberrant DNA methylation in the gastric mucosa. This leads to epigenetic silencing of tumor-suppressor genes and miRNAs, which affects not only cancer cells but also ostensibly normal gastric mucosa. Indeed, aberrant DNA methylation levels in non-tumor tissue correlate with cancer risk and LINE-1 hypomethylation can be used as a surrogate marker for field cancerization gastric cancer (Ushijima and Hattori, 2012). The epigenetic alterations observed in *H. pilori*-associated gastric cancer has fostered the concept of epigenetic field cancerization (Ushijima, 2013) which has been extended to other types of cancers such as colorectal, esophageal, liver, and renal cancers (Baba et al., 2016).

Germline mutations and tissue predispositions to cancers. *"The hereditary predisposition to cancer dates historically to interest piqued by physicians as well as family members wherein striking phenotypic features were shown to cluster in families"* (Lynch et al., 2004). This sentence introduces the outstanding contribution of Henry Lynch who pioneered the field by describing a large set of hereditary cancer syndromes. Indeed, most cancers display a component of hereditary forms representing a fraction of 5–10% of the total cancers. These hereditary forms of cancer are associated with the transmission of germline mutations, the vast majority of which inactivate tumor suppressor genes. Although predisposition to cancer is transmitted in a dominant mode, the underlying mechanism of tumor development is recessive, being driven primarily by the loss of heterozygosity of tumor suppressor genes. Cancers occurring in the context of a hereditary predisposition are generally of early onset. The penetrance of the predisposed phenotype is usually incomplete, being modulated by environmental and/or genetic modifiers. For instance, the risk of melanoma, for *p16INK4* mutations carriers, is at least partly determined by sun exposure. Genetic modifier effects are best illustrated by mouse models of intestinal neoplasia linked to mutations in the *Min1* gene, the murine version of the human *APC* gene. Several *Mom* loci (modifiers of *min*), which change the phenotype of *Min1−/−* mice, have been identified. Of these, Mom1 has been the most studied. The *Mom1* modifying effect is accounted by the activity of the gene encoding secretory phospholipase 2A (*Pla2g2a*). Interestingly, the *Pla2g2a* gene seems to act in a non-cell autonomous fashion. It is expressed from post-mitotic Paneth and goblet cells within the microenvironment, affecting the growth rate of adjacent tumors (Kwong and Dove, 2009). The role of secretory phospholipase 2A in inflammation has provided a rationale for the use of NSAID drugs as a preventive action against colon cancer in humans.

In the context of this review, it is appropriate to ask the question whether cancer predisposition status confers field cancerization properties on all or part of the body's tissues. With the exception of Li-Fraumeni syndrome, linked to germline mutations in the *p53* gene, which affects multiple organs (osteosarcoma, soft tissue sarcoma, acute leukemia, breast cancer, brain cancer, adrenal cortical tumors…), cancers linked to mutations in a given predisposition gene usually affect specific organs. The reasons for this organ specificity are essentially not understood. Knudson's two-hits model has implied that tissues carrying a heterozygote mutation of a tumor suppressor gene have no malignant-related phenotype until loss of heterozygosity occurs. This model has been challenged by the demonstration that these tissues, although ostensibly normal, exhibit haplo-insufficiencies, which may indeed represent the initial steps toward malignant transformation. *In vitro* studies on heterozygous human *BRCA1*$^{+/-}$ mammary epithelial cells have revealed various phenotypes that originate from *BRCA1* haploinsufficiency such as impairments in lineage commitment in differentiation (Proia et al., 2011; Wang et al., 2019), management of replication stress (Pathania et al., 2014) or post-replication repair after UV-induced DNA damage (Pathania et al., 2011). It is noteworthy that none of the phenotypes linked to haploinsufficiency described above have been demonstrated in tissues *in vivo*. Altogether, these observations support the model that field cancerization is a property of tissues carrying heterozygote germline mutation in tumor suppressor genes (Figure 4). Additional genetic events, including loss of heterozygosity of the tumor suppressor gene are required to eventually initiate malignant transformation. The organ specificity of the cancers linked to these germline mutations, which reflects tissue-specific penetrance is a strong indication that the onset of malignant transformation is driven in a non-cell autonomous way, by the physiology of the target tissue. The basis of this specificity is unknown.

Driver mutations in phenotypically normal tissues. Studies using p53-immunostaining reported the existence of cell clones carrying *p53* mutations in keratinocytes in normal human skin (Jonason et al., 1996). This

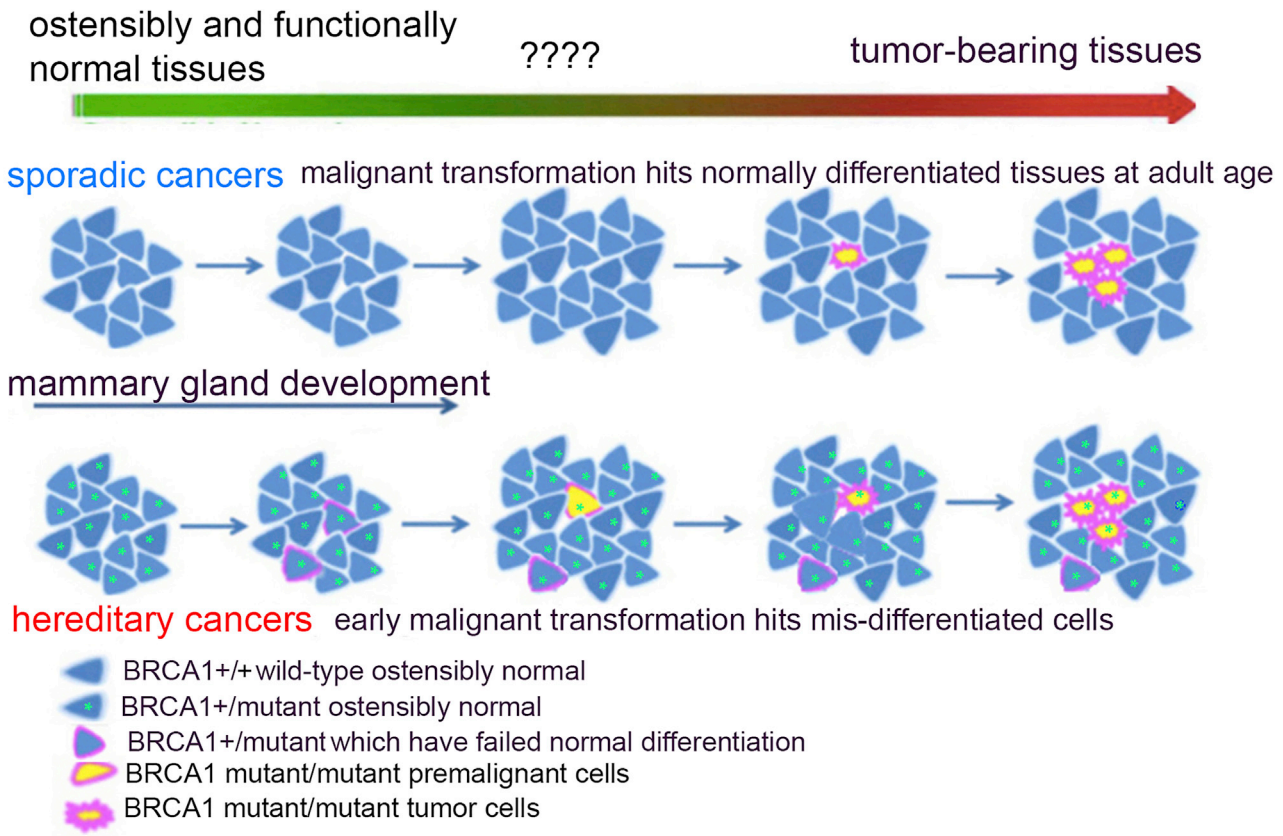

Figure 4. Malignant transformation in sporadic versus *BRCA1* mutation-linked hereditary breast cancers

The onset of tumors is earlier in women carrying a heterozygous *BRCA1*mutation than in sporadic cases. The model proposes that this difference reflects irreversible defects of early differentiation for a fraction of mammary epithelial cells because of BRCA1 haploinsufficiency, which generates local field cancerization within an otherwise ostensibly normal organ.

observation was extended to several other organs, including oral, bronchial, bladder and esophageal epithelia as cited by Dotto (2014). As a follow-up, in-depth explorations of genomes of normal tissues were conducted using whole genome sequencing. Martincorena et al. studying sun-exposed normal skin squamous epithelia reported two major observations. First, they found mutations in most of the key drivers of cutaneous squamous cell carcinomas including *TP53* and *NOTCH* family members. Twenty per cent of normal skin cells carry driver mutations in *NOTCH1*, surprisingly more than in squamous cell carcinoma. Second, the populations of mutations carrying cells are clonal expansion, some of them carrying two to three driver mutations. They estimated that "*sun exposed skin is a patchwork of thousands of evolving clones with over a quarter of cells carrying cancer-causing mutations while maintaining the physiological functions of epidermis*" (Martincorena et al., 2015). Similar clonal expansions driven by cancer genes have also been observed in two independent studies of the mutational landscape in human healthy esophagus (Martincorena et al., 2018; Yokoyama et al., 2019). The accumulation of somatic mutations was found to be most strongly associated with age, with additional effects of heavy smoking and alcohol consumption (Yokoyama et al., 2019). Finally, mutations in driver cancer genes have also been described in normal colorectal crypts (Lee-Six et al., 2019), endometrial glands (Moore et al., 2020) and many other tissues (Yizhak et al., 2019).

Is the traditional multi-stage model of carcinogenesis challenged by the presence in normal tissues of heavy loads of mutations in cancer genes? Probably not, because these mutations occur in different clones scattered throughout the tissue, the probability of a single cell carrying the right combinations of multiple driver events being low. Of interest, whereas the mutations appear to mediate a driving force for cell proliferation into clonal expansions, their oncogenic potentials, restrained by neighboring mutation-free cells, can be released by any alteration in the maintenance of tissue homeostasis. Understanding the factors that govern these protective mechanisms will be invaluable knowledge for cancer treatment. Cell competition

(to be discussed later) might represent one of these mechanisms. Finally, regarding the fate of the clonal expansions in normal tissues, the evidence that any of these cells will ever give rise to tumors is missing.

Genetic alterations in stroma components

"*Genetic alterations present in stromal cells may contribute to or even drive malignant transformation of epithelial cells by perturbing the normal stromal epithelial dialogue*" (Weaver and Gilbert, 2004). Field cancerization can also be promoted by alterations in a tissue compartment different from that, which will eventually undergo malignant transformation. The concept of stromal-induced oncogenesis has been documented for several organs in genetically engineered mice. These models, often designed on the basis of clinical observations, generally provide information highly relevant to the clinical etiology of human tumor pathologies (Trimboli et al., 2009).

Hematopoietic system. In the hematopoietic system, the clinical outcome of driver mutations affecting hemopoietic stem cells may be modulated by mutations in components of the bone marrow stroma. Three illustrations of these stroma effectors among the multiple cases of association of germline mutations in bone marrow microenvironment with dysregulated hematopoiesis that have been reported (Miller et al., 2018) are discussed:

1. Mouse genetic studies have demonstrated that mutations in the *Ptpn11* gene coding for the protein tyrosine phosphatase SHP2, in bone marrow mesenchymal stem/progenitor cells and osteoprogenitors, but not in differentiated osteoblasts or endothelial cells, promote juvenile myelomonocytic leukemia (JMML). The mechanism of leukemogenesis involves hyperactivation of hemopoietic stem cells by pro-inflammatory cytokines produced by invading monocytes (Dong et al., 2016). Interestingly the same juvenile leukemia is observed in 50% of patients with Noonan syndrome carrying germline-activating mutations of *PTPN11*.
2. An activating mutation of β-catenin in mouse osteoblasts induces a "mutagenic" environment in myeloid and lymphoid progenitors leading to development of acute myeloid leukemia (Kode et al., 2014).
3. Katayama et al. have reported that sympathetic nervous system signals regulate normal hematopoiesis in mouse bone marrow (Katayama et al., 2006). Alterations in this crosstalk are observed in the bone marrow of patients with a myeloproliferative neoplasm expressing the JAK2 (V617F) mutation in hematopoietic stem cells. In this context, the survival and functions of mesenchymal stem cells are seriously impaired because the neural innervation of their niche is hampered by the damage to the sympathetic nervous system triggered by interleukin-1β produced by the HSC mutant (Arranz et al., 2014). These results show that the lack of innervation operates as non-cell autonomous condition essential for myeloproliferative neoplasms.

Solid tissues

Skin: The epidermal polarity protein Par3 is part of a complex together with the Ser/Thr kinase atypical PKC (aPKC) and Par6, which plays a major role in apico-basal polarity, asymmetric cell division, and polarization of neuronal and T cells(Macara, 2004). Mouse models, human melanoma cohorts, and functional co-culture experiments reported by Mescher et al. (2017) have demonstrated that loss of Par3 in the epidermis resulting in elevated P-cadherin localization at heterologous keratinocytes-melanocytes contacts, promotes permissiveness for melanocytes transformation, invasion, and metastasis. Interestingly, high P-cadherin expression in melanoma is associated with decreased melanoma patient survival. By controlling melanocytes morphology and motility, epidermal Par3 functions as a non–cell autonomous tumor suppressor for melanoma formation and metastasis *in vivo*. This study reveals a new mechanism of tumor suppression whereby a protein controlling the polarity of one tissue component (epithelium) determines the heterologous cell-cell interactions and the tissue architecture to prevent the formation and progression of cancers eventually originating from another cell component of the tissue (melanocyte).

Liver: The primary response to liver damage is the metabolic activation of quiescent stellate cells, which promotes fibrosis as part of the response to protect organ function. Subsequently a p53-dependent senescence program is activated to eliminate fibrosis and excess of stellate cells. Lujambio et al. (2013) have generated a transgenic mouse model in which this p53-dependent senescence program

has been ablated specifically in stellate cells. They observed that upon chemically induced damage, these transgenic mice exhibit an increased rate of cirrhosis and transformation of epithelial cells into hepatocellular carcinoma, compared to controls. They showed that the effect is mediated by factors secreted by p53-deficient stellate cells, which create an environment prone to premalignant cells transformation. These observations demonstrate that p53 activity in stellate cells acts in a non-cellular autonomous mode to suppress hepatocellular carcinoma. At present, there is no evidence for p53 mutations in cells associated with fibrous lesions adjacent to liver tumors in humans.

Breast: Trimboli et al. provide a final illustration of the role of mutations in stromal components in establishing field cancerization. Trimboli et al. (Trimboli et al., 2009 265) explored the consequences of the ablation of the tumor suppressor gene *Pten* in the mouse mammary stroma. Pten is a dual phosphatase with both protein and lipid phosphatase activities which regulates cell growth/survival and metabolism (Chen et al., 2018). Biallelic *Pten* inactivation results in early embryonic lethality in mice. Single allele *PTEN* germline mutations are associated with three related human autosomal dominant disorders, Cowden disease, Lhermitte-Duclos disease and Bannayan-Zonana syndrome, characterized by susceptibility to tumors of epithelial origin and developmental defects. *PTEN* role as a tumor suppressor has been largely documented (Di Cristofano et al., 1998). Trimboli et al. (2009) have demonstrated the potent tumor suppressor function of *Pten* in murine mammary stromal fibroblasts by showing that biallelic deletion of *Pten*, specifically in this tissue compartment, leads to the development of mammary tumors of epithelial origin with extracellular matrix remodeling, infiltration of immune cells and enhanced angiogenesis. The tumor suppressor activity is mediated by the activation of the pathway controlled by transcription factor Ets2. These authors provided the proof of the relevance of these observations for human breast cancer by the demonstration that a similar loss of *PTEN* and associated changes in gene expression can also be observed in the stroma of human breast tumors (Trimboli et al., 2009). Further demonstration of relevance to human breast cancer has been provided by Yang et al. who showed that the expression level of the *GT198* gene, a steroid hormone receptor coactivator, defines mutant tumor stroma in human breast cancer (Yang et al., 2016).

Phenotypic alterations of tissues: Shaping a tumor-permissive macroenvironment

Throughout life, tissues undergo physiological or pathological processes, which disrupt their homeostasis either transiently or permanently and endow them with phenotypes subject to malignant transformation. These conditions include inflammation, senescence, dysbiosis of the microbiota and changes in the physical structure of the tissue.

Inflammation: Trigger or permission?. Inflammation represents a wide variety of physiological and pathological processes. It is essentially an adaptive response to harmful conditions caused by exogenous agents (microbial or non-microbial) or endogenous conditions such as stress or tissue dysfunction. Its chronic form is associated with several pathological conditions, for instance type 2 diabetes, atherosclerosis, asthma, neurodegenerative diseases and cancer (Medzhitov, 2008). In 1863 Virchow hypothesized that cancer originates at sites of chronic inflammation (Balkwill and Mantovani, 2001). This pioneering definition of field cancerization has received support from prospective epidemiological studies aimed at identifying biomarkers for cancer risk prediction. These studies have identified markers of inflammation as robust predictors of cancer: CRP for the risk of colorectal cancers (Aleksandrova et al., 2014; Zhou et al., 2014); IL-8 and CRP for the risk of lung cancer (Pine et al., 2011 331); CRP for the risk of breast cancer in postmenopausal women and TNF-α and IL-6 in premenopausal women (Agnoli et al., 2017); TNFα, soluble TNF receptors 1 and 2, CRP, IL-6 and IL-1 receptor antagonists for the risk of postmenopausal endometrial cancer (Dossus et al., 2013 333). At the same time, the inflammation-cancer connection has been documented by molecular profiling (Bottazzi et al., 2018; Mantovani et al., 2008) and the central role played by the NF-κβ family of transcription factors well accepted (Karin, 2006). Further support has been brought by the demonstration of the preventive action of anti-inflammatory drugs like aspirin in reducing the incidence and mortality for colorectal cancer (Chan et al., 2012).

The inflammation-cancer connection: what comes first?. The functional aspects of the connection remain ambiguous: what comes first? Do tumors promote an inflammatory status or does chronic inflammation predispose to tumor onset? Bottazzi et al. (Bottazzi et al., 2018 305) rephrased the ambiguity by describing two pathways that connect inflammation and cancer: intrinsic and extrinsic. In intrinsic pathways, the two canonic events involved in oncogenesis, namely oncogene activation and tumor suppressor

inactivation can drive the production of inflammatory mediators. This is highlighted for oncogene activation by RET/PTC1 oncogene expression in normal human thyrocytes (Borrello et al., 2005) or Myc activation in murine pancreatic *beta* cells (Shchors et al., 2006) and for tumor-suppressor inactivation by the loss of RB, which causes oxidative stress, which in turn promotes the secretion of pro-inflammatory cytokine IL-6 (Kitajima and Takahashi, 2017). In extrinsic pathways, chronic inflammation provides a favorable ground for tumor growth. Three key experiments highlight such a field effect: 1) Martins-Green and Bissell showed that the growth of wound-induced tumors in chickens infected with Rous Sarcoma Virus strictly depends on inflammation at the wound site (Martins-Green et al., 1994); 2) Guerra et al. showed that whereas adult mice are refractory to induction of pancreatic ductal adenocarcinoma by K-RasG12V, these same mice subjected to a mild form of chronic pancreatitis develop the tumors (Guerra et al., 2007); 3) Henry et al. observed reductions in the fitness of B cell progenitor populations in aged murine hematopoietic system associated with chronic inflammatory microenvironments. This condition leads to the selection for cells harboring oncogenic mutations and leukemogenesis (Henry et al., 2015).

In humans, inflammatory bowel diseases exemplify the strongest association between chronic inflammation and risk of cancer, as discussed above. An exhaustive list of chronic inflammatory conditions associated with neoplasms has been compiled by Coussens and Werb (2002). Noteworthy, these conditions invariably involve tissue damages. Although the conditions for full tumor development (initiation, *in situ* progression, and metastasis) are likely to involve interplay between intrinsic and extrinsic pathways, regarding the topic of this review, the key question is: Is a chronically inflamed tissue a cancerized field?

Is a chronically inflamed tissue a cancerized field?. Any disturbance in tissue homeostasis activates innate and adaptive immune responses. Macrophages, mast cells, dendritic cells and natural killer cells initiate the inflammatory process by releasing cytokines, chemokines, matrix-remodeling proteases, and reactive oxygen and nitrogen species. This physiological inflammation is activated during healing processes of wounded tissues such as the site of surgery, ischemia–reperfusion, chemically or radiation-induced injuries (Castano et al., 2011; Nakamura, 2020). If pro-inflammatory and anti-inflammatory mechanisms are balanced, the inflammation will subside once the repair is complete. If imbalance occurs, chronic inflammation will establish. Due to such imbalance, chronic inflammation occurs in various disorders. It is referred to as "inflammageing" (also called age-related inflammation or sterile inflammation) in human aging (Franceschi et al., 2017; Leonardi et al., 2018) or « metaflammation » in metabolic diseases such as type 2 diabetes mellitus, obesity (Gregor and Hotamisligil, 2011; Prattichizzo et al., 2018). The similarity of molecular profiles and the increased cancer risks associated with these two conditions suggests a common etiology and fueling by common phenomena. These include (1) constant supply of reactive oxygen and nitrogen species, reactive aldehydes, cytokines, chemokines and growth factors, which can interfere with normal genome maintenance and cell homeostasis (Hussain and Harris, 2007), (2) cellular senescence (Fane and Weeraratna, 2020; Franceschi and Campisi, 2014), (3) endogenous host-derived cell debris (damage-associated molecular patterns, *i.e.*, damaged organelles, cells, and macromolecules) (Franceschi et al., 2017), (4) immunosenescence (Bottazzi et al., 2018; Leonardi et al., 2018), (5) metabolic diseases (Prattichizzo et al., 2018), (6) gut microbiota dysbiosis (Tilg et al., 2020) and (7) nutrition (Zitvogel et al., 2017b).

Cellular senescence: Modulating tissue permissivity for cancers?. Observations of the accumulation of senescent cells in aged tissues have linked senescence *in vitro* and aging *in vivo* and led to a large body of research data highlighting the role of senescence in homeostasis of normal tissue and in pathological disorders such as diabetes and cancer. Cellular senescence has been included as one of the hallmarks of aging by Lopez-Otin et al. (2013) and discussed by Hanahan and Weinberg as an important component of cancer hallmarks (Hanahan and Weinberg, 2011). The role of senescence in cancer has been extensively reviewed over the past decade (Campisi, 2013; Faget et al., 2019; Fane and Weeraratna, 2020; Lee and Schmitt, 2019). Cellular senescence was initially viewed as a cell autonomous program aimed at eliminating damaged or potentially harmful cells, including cancer cells, thereby expressing tumor suppressive activity. The spectrum of its activities widened when its ability to influence the neighborhood in a non-cell autonomous mode was demonstrated (Acosta et al., 2013; Davalos et al., 2010). These paracrine functions are carried out via a secretome coined Senescence-Associated Secretory Phenotype (SASP) or senescence-messaging secretome (Rodier and Campisi, 2011). SASP is part of the «*cellular communicome*», a term proposed to «*encompass those mediators within an organism that carry information from one cell to another*» (Ray et al., 2007). It is a mix of mediators and enzymes: cytokines, chemokines, growth factors, proteases … whose action vis-à-vis tumorigenesis is complex, the distinction between desirable and detrimental

SASP-mediated effects being sometimes difficult to assess. The production of SASP in response to diverse stimuli of cellular senescence engages the cGAS–STING pathway activated by cytoplasmic DNA fragments generated by nuclear genome damages (Dou et al., 2017; Gluck et al., 2017; Yang et al., 2017). By activating SASP and particularly the set of cytokines and chemokines IFN-β, IL-1β, IL-6, and IL-8, the cGAS–STING pathway provides a critical paracrine signal sustaining cellular senescence and determines the immunological outcomes of DNA damage (Li and Chen, 2018). Fane et al. qualified senescence as antagonistic pleiotropy, meaning that it triggers a beneficial phenotype early in life but becomes detrimental in an elderly organism (Fane and Weeraratna, 2020). Indeed, SASP can either restrain or promote tumor growth (Campisi, 2013; Faget et al., 2019; Fane and Weeraratna, 2020; Rodier and Campisi, 2011).

Senescence restrains tumor growth. SASP-mediated suppression of tumorigenesis can result from autocrine or paracrine growth arrest or paracrine induction of antigen-specific innate and adaptive immune responses against premalignant or malignant cells in established tumors. Collado et al. reported the first demonstration of such an effect induced by oncogene-induced senescence (OIS) in KrasV12 knockin mice that develop lung adenoma which rarely progress into tumors. They showed that progression is restricted by OIS (Collado et al., 2005). Similar conclusions have been reached in various mouse models (Baker et al., 2017; Bennecke et al., 2010; Xue et al., 2007). Senescence-mediated suppression of tumorigenesis can also be achieved in a non-cell autonomous mode as demonstrated in a murine model in which a stromal-derived SASP program triggered by p53 suppresses cancer initiation in the liver (Lujambio et al., 2013). A murine Pten-deficient prostate tumorigenesis model is another illustration of p53-dependent cellular senescence preventing malignant transformation (Chen et al., 2005). It is important to note that OIS-driven markers of senescence are found in premalignant lesions in mouse models such as those cited above and also in human lesions such as cutaneous nevi, carrying an activating BRAF mutation, which can remain benign for years (Bennett, 2003). This suggests that senescent cells present in the premalignant lesion or/and in the stroma could hinder the development of the tumor at the early stage of tumorigenesis (Lasry and Ben-Neriah, 2015).

Senescence promotes tumor growth. The first evidence for pro-tumorigenic effects of cellular senescence was provided by the demonstration that senescent fibroblasts promote epithelial cell growth and tumorigenesis (Krtolica et al., 2001; Rodier and Campisi, 2011). As pointed out by Tasdemir and Lowe, "*In cases where the senescent cells in a tissue are not cleared, the pro-mitogenic arm of the SASP signal could persist long enough to have an overall pro-tumorigenic effect*" (Tasdemir and Lowe, 2013). The pro-tumorigenic arm of the SASP signal is pleiotropic. It potentially stimulates cell proliferation, angiogenesis, epithelial-mesenchymal transition, epigenetic remodeling and inflammation (Lee and Schmitt, 2019). Senescence-induced inflammation stands out among the other mitogenic mechanisms by the fact that it acts as a promoter of immunosuppression conducive to tumor progression (Ruhland et al., 2016). Immunosuppression is also elicited by aging-induced immunosenescence. It is manifested by a decline in innate and adaptative immune functions which globally impairs anti-tumor immunity (Fane and Weeraratna, 2020). Another pro-mitogenic arm of SASP relies on its proteases component capable of disrupting tissues physical architecture and vasculature integrity thereby facilitating the growth of premalignant cells in culture (Coppe et al., 2010). As mentioned above, the impact of senescence on tumorigenesis, *i.e.*, promoting or inhibiting tumor growth, is governed by multiple parameters: Tissue type, cell of origin (stromal vs tumor cells), senescence trigger (oncogene activation, DNA damage …). In addition, senescence is more dynamic than the common view of an irreversible condition had suggested. As the compartments of senescent cells increase with age, presumably with different extent in different tissues, the activities of the secreted SASP factors shift from suppressive to pro-tumorigenic activity. The balance between these two statuses may provide a clue to the question formulated as a title of this section: does cellular senescence modulate tissue permissivity for cancers? Fields of premalignant cells can be generated as endpoints of plausible sequences of events such as DNA damage (physiological or induced) producing cytoplasmic DNA fragments activating the cGAS-STING pathway leading to the SASP excretome. As long as the suppressive status, which restrains the growth of premalignant cells, dominates, the tissue displays the properties of a field cancerization, an escape from this status initiates tumor progression.

Microbiota dysbiosis. The human microbiota refers to the flora of microorganisms – bacteria, viruses, fungi, protozoa, etc.–which are important players in the body's ecosystem. Most organs have their own flora, particularly those that are directly exposed to the external environment, namely the oral cavity, skin, vagina, esophagus and gut. Microbiota dysbiosis is a condition characterized by reduced diversity and/or changes in resident species. It is induced, for instance in the gut by malnutrition, diet enriched

with fats, pharmacological treatments, etc. and is correlated with inflammatory conditions, locally such as inflammatory bowel disease but also at a distance such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis and cancers (Tilg et al., 2020). Over the past decade, the gut and the respiratory microbiota have been best characterized; their contribution in the body ecosystem and the correlation of dysbiosis with several diseases, including cancer, well assessed (Gilbert et al., 2018). The question addressed in the context of this review is whether microbiota dysbiosis can elicit field cancerization? The first clue for a link between the microbiota and cancer was provided by a large-scale epidemiological study from the Finnish Cancer Registry demonstrating that repeated use of antibiotics is associated with an increased risk of most type of cancers (Kilkkinen et al., 2008). However a recent meta-analysis of association between antibiotic use and risk of cancer showed «*moderate evidence that excessive or prolonged use of antibiotics is associated with slight increased risk of various cancers*» (Petrelli et al., 2019). Hence, with the exception of *H. pilori* infection, which shapes a tumor-permissive microenvironment in the gastric mucosa, the question of whether microbiota dysbiosis has a direct impact on cancer onset remains open. The demonstration of causality will have to await the existence of an animal model in which an increased risk of cancer will be observed upon transplantation of specific flora. This could be complex to achieve because microbiota dysbiosis effects are likely to be context-dependent of host genomics and immunity, environmental exposures, and tumor-autonomous factors. Nevertheless, assuming that cancer can only develop and progress in the context of failed immunosurveillance (Mittal et al., 2014; Zitvogel et al., 2015), the systemic pro-inflammatory and immunosuppressive effects of microbiota dysbiosis represent conditions conducive to the subversion of anticancer immunosurveillance and the shaping of field cancerization. Aside from this systemic activity, several mechanisms that may account for a direct role of the microbiota in tumor onset have been proposed. Some have been reviewed by Barrett et al. (2020) who identify pathways turned on by the microbiota with the potential for altering the integrity of the host genome: (1) production of genotoxins by the microbes (colibactin, cytolethal distending toxin …), by immune cells (production of hypochlorous acid by neutrophils and hypobromous acid by eosinophils …), or through microbiota-diet interactions (N-nitroso compounds, acetaldehyde); (2) ectopic expression of Activation-Induced Cytidine Deaminase (AID); (3) disruption of the response to DNA damage by depletion of mismatched repair proteins MSH2 and MLH1 by *E. coli* or *H. pylori*. Other more specific mechanisms that can affect the host cell metabolism to generate tumor-permissive microenvironment have been proposed: (1) *Fusobacterium nucleatum*, a significant contributor to colorectal cancer encodes an adhesin FadA which binds to E-cadherin on the colon mucosa cell surface and activates oncogenic Wnt/*beta*-catenin signaling (Rubinstein et al., 2019), (2) interleukin-17-mediated inflammation induced by macrobiome in lower airways of non-small-cell lung cancer patients can reprogram host transcription (Tsay et al., 2020; Zitvogel and Kroemer, 2021). In this specific case the reprogramming exacerbates lung cancer progression but in other contexts it may generate field cancerization.

Although the capacity of the microbiota in shaping field cancerization remains hypothetical, by contrast, its role in influencing cancer progression and therapies has been largely documented (Garrett, 2019; Helmink et al., 2019; Zitvogel et al., 2017a).

Changes in physical structure of tissues: Creating an environment conducive to the growth of indolent cancer cells. The links between cancer and a large set of conditions like aging, chronic inflammation, wound healing, surgery, chemical aggression or irradiation … rest, at least in part, on their effects in causing major changes in the physical structure of tissues, hence creating an environment conducive to the growth of indolent cancer cells (Castano et al., 2011).

Stiffness of the extracellular matrix (ECM). An underlying mechanism for these effects has been reported by Panciera et al. in elegant studies which demonstrated that an appropriate mechanical environment, determined primarily by the stiffness of the extracellular matrix (ECM), is required for the expression of fully HER2-driven oncogenicity in mammary epithelial cells both *in vitro* and *in vivo*. They showed that the mechanotransduction was mediated by the transcription factors YAP and TAZ (Panciera et al., 2017, 2020). Indeed, YAP and TAZ have been shown as important mediators of tumor emergence in the mammary gland (Zanconato et al., 2018) and pancreas (Gruber et al., 2016). These findings suggest that excessive production of ECM proteins and extensive proliferation of stromal fibroblasts (desmoplastic reaction), resulting in an increase in the stiffness of the tissue environment of indolent cells carrying driver oncogene(s), activate their oncogenic potential. This might account for higher risk of breast cancer associated with age-related changes in the gland density (Boyd et al., 1995).

Centrosome aberrations. Another non-cell autonomous mechanism capable of inducing changes in the biomechanical properties of epithelia has been uncovered in tissues harboring cells with centrosome aberrations. Centrosome aberrations are associated with aneuploidy, defective cell division symmetry and altered ciliogenesis. Although these manifestations *a priori* hamper the ability of cells to divide successfully, they do generate chromosomal instabilities necessary for the few surviving cells to acquire malignant properties, thus suggesting that they are not bystanders in the development of the tumor, but true drivers of tumorigenesis. Indeed, the amplification of centrosomes is a hallmark of most human cancer although it usually affects only subsets of cells within the tumors. Centrosome aberrations can be observed in lesions or during the early stage of tumorigenesis in different types of pre-neoplastic lesions such as breast ductal carcinoma *in situ*, prostate intraepithelial neoplasia, suggesting that they could promote the early stage of tumorigenesis (Chan, 2011). Centrosome aberrations can arise via several mechanisms such as deregulation of centrosome duplication cycle, failure of cytokinesis or cell fusion. The most prevalent among these is centrosome amplification, which arise from alterations of master regulators of mitosis. Several observations have highlighted changes in the status of centrosomes as epigenetic regulators of tumor growth. In mice, Polo-like kinase 4-mediated centrosome amplification in the developing skin epidermis leads to abnormal mitosis and aneuploidy, the outcome being different whether or not P53 is functional. In the presence of active p53, the cells with supernumerary centrosome are eliminated by apoptosis, leading to a delay in skin stratification highly deleterious for cell fitness and epidermal development. In a p53-deficient background some aneuploid cells survive, which become precursors of skin tumors (Sercin et al., 2016). Arnandis et al. have explored the non-cell autonomous roles played by the fraction of tumor cells carrying centrosome aberrations that could benefit the neighbor cells and explain their persistence in tumors (Arnandis et al., 2018). Using models of cells in which centrosome amplification is driven by transient expression of Polo-like kinase 4, the authors showed that cells with extra centrosomes activate HER2 in their neighbor cells via paracrine secretions. Secretome activates HER2 in neighbor cells and promotes invasion in primary mouse mammary organoids. The authors concluded that centrosome aberrations could alter the physical structure of the tissue to trigger cell dissemination through a non-cell autonomous mechanism. Ganier et al. using atomic force microscopy provided the formal demonstration that centrosome aberrations induce changes in the physical structure of epithelia. They showed that epithelia harboring centrosome aberrations induced by overexpression of ninein-like protein display increased stiffness which triggers budding of «normal» mitotic cells from mosaic epithelia (Ganier et al., 2018). The authors proposed that the budding process represents a model of tumor cell migration. However, the link between increased stiffness and migration seems paradoxical because, intuitively, one would rather expect migration to be promoted by tissue loosening. Changes in stroma properties induced by exogeneous interventions such as chemical aggression, irradiation or wound healing in initiating tumor development have also been documented. Maffini et al. provided an illustration of the effects of chemical aggression on the properties of stroma, with the observation that mammary tumors grow in cleared rat mammary fat pads treated with carcinogen, regardless of whether the injected epithelial cells were treated with carcinogen *in vitro* (Maffini et al., 2004).

NON-CELL AUTONOMOUS EFFECTORS IN INTRATUMORAL ECOSYSTEMS: CELL COMPETITION SHAPE TUMORS

A tumor is a complex ecosystem involving interactions between tumor cells and stroma, but also between tumor cells within the tumor mass. The constituents of the tumor microenvironment, namely cancer-associated fibroblasts, fat cells, inflammatory/immune cells and blood vessels unquestionably provide non-cell autonomous contributions in the intratumoral ecosystem. However, as mentioned above, their role being widely reviewed elsewhere, our choice was to leave them aside and rather focus on one aspect of intratumoral interactions, namely dominance and competition between normal cells and tumor cells as well as between tumor cells themselves. These processes that help shape tumors throughout their lifespan are hallmarks of these interactions in a mode formally distinct from the microenvironment-driven effects. Furthermore they provide the rationale for the so-called adaptive cancer therapy, which will be discussed in the last chapter.

Early studies of mouse mammary tumors have provided evidences for phenotypic and functional heterogeneity of tumor cell populations (Heppner, 1984). Tumor evolution cannot be explained solely by a positive selection of the fittest clone and as Poste pointed out: «*the various clonal subpopulations somehow interact with one another to "stabilize" their relative proportions*» (Poste et al., 1981). Today, whole genome and single cell RNA sequencing have provided formal proofs of the polyclonality of tumors

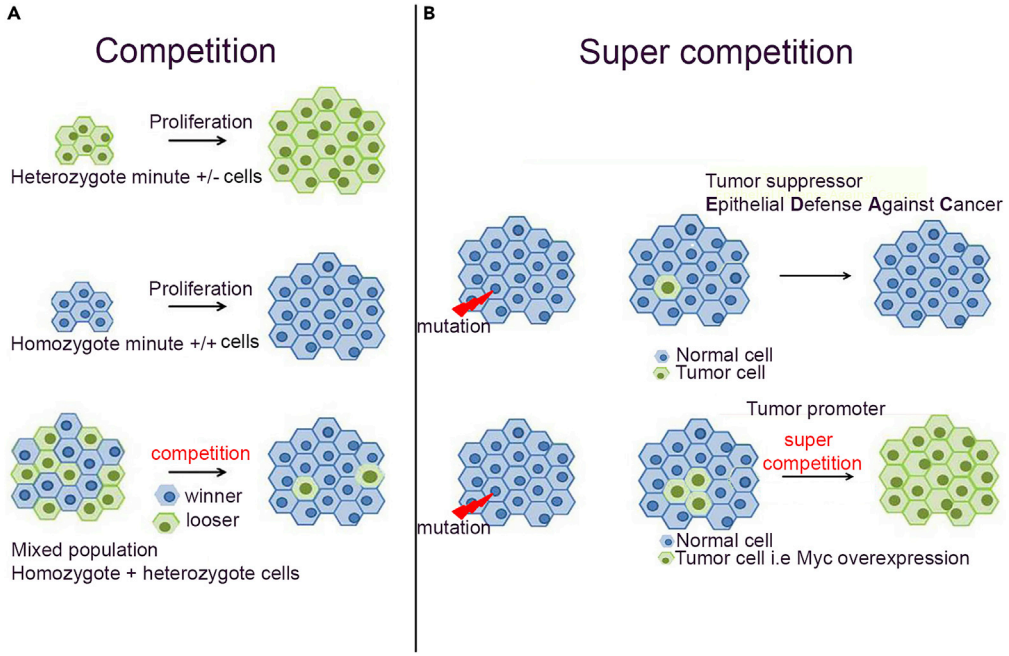

Figure 5. Cell competitions leading to either tumor suppression or promotion

(A)No difference in proliferation is observed between homogeneous populations of Drosophila heterozygote minute +/− versus wild-type minute +/+ cells. In a mosaic setting when the two populations are mixed a severe competition operates leading to overgrowth of wild-type cells (winners) and elimination of heterozygote cells (loosers).

(B)In a mosaic tissue created by the appearance of tumor cells in normal tissue, either of two mechanisms may operate: Epithelial defense against cancer (EDAC) by normal tissue exerts a tumor suppressing effect by shedding tumor cells. By contrast, a supercompetition leading to the proliferation of tumor cells can operate between cells expressing different levels of MYC. Overexpression of MYC (often seen in human cancers) makes cells win against cells with physiological level.

and helped to decipher the chronological and geographical parameters of their architecture. Although there is no doubt that genetic selection of combinatorial mutations in driver genes in the malignant cells compartment governs at least in part the evolution of tumors, the need for cooperation between distinct subpopulations, including minorities, for their maintenance, is well documented (Marusyk et al., 2014; Tabassum and Polyak, 2015). Dominance of a subpopulation within heterogeneous mixed mammary tumors of mice has long been observed (Miller et al., 1988), however the concept of somatic cell competition as a mechanism of tumor formation and progression has been considered only recently (Claveria and Torres, 2016). Somatic cell competition was originally described in Drosophila as a cellular mechanism contributing to tissue homeostasis and organ function (Claveria and Torres, 2016). «*If cellular heterogeneity occurs in a tissue, the least-fit cells are eliminated, whereas the fittest prevail and contribute in full to the tissue*» (Ramos et al., 2020). The eliminated cells are called losers those that remain are winners. In Drosophila, a broad range of mutations affecting basic cell biological functions, such as signaling, growth, anabolism, polarity and endocytosis, can trigger competition between loser and winner cells (Gutierrez-Martinez et al., 2020; Merino et al., 2016; Vishwakarma and Piddini, 2020)}. Cell competition may play a beneficial role in tissue homeostasis as a quality control mechanism to eliminate misspecified or damaged cells but also be deleterious by causing the expansion of unwanted cells and the elimination of healthy ones. Heterozygote *minute +/−* Drosophila mutants highlight the beneficial role of cell competition. Cells harboring a monoallelic *minute* mutation (*minute +/−*) affecting a ribosomal protein gene, whereas viable in a homogeneous *minute +/−* population of cells, are eliminated when they are mixed with *minute* + / + wild-type cells (Morata and Ripoll, 1975) (Figure 5). Cells expressing elevated Myc activity are representative examples of winners in cell competition. They shift their metabolism to promote their own survival and eliminate neighboring wild-type cells (de la Cova et al., 2014). This process in which growing cells not only outgrow but also trigger the elimination of neighbor wild-type cells has been called supercompetition or tumor-promoting competition. Both competition and supercompetition processes are conserved from Drosophila to mammals (Pelham et al., 2020). Natural competition between cells of the same genotype is highlighted by two examples. First, in rat liver regeneration

models, transplanted fetal hepatocytes outcompete adult hepatocytes leading to a progressive repopulation with fetal hepatocytes (Oertel et al., 2006). A similar process occurs in mice thymus where T lymphocytes develop from precursors that are constantly replaced by bone-marrow-derived progenitors. This renovation operates through cell competition in which, in spite of their genetic identity, "young" bone-marrow-derived progenitors replace "old" thymus-resident progenitors. Disruption of cell competition leads to T cell acute lymphoblastic leukemia (T-ALL), hence demonstrating that cell competition is a tumor suppressor mechanism in the thymus (Martins et al., 2014).

Cell competition shapes tumors

A growing body of evidence supports the role of cell competition as a determinant of the fate of incipient cell clones expressing oncogenic or tumor suppressor mutation factors in normal tissues has been reviewed by Vishwakarma et al. (Vishwakarma and Piddini, 2020). The list of known mutations in cancer-associated genes involved in cell competition presented by these authors shows that they can function either as winners or losers. The review presents the evidences that cell competition acts either as a tumor-suppressing or tumor-promoting mechanism depending on the context.

Cell competition as a tumor suppressor

Competition operates when cells carrying driver mutations are sensed as misspecified and eliminated by normal cells. This occurs when cells harboring oncogenic mutations, such as *RAS- G12V* (Hogan et al., 2009), *SRC* (Kajita et al., 2010) or constitutively active *YAP* (Chiba et al., 2016), but also mutant tumor suppressor p53 (Watanabe et al., 2018), can be outcompeted by wild-type cells. The mechanism called Epithelial Defense Against Cancer (EDAC) is a form of cell-to-cell communication, in which cells can compete in tissue for space and survival. «*Normal epithelial cells are able to sense the presence of the neighboring transformed cells and actively eliminate them*» (Tanimura and Fujita, 2020). EDAC is regionally modulated and sensitive to tissue type and physiological conditions. For instance, oxydative stress can change the status of an incipient clone from winner to loser or vice-versa. Fernandez-Antoran et al. (2019) showed that, whereas exposure to a low dose of irradiation of the murine esophagus promotes the expansion of mutant p53 clones, when combined with antioxidant treatment, wild-type cells win and deplete p53 mutant-carrying cells from tissue. Cellular competition behaves as a "natural" tumor suppression mechanism in the example of T cell differentiation in mouse thymus cited above. «*Disruption of this cell competition leads to long-term persistence of T cell precursors in the thymus and to their oncogenic evolution, leading to T cell acute lymphoblastic leukemia* » (Martins et al., 2014). A mechanism of cell competition has also been invoked by Moya et al. to explain the non–cell autonomous tumor suppression driven by the Hippo pathway effectors YAP and TAZ in a mouse model of hepatic tumors. In this model the relative levels of YAP/TAZ in tumor cells and neighboring hepatocytes enable non-tumor cells to behave as winners relative to tumor cells (Moya et al., 2019). In summary, EDAC and other tumor suppressor functions connected to cell competition that occur at the initial stage of carcinogenesis potentially determine permissiveness of tissues for malignant transformation and hence potential field cancerization.

Cell competition as tumor promoter

Competition operates as tumor promoter when premalignant cells behave as supercompetitors and free the space for their expansion in adjacent host tissue by eliminating normal cells. This function and the underlying mechanisms have been abundantly documented in Drosophila and mammals (Gogna and Moreno, 2020). The role of Myc dosage in eliciting supercompetition (Figure 5), originally identified in Drosophila has been further substantiated by observations in mouse embryonic cells (Claveria et al., 2013; Sancho et al., 2013). Cell competition functions at initiation but also within an established tumor mass between cancer cells. Immuno-histochemistry analyses on human breast, lung and colon cancer samples show patterns of *MYC*-mediated cell competition at the tumor/stroma interface, with *MYC* low-expressing cancer cells undergoing cell death when adjacent to or surrounded by *MYC* high-expressing tumor cells (Di Giacomo et al., 2017). Furthermore, in heterotypic co-cultures of human cancer cell lines, inhibition of *MYC* expression in prospective winners is sufficient to turn them into losers (Paglia et al., 2020). Given that overexpression of MYC is a hallmark of major human cancers and plays a key role as a master coordinator of tumor-stromal interactions (Sodir et al., 2020) suggests that *MYC*-mediated cell competition might promote field cancerization manifested by an increased reactivity to the effect of second mutations that would remain silent in the context of a wild-type epithelium as demonstrated by Sollazzo et al. in Drosophila (Sollazzo et al., 2018). A similar mechanism of cell competition occurs in human glioma with high *YAP*-expressing cells behaving as winners against low YAP-expressing cells (losers) (Liu

et al., 2019) or in tissues mosaic for p53 activity levels (Baker et al., 2019; Vishwakarma and Piddini, 2020). Flower isoform switching is another mechanism of achieving supercompetitor phenotype. In human, the *FLOWER* gene functions as a fitness modulator. It yields four protein isoforms; two human Flower isoforms (hFWE1 and hFWE3) behave as Flower-Lose proteins, whereas the other two isoforms (hFWE2 and hFWE4) behave as Flower-Win proteins. Interestingly, human cancer cells show increased Win isoform expression conferring a competitive growth advantage to proliferate within lose-expressing stroma (Madan et al., 2019).

Finally, cell competition determines the type of tumor cells, which emerge in myeloproliferative disorders associated with the two driver mutations in *JAK2* and *TET2*. The order in which these mutations are acquired affects the clinical course of the disease. The hematopoietic stem and progenitor cell compartment is dominated by *TET2* single-mutant cells in *TET2*-first patients but by *JAK2–TET2* double-mutant cells in JAK2-first patients. Somehow the TET2 mutation defines a « cancer field » in a cell-autonomous mode (Ortmann et al., 2015). Recently, mechanical cell competition has been proposed as a mechanism promoting competitive advantage for cell populations with high proliferation rates (tumor cells), which can compact and eliminate neighboring cells more sensitive to compaction (non-tumor cells) (Levayer, 2020). The essential features and mechanisms of cell competition have been reviewed by Baker (2020). At the early stage, tumor cells must compete fiercely to overgrow normal cells, whereas in an established tumor, competition between individual clones needs to be more "civilized". Conceptually, the role of cellular competition in shaping tumors offers interesting therapeutic opportunities that will be discussed later.

TUMOR AS AN INTEGRAL PART OF THE HOST ORGANISM EXTENDED ECOSYSTEM

In 2014, McAllister and Weinberg reviewed data indicating that tumors can affect distant sites that might in turn exert effects on primary or secondary tumor development, thus providing empirical support to the view of cancer as a systemic disease (McAllister and Weinberg, 2014). Recently, Lopez-Otin and Kroemer have defined health as a «*compendium of organizational and dynamic features that maintain physiology*» (Lopez-Otin and Kroemer, 2020) and proposed eight hallmarks for it. Cancers develop in an organism as the consequence of perturbations of usually more than one of these hallmarks, therefore, viewing a tumor as part of the host organism system means to extend the macroenvironment beyond the target tissue itself to the whole body ecosystem. Laplane et al. stated "*tumor microenvironment-centric view is too narrow to accurately reflecting the complexities of the interacting networks involved in tumor development*" and dubbed the whole body ecosystem as 'tumor organismal environment' (TOE) (Laplane et al., 2019). These authors have identified six layers of environment-tumor interactions: (1) The tumor cell-only environment, (2) niche, (3) confined, (4) proximal, (5) peripheral, and (6) organismal tumor environment (Laplane et al., 2018). They have discussed the association of these different layers with distinct tumor promoting or tumor suppressing mechanisms, and ultimately with distinct therapeutic approaches. To address this highly complex issue, we decided to focus on two topics, first on the crosstalks between tumors and organs located at anatomical sites remote from it and second on four components of the host system which influence the tumors' fate: microbiota, circadian clock, metabolic dysregulations and nervous system. Although we recognize that the metastatic process is an integral part of the host organism-tumor ecosystem, we have chosen not to address it here, as it is the subject of specific reviews.

Systemic interactions between tumors and host organs at distant anatomic sites

Tumors behaving as endocrine organs spread metabolites and other secreted factors throughout the body via circulating blood. Lee et al. proposed that «*solid tumors behave as systemic metabolic dictators and control whole body homeostasis in an endocrine organ–like mode* » (Lee et al., 2016). Paraneoplastic syndromes highlight the manifestations of these paracrine effects. For instance, Cushing syndrome, characterized by a collection of signs and symptoms collectively due to prolonged exposure to cortisol, arises from pituitary tumor or small-cell lung cancer secretion of adrenocorticotropic hormone or corticotropin-releasing factor (Bertagna, 2017; Richa et al., 2018). Paraneoplastic thrombocytosis results from an increased synthesis of hepatic thrombopoietin in response to ovarian tumor-derived interleukin-6, thereby increasing platelet production, which in turn fuels tumor growth (Stone et al., 2012). Diabetes and weight loss, which manifest several months before the onset of cachexia, are paraneoplastic phenomena induced by pancreatic cancer (Lee et al., 2016). Other systemic alterations associated with the presence of a tumor include changes in bone marrow functions, where myelopoiesis perturbed under the effects of inflammatory cytokines produces abundant myeloid-derived suppressor cells (MDSC) (Rutkowski et al., 2015). Finally, pre-metastatic niches have been described as tissue structures shaped by primary tumors in distant

organs that are conducive to the survival and outgrowth of tumor cells before their arrival at these sites (Peinado et al., 2017). McAllister and Weinberg have presented an exhaustive list of known tumor-derived factors that act systemically (McAllister and Weinberg, 2014).

Host system influences tumors' fate

It is widely accepted that tumors are not autonomous neo-organs but rather develop within the context of the body system. This system includes obvious components such as innate and acquired immunity, microbiota, hormonal impregnation and nutrition; but recently attention has been paid to seemingly less obviously connected components like circadian clock, metabolic regulation (nutrition) and nervous system. We recognize that the role of immunity and hormonal impregnation on tumor development is well within the scope of this review. However, because these topics are regularly reviewed in depth, we have chosen to leave them aside to focus on microbiota, circadian clock and nutrition.

Microbiota

The role of microbiota dysbiosis in shaping a tumor-permissive macroenvironment has been discussed in the above chapter dedicated to cancer-prone tissue phenotypes. This discussion was focused on local effects of the microbiota at epithelial barriers. However, evidences have accumulated showing that microbiota, in particular enteromicrobiota, exerts systemic effects, highlighted for example by its influences on allergic airway disease, hematopoiesis (Trompette et al., 2014) and maturation and function of microglia in the central nervous system (Erny et al., 2015). Microbiota is also considered as an influent regulator of cancer, at every stage of its development (Dzutsev et al., 2017) and its impact on the clinical efficacy of therapies against extra-intestinal tumors is well documented (Zhouet al., 2021; Zitvogel et al., 2018).

The circadian metabolic clock

Another component of the body system shown to connect with cancer is the circadian metabolic clock. The human circadian timing system is composed of a central (master) clock in the hypothalamic suprachiasmatic nucleus which integrates external light information conveyed to peripheral cellular clocks in tissues where it regulates physiological rhythms and functions (Astiz et al., 2019). The first clue to the connection with cancer came from epidemiological studies. Indeed, circadian disruptions of lifestyle by activities such as shift-work or late eating are risk factor for various cancers, including breast, endometrial, prostate, lung, colorectal and liver cancers, and non- Hodgkin lymphoma (Kinouchi and Sassone-Corsi, 2020). As one expects for a system-level connection, the network of communication between the host and the tumor is reciprocal. On one side, perturbations of the circadian clock are observed in tumor-bearing host and conversely changes in circadian rhythm affect tumor development. Indeed, patients with cancer frequently exhibit circadian disruption of the activity and/or plasma levels of melatonin, cortisol and lymphocytes (Mormont et al., 2002). At the cellular level, impairment of the circadian clock in tumor cells causes a drastic decrease of the number of rhythmic transcripts in murine mammary tumors compared to normal tissues (Oh et al., 2010). This has fueled the hypothesis that clock regulators may function as tumor suppressors (Fu and Lee, 2003). Detailed studies on the expression of the *PER* genes, one of the clock master genes family, have concluded that the circadian clock is repressed during cancer progression probably under the influence of factors secreted by the tumors (Kinouchi and Sassone-Corsi, 2020). The $Kras^{LSL-G12D/+}$; $p53^{fl/fl}$ mouse model illustrates this effect in which lung adenocarcinoma distally rewires the circadian transcriptome and metabolome in the liver through tumor-dependent inflammation that releases IL-6 (Masri and Sassone-Corsi, 2018). This reflects the vulnerability of the clock machinery to metabolic fluctuations caused by factors secreted by the tumor. Conversely, the roles of the clock genes *BMAL1, CLOCK, PER1, PER2, CRY1 and CRY2* in tumorigenesis have been firmly established both in tissue culture cells and in transgenic mouse models. With the exception of *CRY1*, their expression is downregulated in cancer cell lines and human cancer samples, thus supporting a tumor suppressor function. However, when assayed *in vitro*, either by overexpression or by silencing in cultured cells, they behave either as an oncogene or as a tumor suppressor (Kinouchi and Sassone-Corsi, 2020). Mouse tumor models have provided the demonstration that tumor development *in vivo* is affected by changes in the circadian clock. Defects in the circadian clock in mice with a loss-of-function mutation in the Per2 gene result in spontaneous salivary gland hyperplasia and teratoma at a high rate, even enhanced by loss of p53 (Fu et al., 2002). Similarly, *Bmal1−/−* mice are prone to hepatocellular carcinoma. Interestingly, *PER1* and *PER2* contribute to the pathophysiology of hormone-dependant cancers like prostate and breast cancers respectively, through the regulation of androgen receptor-mediated transcription (PER1) and estrogen receptor-mediated transcription (PER2). Finally, PER2 regulates the traffic of p53 from between the cytosol and the nucleus thus controlling the tumor-suppressive functions of p53 (Kinouchi and Sassone-Corsi, 2020).

Metabolic dysregulations

Metabolic alterations have been recognized as hallmarks of cancer cells (Hanahan and Weinberg, 2011). A constellation of metabolic risk factors collectively referred to as the metabolic syndrome (MetS) includes as main components: abdominal obesity, hyperglycemia, high blood pressure, hypertriglyceridemia, low HDL cholesterol levels, and central circadian dysrhythmia. Among these conditions, obesity and hyperglycemia link MetS to cancer via several mechanisms including inflammation, oxidative stress, immunity and cell signaling pathways (Yu et al., 2020). For example, hyperglycemia promotes hepatocellular carcinoma cells survival and progression by inducing the Wnt/β-catenin signaling pathway (Chouhan et al., 2016). Hyperglycemia is also the component of MetS most primarily related to the incidence of breast cancer in a Korean population (Kim et al., 2015). MetS is associated with an increased risk of colorectal cancer incidence mostly related to hyperglycemia and excess of body fat as demonstrated in a meta-analysis of 17 studies with 11.462 cancer cases (Esposito et al., 2013). Nutritional behaviors are at the origin of the majority of MetS. The first evidences for connecting nutrition and obesity to elevated cancer incidence in human have been provided by epidemiologic studies which showed that 14 and 20% of all cancer deaths in men and women, respectively, are due to overweight and obesity (Calle and Kaaks, 2004). Obesity is a dramatic consequence of ''westernized'' lifestyle, of which hypercaloric nutrition is the major component. Obesity because of overconsumption of unhealthy foods and associated with a sedentary lifestyle increases the risk of developing malignancies through physiological alterations including systemic inflammation, dysregulation of adipokines, insulin resistance, hyperglycemia, changes in hormone and growth factor concentrations and immune system dysfunctions (Buono and Longo, 2018; Font-Burgada et al., 2016; Zitvogel et al., 2017b). Collectively, these alterations promote tumor cell survival and proliferation primarily mediated by adipose tissues-derived factors. Several genetically engineered mouse models are available for studies of environmental factors, including the diet, which influence cancer risk (Tammariello and Milner, 2010). Improving the translational fidelity of preclinical mouse models, making animal diets more relevant to at-risk human populations, is in progress. For instance, American Institute of Nutrition diet AIN93G has been shown to be a more suitable basal diet to model colorectal cancer than the total western diet (TWD) (Hintze et al., 2018). Esposito et al. have promoted the common soil hypothesis as: *"The common soil hypothesis: metabolic syndrome and certain cancers may share common dietary risk factors that predispose susceptible individuals to both conditions* via *low-grade inflammation and oxidative stress"*. The claim is: *"MetS may be considered a surrogate marker for dietary risk factors of cancer, and a warning sign for susceptible individuals exposed to an unhealthy diet"* (Bellastella et al., 2018).

Nervous system and cancer

Several observational epidemiologic studies have identified conditions in which correlations between chronic stress and clinical outcome in cancer patients are suggested (Hanoun et al., 2015). Given the role of sympathetic nervous system signals in regulating normal bone marrow hematopoiesis and myeloproliferative neoplasms cited above (Katayama et al., 2006 270), the possibility that neural-mediated stress signals may affect tumor cell growth and vice versa is not unlikely. Indeed, autonomic nerves are recruited into prostate, colon, bladder, and esophageal tumors, in a way resembling neo-angiogenesis (Magnon, 2015) and connect cancer cells to the whole organism. Interactions between the nervous system and cancer involve paracrine signaling between nerve cells and cancer cells and systemic neural-cancer crosstalks (Monje et al., 2020). Interestingly, cancer cells have an innate ability to actively migrate along axons in a mechanism called neural tracking (Amit et al., 2016).

THERAPEUTIC OPPORTUNITIES IN TARGETING NON-CELL AUTONOMOUS EFFECTORS

In their review entitled « The Tumor Macroenvironment: the cancer-promoting networks beyond tumor beds »Rutkowski et al. (2015) pointed that *"Understanding the reciprocal interactions between the cells and soluble factors within the macroenvironment and the primary tumor will enable the design of specific therapies that have the potential to prevent dissemination and metastatic spread"*. This statement sums up fairly precisely the objectives that were set for this review. The above chapters have highlighted the complexity of the ecosystem in which tumors thrive, which implies that cancer therapies must extend the spectrum of their targets to the non-tumor components of the system. This statement is not unanimous. According to Evan (Dhillon and Evan, 2019): "*it is a legitimate question to ask where, would be the best place to target in order to make the tumor collapse – in the tumor cells themselves or in the stroma? From our data the answer is clear – you target the oncogenes in the tumor cells because these are the engines that drive the release of the instructive signals that create the tumor microenvironment.*" Indeed, the

advent of detailed molecular pictures of tumors has prompted tailoring of cancer therapeutic strategies to target druggable mutations identified in tumors and classified as tumor intrinsic targets by Hahn et al. (2021). Nevertheless, the prominent and long overlooked role of non-cell autonomous effectors in tumors' ecosystem, classified as extrinsic targets, offers a strong rationale for considering them as potential targets for cancer therapies. Proof-of-principle for extrinsic cancer therapy was achieved by the discovery that inhibition of vascular endothelial growth factor prevents the tumor's recruitment of new blood vessels (Apte et al., 2019). The therapeutic opportunity offered by extrinsic classes of targets was successfully exploited in immunotherapies of solid tumors based on inhibitors of immune checkpoints such as PD-1/PD-L1 and CTLA-4 (Larkin et al., 2019), and in adoptive T cell therapies effective for hematologic malignancies (Rosenberg and Restifo, 2015). Both the cellular entities (immune cells, fibroblasts, endothelial cells, adipocytes, neurons, osteoblasts …) and the non-cellular extracellular matrix constitutents of the tumor microenvironment represent potential therapeutic targets (Monje et al., 2020; Valkenburg et al., 2018; Venkatesh et al., 2015). Note the bivalency of certain components, such as endothelial cells or adipocytes, that support tumor growth but also contribute to the resistance to treatment (Valkenburg et al., 2018). We recognize the importance of the tumor microenvironment in cancer progression and as therapeutic targets; however, as previously stated, we have opted to focus on intra-tumor or macroenvironmental targets and systemic factors, *de facto*, considering the microenvironment as beyond the scope of this review. Therefore, this chapter focuses on therapeutic opportunities offered by cell competition, metabolism, circadian clocks and senescence.

Cell competition therapy

As shown above, emerging evidence supports the role of cell competitions at all stages of tumor development, from early lesions to overt metastasis, pointing to a general pattern in which tumor cells must win the competition with normal host tissues to support their growth (Pelham et al., 2020). The capacity to behave as a winner is a crucial step in the early life of a tumor, when a single cell, having acquired driver mutations, is to emerge within a field of wild-type tissue. Therefore therapeutic strategies aimed at modifying the strength and direction of cell competition, turning tumor cells back from winner to loser status, could induce cancer cell killing. This can be achieved by strengthening the surrounding healthy tissue as highlighted in experimental models such as the Drosophila *Apc−/−* intestinal tumor model (Suijkerbuijk et al., 2016) and a mouse model of hepatic tumors (Moya et al., 2019), whereby adjusting the relative dosage of the *Hippo* pathway between tumors and tumor adjacent tissues make non-tumor cells the winners. An alternative competition-based strategy is to facilitate EDAC by i) taking advantage of EDAC activation by nonsteroidal anti-inflammatory drugs, ii) reducing the toxicity of chemotherapy or radiotherapy to non-tumor cells (periodic fasting (Nencioni et al., 2018)), iii) manipulating the redox status (Fernandez-Antoran et al., 2019). In theory, inhibition of the supercompetitor status of tumors (targeting *MYC* or *YAP*) or unmasking loser status of cancer cells should also affect tumors' fate (Vishwakarma and Piddini, 2020). With the exception of nonsteroidal anti-inflammatory drugs, which have been shown to be effective in reducing the risk of certain cancers, these strategies remain conceptual. However, of note is a cell competition-based high throughput screening which has identified small compounds that promote the elimination of RasV12-transformed cells from epithelia (Yamauchi et al., 2015). Cell competition between chemotherapy sensitive and resistant cells has been exploited in adaptive cancer therapy with the aim of limiting the amplification of resistant cells in the course of chemotherapy. It relies on differences in fitness between resistant and sensitive cells in the presence or the absence of chemotherapy. Resistant cells are better adapted to chemotherapy whereas the respective fitness is reversed in the absence of treatment because of the metabolic cost of the resistance mechanisms (energy-dependant membrane extrusion pumps for example). The feasibility of this approach has been illustrated in experiments carried in preclinical models of breast cancer. "*By using drug dose modulation or treatment vacations, adaptive therapy strategies control the emergence of tumor drug resistance by spatially suppressing less fit resistant populations in favor of treatment sensitive ones.*" (Gallaher et al., 2018).

Targeting metabolic disorders and circadian clock

The most common conditions linking metabolic disorders (MetS) to cancers, namely hyperglycemia and obesity, are both actionable, with drugs like metformin and with lifestyle interventions, respectively (Nencioni et al., 2018). Furthermore, emerging evidence indicates a tight control of cells and organisms metabolism by the central circadian clock (Kinouchi and Sassone-Corsi, 2020). The link between metabolic rhythm of the host organism with that of the tumors is highlighted by the effects of tumor growth suppression induced by timed food intake versus *ad libitum* feeding on pancreatic adenocarcinomas in mice. In this

model, restoration of circadian rhythm by timed food intake correlates with inhibition of tumor growth, suggesting that changes in host metabolism affect the circadian rhythm in tumor cells, leading to growth arrest (Li et al., 2010). Therefore, adding the circadian approach and food intake control to conventional and possibly also targeted cancer therapies may open new avenues for cancer therapy.

Senotherapy of tumors: To induce senescence or to clear senescent cells?

As discussed above, cell senescence has been recognized as a central component of the tumor ecosystem, contributing to tumor development and the response to therapies. As such, senescence should be considered as a potential target in anti-tumor strategies under the name of senotherapy. Qualified by Fane et al. (Fane and Weeraratna, 2020) as antagonistic pleiotropy, senescence is a two-edged sword that can trigger immune recognition and tumor suppression but also create a permissive environment for tumor growth. This bivalency is at the origin of two senotherapy strategies. The first strategy is pro-senescence therapy, which aims at driving tumor cells into a harmless and potentially irreversible "dormant" state. Being essentially a cell autonomous process, pro-senescence therapy is beyond the scope of this review. The second strategy is senolytic therapy, which relies on the observation of the persistent presence of senescent cells at all stages of tumor development, either in the tumor mass itself or in the stroma, which putatively exert SASP-mediated pro-tumorigenic activity (Faget et al., 2019). By clearing senescent cells, senolytic therapy aims at depriving tumors of this pro-tumorigenic activity. As discussed above, cellular senescence can be activated in cells exposed to various stressful conditions associated with dysfunctions linked either to aging (replication stress, telomere shortening, mitochondrial dysfunction …), or pathological disorders (cancer, diabetes), or genotoxic insults (chemotherapy, radiotherapy). Senescent cells accumulated in normal tissues bring about potential permissivity for proliferation of driver-mutation carrying cells. The homeostasis of senescent cells compartment is not well understood but it is established that senescent cells can be cleared by the immune system (Prata et al., 2018). Chemotherapeutic strategies designed to kill cancer cells induce cellular senescence *in vivo* in their intended target but also in non-tumor adjacent cells, either directly or via SASP components in a paracrine fashion. These effects are termed therapy-induced senescence (TIS). « *It is now largely accepted that senescence is likely to be an undesirable outcome of cancer therapy in terms of the detrimental effects of the secretions from senescent cells as well as the potential of senescent tumor cells to escape from arrest and regenerate the disease* »(Carpenter et al., 2021). TIS and cancer cells can evade clearance by the immune system and produce SASPs that affect tumor progression and therapeutic outcome (Mavrogonatou et al., 2020). Saleh et al. have listed and discussed FDA-approved antineoplastic agents that have been reported to induce TIS (Saleh et al., 2020). Of note, the list of these agents includes all classes of conventional therapies but also target therapies. An additional feature of cell senescence relevant to senotherapy is its cell-autonomous capacity to promote cancer stemness, a property obviously detrimental to cell cycle blocking therapies (Milanovic et al., 2018). Overall, senescence is an important determinant of the response to anticancer therapies for both tumor relapse and premature aging in cancer survivors (Short et al., 2019 510). Therefore, pharmacological strategies to specifically clear senescent cells and/or eliminate the adverse effects of TIS have been considered as potential adjuvant to conventional therapies. Two classes of compounds have been developed to achieve this goal. In the first class are senolytics, which kill senescent cells through targeting essential survival pathways; in the second class are senomorphics or senostatics, which suppress SASP paracrine signaling. Many compounds with different mechanisms of action have been described as senolytics: dasatinib + quercetin (D + Q), cardiac glycosides and HDAC inhibitor (panobinostat). They have been reviewed in Carpenter et al. (2021). The most successful senolytic in preclinical cancer models has been Navitoclax, an inhibitor of BCL-2 family members. However, its use faces serious limitations. First, its action is highly dependent on the expression levels of its targets which are indeed highly variable in different models (Carpenter et al., 2021). Second, it eliminates senescent cells, both in tumors and in several aging-related pathologies, causing considerable toxicity including thrombocytopenia and significant side effects in clinical trials in patients with leukemia, lymphoma, lung and other cancers (Short et al., 2019). Many substances with senostatic activities have been identified, most notably interfering with the NF-κappaB pathway, or inhibiting JAK, or carrying anti-inflammatory and antioxidant effects (Mavrogonatou et al., 2020). Although the mechanisms of action of senostatics remain unclear, their limited toxicity and their synergies with conventional chemotherapy and radiotherapy make them more prone to future developments than senolytics (Short et al., 2019). Thus, targeting senescent cells by senolytic or senostatic agents, which selectively ablate the adverse effects of TIS constitutes a clinically relevant strategy to prevent cancer occurrence and relapse. However, it should be emphasized that senotherapy is intrinsically limited to conditions in which SASP is pro-tumorigenic. It is undesirable in conditions in which SASP plays the second edge of the sword such as that illustrated by Lujambio et al. (2013) who showed that in the liver, hepatic stellate senescent cells communicate a tumor-suppressive program toward epithelial cells. Ablation of this program leads to hepatocellular carcinoma.

CONCLUDING REMARKS

The concepts of tumor niche and field cancerization have been considerably enriched over the past 60 years. Nowadays, they appear as local manifestations within a large ecosystem in which the tumor behaves as a neo-organ. One dimension, which has only been touched upon briefly so far, is the temporal link between aging and cancers. This link has been widely documented and is so evident from the striking similarity of the incidence curves for most common cancers, which increase after age 50, despite the large variance in the natural history of these cancers (driver mutations burden, size of stem cell pools …) (Laconi et al., 2020). Furthermore, the accumulation of somatic mutations is most strongly associated with age, with additional effects of heavy smoking and alcohol consumption (Yokoyama et al., 2019). This lends weight to non-cell autonomous contributions in the initiation and progression of tumors. An explanation for this uniform age distribution of cancer onset is the age-related differential "permissiveness" of tissues for tumor growth. «*Typically, young healthy tissues are tumor suppressive; that is, they eliminate or limit the expansion of cells that have acquired somatic mutations, whereas aging or damaged tissues become tumor tolerant and even promoting; they are progressively unable to eliminate these cells and counteract their selection*» (Laconi et al., 2020). These assumptions lead a system ecology approach to oppose cancers, based on maintenance of tissue landscapes that favor non-malignant cells. Such approach implies avoiding well-identified lifestyle insults, adopting favorable behaviors such as caloric restriction or balanced diet and exercise, which have been demonstrated to increase autophagy and improve proteostasis, augmenting tissue maintenance and reducing chronic inflammation (Solary, 2020). Another aspect of ecologically paradigm in cancer treatment is "adaptive therapy" as discussed above which allows a significant population of drug-sensitive cells to survive which in turn suppresses proliferation of the less-fit resistant cells (West et al., 2020).

In conclusion, the malignancy of tumor cells should be described not only as an intrinsic phenotype of oncogenic events-bearing cells but as a complex trait incorporating parameters from tissue and whole organism system. This implies that cancer therapies must aim at extending the spectrum of their targets to the non-tumor components of the system.

DEDICATION

This review is dedicated to Professor David M. Livingston, Chief of the Charles A. Dana Division of Human Cancer Genetics at the Dana-Farber Cancer Institute and the Emil Frei Professor of Genetics and Medicine at Harvard Medical School (Boston) who passed away in October 2021. For nearly 50 years, Jean Feunteun shared with David a passion for understanding cancer. Over those years, they built a warm friendship and productive scientific collaboration that will forever remain exemplary.

STRATEGY OF BIBLIOGRAPHY

Keywords: Non-cell autonomous; Tumor ecosystem; Macroenvironment; Field cancerization; Niche; Inflammation; Senescence; Microbiota; Circadian clock; Metabolic dysregulations; Nervous system and cancer; Cell competition; Senotherapy.

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GRAPHICAL ABSTRACT

Breast tumor illustrates tissue-tumor-body ecosystem

Normal stroma: Healthy breast tissues are made up of epithelial cell compartments (canals and lobules) (green) embedded in a normal stroma composed of fibroblasts (brown), fat cells (blue), inflammatory/immune cell (pink)s, and endothelial cells (red).

Stroma with tumor: Breast carcinoma results from the malignant transformation of epithelial cells. Within the organ (beige), the stroma macroenvironment (blue) distal from the tumor provides a tissue context conducive to tumor growth. The microenvironment (yellow) is the stroma in proximal contact with the malignant. It undergoes phenotypic changes and in turn supplies the malignant cells with various metabolic signals. This crosstalk defines a physiological status fundamentally unrelated to the physiology of the host organ thus giving to the tumor the status of a neo-organ.

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DECLARATION OF INTERESTS

The authors declare no competing interests

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