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Systemic inflammation in response to radiation drives the genesis of an immunosuppressed tumor microenvironment

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ABSTRACT

The composition of the tumor immune microenvironment has become a major determinant of response to therapy, particularly immunotherapy. Clinically, a tumor microenvironment lacking lymphocytes, so-called "cold" tumors, are considered poor candidates for immune checkpoint inhibition. In this review, we describe the diversity of the tumor immune microenvironment in breast cancer and how radiation exposure alters carcinogenesis. We review the development and use of a radiation-genetic mammary chimera model to clarify the mechanism by which radiation acts. Using the chimera model, we demonstrate that systemic inflammation elicited by a low dose of radiation is key to the construction of an immunosuppressive tumor microenvironment, resulting in aggressive, rapidly growing tumors lacking lymphocytes. Our experimental studies inform the non-mutagenic mechanisms by which radiation affects cancer and provide insight into the genesis of cold tumors.

Introduction

Radiation is a double-edged sword, used to effectively treat cancer, but also a risk factor for cancer. Most models of cancer risk focus on mutations that can be a consequence of radiation-induced DNA damage. But cancer evolves dynamically and becomes clinically detectable upon the failure of cell, tissue and systemic processes. Hence, the process of radiation carcinogenesis is not just the sum of malignant mutations but a response to altered tissue factors that impact the construction of the tumor microenvironment (TME) [1,2]. These cell-intrinsic and tissue-related factors select for a malignant clones that are also acted upon by the host via the distributed immune system [3–6]. Immune surveillance that initially eliminates preneoplastic clones subsequently edits the malignant cell population until escape occurs, so called immuno-editing described by Schrieber and colleagues [7,8]. The inevitable escape from immune surveillance results broadly in three types of tumor immune microenvironment: infiltrated tumors, rich in lymphocytes and myeloid cells that are ineffective in controlling tumor growth due to antigen desensitization, excluded tumors in which lymphocytes are restricted to the fibroblast-rich interface with parenchyma, and desert tumors that are devoid of lymphocytes [9]. The composition of the TME immune components is widely considered key to predicting outcomes in immunotherapy [10].

Recent studies, including our own, suggest that radiation-preceded breast cancers are enriched in a subtype that does not respond well to clinically available treatments with an immunosuppressive microenvironment [11,12]. Data showing that radiation exposure elicits cancers that are compositionally distinct from spontaneous cancers is relatively recent, due in large part to the omics revolution in biology that allows a more nuanced characterization of cancers. In this review, we first discuss the carcinogenic process and the mechanisms by which radiation can alter it. We then describe the composition of the tumor immune microenvironment and features that affect response to existing immunotherapies. Finally, we use this context to explain our experimental studies using a radiation-genetic mammary chimera model that separates radiation effects on the host from radiation-induced mutation in the target epithelium, and show that host effects contribute to the evolution of the tumor immune microenvironment. We end by suggesting that by defining the effects of host systemic status and tissue microenvironment on tumor progression, this model underscores potential strategies for modulation of cancer risk after radiation and informs our understanding of the genesis of the TME.

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Radiation alters cancer evolution

Over recent decades clinical and laboratory studies have documented cancer development and progression as a dynamic process, defined as cancer evolution [13–23]. Evolution requires both diversity and selection. The advent of biotechnologies, especially next-generation sequencing (NGS) technologies, has allowed us to reveal contingencies inherent to cancer evolution that involve somatic mutations and genomic alterations, acquisition of cancer cell plasticity, and construction of the tumor microenvironment [23,24]. In the following, we will discuss the multifaceted role of radiation in stepwise cancer evolution.

Cancer evolution is driven by two major forces, i.e., mutations in somatic cell populations and natural selection for cells that harbor mutations favoring their cellular fitness relative to competing cells in their microenvironment [16,17,23,24]. Somatic mutations result from internal factors, such as aging, and external factors, such as radiation [25,26]. However, only cancer-driving mutations are selected for and accumulate in clonal populations [27,28]. A continuous interplay between mutation and selection leads to the series of clonal expansion of the mutated cells that eventually develop into cancer [24,29]. The NGS analysis of thousands of human cancers has provided a landscape of mutations in cancer genomes across many human cancer types, uncovering inter-cancer heterogeneity [30–32]. Recently, NGS single-cell sequencing analysis of cancers further reveals intra-cancer heterogeneity, helping us to further understand the evolutionary forces that make cancer growth and development [33–36]. Moreover, NGS not only allowed us to detect the specific genetic mutations but also to reveal the temporal order in which they occur in carcinogenesis, which resolves patterns of cancer evolution [22,37].

Radiation acts as a significant factor in cancer evolution by directly damaging DNA, which causes mutations in oncogenes and tumor suppressor genes, chromosomal aberrations, and DNA breaks (single- and double-strand), particularly when DNA repair mechanisms are overwhelmed or faulty [38]. In addition, radiation can destabilize the genome, i.e. genomic instability, making it more prone to further mutations across generations of irradiated cells [39,40]. When cancer cells are exposed to radiation, the cells that are most resistant to DNA damage are more likely to survive and proliferate, resulting in the selection of more aggressive cancer cell clones [38].

There is increasing appreciation that the heritable nongenetic determinants, such as cell plasticity and the cancer microenvironment, contribute to cancer evolution [18,20,24,29]. Cell plasticity enables cancer cells to acquire new phenotypic and functional features by switching between different states in response to their environmental stresses. Cancer cell plasticity has been recently reported in many cancer types [41,42]. The best-known example of cancer cell plasticity is epithelial-mesenchymal plasticity [43]. Epigenetic modifications have been well-documented as drivers of plasticity [24,44,45].

Epigenetic phenomena, such as DNA methylation and histone modifications, can directly influence chromatin accessibility, thereby regulating which genes are actively transcribed and allowing cells to switch between different functional states depending on their environmental context. Epigenetic changes help cancer cells adapt to changes in their microenvironment, which can favor cancer progression and metastasis. Advanced biotechnologies have revealed that human cancer cells harbor global epigenetic abnormalities, in addition to numerous genetic alterations. Furthermore, like genomic heterogeneity, epigenetic heterogeneity has been found within and between cancers [46–48]. Epigenetic heterogeneity is often caused by the clonal evolution of a single tumor through DNA methylation, histone modifiers and readers, chromatin remodelers, microRNAs (miRNAs), and aberrant expression of chromatin-modifying enzymes and their associated proteins. Epigenetic evolution deepens our understanding of cancer evolution [46–48].

Epigenetic mechanisms are adaptable and capable of altering genome function in response to external environmental effects. In addition to the well-known deleterious effects of radiation on genomic integrity, radiation also initiates non-mutational, but transmissible alterations in the progeny of surviving cells [40] and organisms [49]. Radiation can lead to changes in the methylation status of certain gene promoters [50,51] and the expression of DNA methyltransferases [52]. These effects of radiation foster the evolutionary process of cancer.

Another nongenetic determinant of cancer evolution is the specific tissue composition, which includes stromal cells, endothelial cells, immune cells, and the extracellular matrix. Many studies have revealed continuous bidirected interactions between tissue microenvironment and mutated cells during cancer evolution [17,23,24]. The tissue microenvironment initially influences cancer evolution by suppressing mutated cells but becomes warped over time to provide a conducive environment for further growth and evolution. Radiotherapy also alters the composition of the TME. For example, multi-omic profiling of glioblastomas following radiation revealed the emergence of a post-treatment fibrotic niche that promoted tumor cell survival and recurrence [53]. Hence, cancer evolution also shapes TME to create a favorable environment for the mutated cell. For example, cells with certain mutations can actively suppress immune responses by releasing immunosuppressive factors or recruiting regulatory immune cells and induce extracellular matrix remodeling by secreting enzymes that degrade or reorganize the matrix components. Single-cell RNA sequencing and, more recently, spatial transcriptomics and proteomics approaches enable us to interrogate the microenvironmental landscape of cancer, revealing heterotypic cellular interactions within the cancer microenvironment [22,34,54].

Immunoediting is a crucial step in cancer evolution [17,24,55]. Immunoediting describes the process where the immune system interacts with cancer cells, typically described in three phases: elimination, equilibrium, and escape [56,57]. During the elimination phase, the immune system actively detects and destroys mutated cells through mechanisms like natural killer cells and cytotoxic T lymphocytes. During the equilibrium phase, a dynamic balance is established where the immune system partially controls tumor growth, but cancer cells may still be present at a low level, potentially undergoing genetic changes that could make them less recognizable to the immune system. During the escape phase, cancer cells acquire mutations that allow them to evade immune surveillance, leading to the emergence of more aggressive and clinically detectable cancers.

The challenge of predicting cancer risk, whether following radiation or as a function of aging, is that, as an evolutionary process, there is not a simple relationship between the dynamic interactions of intrinsic cellular changes and extrinsic selective forces. The effects of radiation on the host and tissue microenvironment are complex and depend on the dose, timing, and site of the radiation [58,59]. Radiation can promote anti-cancer immune responses by activating dendritic cells and releasing cancer antigens but it also can cause the accumulation of suppressor cells, such as cancer-associated macrophages and regulatory T cells, which leads to immunosuppression. In addition, radiation can affect immune composition, extracellular matrix remodeling, and blood vessel formation. Understanding how radiation influences the interactions between the immune system, tissue microenvironment, and mutated cells during cancer evolution is complex but crucial. Identifying the relative contributions of each factor could help predict who is at the highest risk and inform potential mitigation strategies.

The immune composition of the TME

Immunotherapy has expanded in benefit and indication in the last decade, essentially coming of age with the discovery of immune checkpoints and the implementation of blocking antibodies that can reinvigorate exhausted T cells [60]. This benefit is not afforded to all, even in cancers like melanoma, leading to searches for predictive biomarkers. The clinical successes in immunoncology over the last decade have led to the identification of the mechanisms that disrupt the pathological equilibrium between the tumor microenvironment and

anti-tumor immunity. Several strategies have been proposed to classify cancer in terms of its immune composition. Broad tumor immune classification-based patterns of lymphocytic distribution were introduced by Mellman and Chen, along with the conceptualization of the tumor immunity cycle a decade ago [61]. These histological patterns are commonly referred to as infiltrated (or inflamed), excluded, and desert. The immune system can effectively eliminate cancer, but only when it is no longer subject to cancer's ability to suppress immune function, exclude immune cells, or cloak itself from surveillance. There is now abundant evidence that these patterns, regardless of the cancer's tissue of origin, are significantly associated with response to both immunotherapy and other cancer therapies [62–64]. Alternatively, cell type gene expression signatures based on deconvolution techniques, such as CIBERSORT [65–67] in conjunction with RNAseq of bulk tissue exemplified by The Cancer Genome Atlas. are broadly employed [68–71].

It is also common to depict tumor immune composition as binary. The immune composition of single cancer types or mouse models has been coarsely categorized into immune rich and immune desert [64,72,73]. The immune rich ('hot') TME, in which the tumor is inflamed with infiltrating T cells that are incapacitated whereas the immune poor ('cold') characterized lack of T cells and abundant suppressive myeloid cells. Immune checkpoint inhibitors (ICI) are thought to be mostly effective in patients whose tumors are hot, whereas patients with cold tumors are considered unlikely to benefit, and even have poor outcomes to standard therapy [74]. Consequently, a major objective has been to devise combination therapies to convert cold tumors into hot [63,64]. However, it is well-appreciated that such a classification belies the nuanced phenotypes of cancer-infiltrating immune cells that reflect the cancer-immunity equilibrium spanning cancers from different organs. The immune system is a distributed organ that has a repertoire of mechanisms to suppress cancer, hence, although cancers are extremely heterogeneous, the mechanisms by which they escape anti-tumor immunity have inherent commonalities.

Cancer research has begun moving toward classifying cancer immunity as a tissue-agnostic process [72,75–77]. Tissue-agnostic classification is an exciting new concept generated from fine-grain immunoprofiling of human cancer [10]. One example of this strategy was generated from a holistic survey of 364 fresh surgical tumor specimens across 12 tissues of origin [78]. Coordinated tissue processing and systematic profiling assays using an immunoprofiler pipeline analysis of cancers led to the identification of immune archetypes that span tissue of origin. Immune cells isolated from cancers were profiled to generate 10 independent cell signature features, which together consist of 4096 binary variables. However, computational modeling of these features using unsupervised clustering coalesced into only 12 distinct clusters. Each immune archetype has a unique combination of immune cell composition and tumoral transcriptomic phenotypes. Notably, multivariate survival regression of the different immune archetypes showed that, regardless of the tissue of origin, archetypes that have similar T cell subset enrichment share survival outcomes. This analysis defined unique relationships between immune cell densities and chemokine networks that resulted in 3 immune-rich archetypes and 3 immune deserts; the remaining 6 immune archetypes have either stromal or myeloid contributions.

The immune archetype and other classification systems provide a framework for tissue-agnostic comparison of the immune composition of TME and provide a broader conceptual framework for understanding immune tolerance mechanisms in cancer, independent of tissue of origin. The growing recognition that cancer variably impacts the three interrelated control mechanisms that regulate immune tolerance—T cell localization, target recognition, and activation/differentiation–illustrates how tumors exploit physiologically essential immune homeostatic processes to evade immune surveillance, as reviewed recently [79–81].

The holistic framing of cancer immune composition as an emergent phenomenon, that is, one that forms from dynamic interactions, could change how cancer is treated in the next decades. Therapies like radiation that destroy the components, i.e., cells, can fail when not all cells are eradicated, whereas cancers can rewire in response to immunotherapies that target specific escape mechanisms, like programmed cell death ligand (PD-L1) or its receptor (PD-1). Because cancer-immune interactions have yet to be codified, the potential eradication of cancer by harnessing the immune system's arsenal of anti-tumor defense mechanisms is still poorly understood.

Given that a durable response to immunotherapy significantly benefits a subpopulation of patients, considerable effort has been put into determining who will likely respond and why. One study identified an association between response and mismatch repair deficiency (dMMR) or high microsatellite instability in colon cancer patients [82]. Investigators argued that the benefit to colorectal cancer patients whose tumor exhibits dMMR could cut across tissue origin classification, which motivated a 'basket-trial' based on the selection of dMMR phenotype [83]. In another example, the correlation between tumor mutational burden (TMB) and response to PD-1/PD-L1 checkpoint inhibitors [84] provoked further investigations about its utility as a means to select patients with the thought that these tumors are primed for greater neoantigen load, and hence immunogenicity. Recent studies have sought to exploit a defective DNA damage response, including combinations of immunotherapy with radiotherapy, which is thought to act as an *in situ* vaccination [85], and agents to compromise DNA repair, such as the poly(ADP-ribose)polymerase inhibitors that are thought to activate the cGAS/STING pathway [86].

Notably, mutational burden and lymphocyte infiltration are important biomarkers of ICI responsiveness. High TMB is thought to raise the probability of immunogenic epitopes. Patients whose tumors are infiltrated with lymphocytes respond well because ICI targeting PD-1 and its ligand, PD-L1, are directed toward restoring lymphocytic activation [87]. Notably, these biomarkers are linked, exemplified by cancers with dMMR. Independent of tumor type, patients with dMMR tumors have a remarkably high rate of pathological complete response [88]. The NICHE-2 trial showed that most colorectal cancer patients with dMMR respond to neoadjuvant ICI therapy; moreover, the association of dMMR with response rate and duration to ICI is also predictive in 12 other tumor types [89]. Misrepair of intrinsic or extrinsic DNA damage in the dMMR context is believed to provoke immune recognition through increased neoantigen production, release, and presentation [90,91]. Consistent with this, dMMR tumors are highly inflamed due to cytosolic DNA sensing mediated by cGAS/STING that elicits type I interferon (IFN) signaling to provoke lymphocyte recruitment [92].

Most failures of cancer immunotherapy are ascribed to the tumor immune microenvironment, which often promotes immunosuppression to prevent effective antitumor immune responses [93]. Breast cancer is a highly heterogeneous disease, whether assessed traditionally by hormone receptors and HER2 amplification or, more recently, by molecular classification using gene expression patterns described as intrinsic subtypes. Unfortunately, despite the gains in other cancers, most breast cancer patient populations have yet to see a substantial benefit from ICI. Recent clinical trial testing of ICI in the (neo)adjuvant setting has shown clinical benefits in some breast cancers. A recent meta-analysis involving 5,114 patients showed that neoadjuvant ICI therapy was associated with improved efficacy outcomes in early-stage triple-negative breast cancer and PD-L1–positive, hormone receptor-positive/ERBB2-negative tumors [94]. Nonetheless, several features of breast cancers appear to underlie the lack of response to ICI, including low mutational burden and lack of lymphocytic infiltrate, the so-called cold tumor. Notably, radiation-preceded breast cancers are enriched for aggressive cancers with a cold, immunosuppressive TME [12], which leads to the question of how radiation promotes their evolution.

The irradiated host shapes cancer evolution

The concept of the "microenvironment" has led to the recognition

that interactions between epithelial and other cell types and matrix components are key factors in cell survival and development. The stability of the microenvironment is essential for maintaining normal cell proliferation, differentiation, metabolism, and functional activities. Abnormal changes in the components of the microenvironment can lead to cytopathy. The toxic effects of radiation on normal tissues are not only reflected in intracellular effects (such as DNA damage and gene mutations) but also in the activation of various cytokines that alter the tissue microenvironment. Changes in the tissue microenvironment after radiation exposure may cause normal tissue dysfunction or carcinogenesis. This is especially evident in the occurrence of breast cancer, where adolescent women who have received radiation therapy involving breast exposure have a higher risk of developing breast cancer later in life compared with women who have not received radiation therapy [95,96]. According to the Childhood Cancer Survivor Study, breast cancer risk is elevated among women who received chest radiation (e.g., mediastinal, lung) for pediatric and young adult cancers, such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, Wilms tumor, leukemia, bone cancer, neuroblastoma, and soft tissue sarcoma [97]. Unexpectedly, and in conflict with the mutation-centric radiation carcinogenesis paradigm, radiation-preceded breast cancer is distinct from that of age-matched sporadic breast cancer. Radiation-preceded breast cancer is more likely to be aggressive triple-negative breast cancer that has a poor prognosis [11,98,99]. Our studies in a mouse model combining radiation and genetic deletion of the p53 gene recapitulate the increase in aggressive cancers and show that they result from radiation-induced changes in the host [12,100–107].

The tumor suppressor gene *Trp53* is commonly mutated in human breast cancers but deletion of the p53 gene in mouse models (*Trp53-/-*) rarely results in mammary tumors due to the early death of *Trp53-/-* mice from lymphomas and other tumors. The compelling evidence that p53 is critical in breast cancer motivated Medina and colleagues to transplant the *Trp53-/-* mammary epithelium into the syngeneic wild-type inguinal mammary fat pad divested of endogenous epithelium prior to puberty at 3 weeks of age, creating a genetic chimera model [108]. The transplanted *Trp53-/-* mammary epithelium develops into a morphologically normal mammary ductal tree, but the null epithelial cells stochastically transform at a high frequency, resulting in diverse mammary carcinoma. With a tumor incidence of over 60 % and a long latency, this model provides sufficient time to track changes in the target and host during the mammary tumorigenesis process and serves as an *in situ* method to investigate the molecular mechanisms of carcinogenesis. Moreover, mouse mammary tumors derived from the *Trp53* null mammary epithelium chimeric model exhibit important characteristics aligning with human breast tumors in regard to most criteria, including hormone receptors, histology, metastasis capacity, and genomic features [108,109]. This is one of the most useful- and ultimately fascinating-aspects of the p53 null mammary chimera—rather than one tumor type, the lack of p53 gives rise to a spectrum of cancers that recapitulates the diversity of human breast cancer [110,111].

Radiation is an unequivocal carcinogen, but it is not a highly efficient carcinogen. While multiple tumor types can be induced by radiation in mice, this often occurs at low frequency with long latency [112]. Radiation exposure increases the development of tumors in which *Trp53* has been tissue-specifically deleted in BALB/c mice [113–116]. However, the genetic chimera model allows for specific questions about how radiation increases tumors because it effectively separates the targeted epithelium and the host, making it possible to investigate cell-intrinsic effects and extrinsic modulators in carcinogenesis separately. In order to separate radiation effects on the mammary epithelium and potential consequences on host biology, we created a "radiation-genetic chimera" model [101]., in which the host is irradiated before transplanting unirradiated *Trp53-/-* mammary epithelium, which although it limits the role of p53 specifically to that in the epithelium, can also have cell-autonomous effects.

Initial studies using the radiation-genetic chimer showed that partial body shielding of the left versus right half of the mouse increased tumor frequency only when the mammary gland was irradiated and that this effect was evident even when transplantation was 14 days later [117]. Moreover, high radiation doses (> 1 Gy) compromise ovarian function, which compromises mammary epithelial growth [101]; hence we focus on radiation-induced microenvironmental changes within the dose range of 10 cGy to 1 Gy, which are also more relevant to medical and occupational exposure. Subsequent studies in our laboratories used total body irradiation and a 3-day delay. Total body irradiation models radiation exposure that might occur in the real world from medical procedures, space travel, or occupational exposures.

Low dose host irradiation significantly altered tumor latency and growth rates [101,105]. More interestingly, the molecular and genetic features of cancers arising in irradiated hosts as a function of the age at transplantation were distinct. Tumors from transplantation of 10-week old irradiated hosts were more likely to be ER-negative and molecularly classified as the basal-like intrinsic subtype [103,105,118]. Concordant with mouse to human classification, the metaprofiles, which are a type of transcriptomic signature, from the cancers arising in the radiation-genetic chimera clustered basal-like subtypes of human breast cancer [104,119].

Aged hosts were used in studies performed to better understand occupational radiation risk for astronauts during space missions by comparing sparsely ionizing radiation typical on Earth to densely ionizing radiation that typifies the space radiation environment [105]. Mice in which mammary fat pads were cleared at 3 weeks were aged to 10 months, roughly equivalent to a 45-year-old human (average age of astronauts), and then transplanted with *Trp53-/-* mammary epithelium three days after irradiation with sparsely ionizing radiation or densely ionizing radiation [107]. Both host age and radiation quality affect the frequency and spectrum of *Trp53-/-* mammary carcinomas. In aged hosts, irradiation led to faster tumor growth compared to younger hosts (10 weeks of age). Tumors from aged, irradiated hosts also exhibited distinct expression signatures associated with mammary stem cells, transforming growth factor β (TGFβ), leukocyte trafficking, apoptosis-related processes, inflammation, and immune response.

In both aged and young mice, the inflammatory signatures and immune cells of tumors from irradiated hosts were pronounced compared to unirradiated hosts [12,105,107]. Tumors from irradiated hosts displayed an immunosuppressive TME with high levels of cyclooxygenase (COX) 2, TGFβ, and PD-L1 [12,107]. These immunosuppressive tumors exhibited an immune "desert" pattern with few cytotoxic CD8+ T cells within the tumor or an "excluded" pattern in which cytotoxic CD8+ T cells accumulated at the tumor edge but not inside the tumor. Tumors arising in hosts irradiated with densely ionizing high-energy particles exhibited more genes associated with inflammation than those in hosts exposed to sparsely ionizing radiation [105,107]. Transcriptomes of carcinomas arising in the radiation-genetic chimera revealed that key genes involved in immunity and inflammation, such as *IL1B* and *PTGS2*, were significantly elevated in tumors from irradiated hosts. Inflammatory gene signatures distinguished tumors between irradiated hosts from those in sham-irradiated hosts, raising the question of whether the host response to radiation is inflaming the tissue locally, causing a low-grade systemic inflammation, or both [12,107].

The observation that tumors arising in an irradiated host are distinct supports the idea that radiation exerts an immune-mediated evolutionary pressure on cancer development. Systemic inflammation arising from host irradiation during the equilibrium phase of cancer-immune interaction could, from an evolutionary perspective, eliminate certain malignant cells and select for cancer cell clones capable of resisting radiation-induced immune rejection, leading to immune escape. This aligns with the concept that immune evasion is not merely a consequence but a fundamental requirement for cancer progression [56,57,120]. Radiation induces low-grade systemic inflammation by generating free radicals that activate pro-inflammatory factors that have become an important consideration in radiotherapy. For example, low-dose

exposure of immune poor murine tumors can promote T-cell infiltration, thus, promoting response to immunotherapy [121], and the concept of priming immunotherapy with relatively low therapeutic doses (4-7 Gy) has been moved into clinical trials [122] Mechanistically, radiation induces cell damage through direct energy deposition or indirect generation of reactive free radicals that stimulates inflammation through various routes, including cell killing that initiates changes in tissue function, or cell phenotype that alter cytokines and chemokines, and may persist for months to years after exposure [123].

Macrophages play a crucial role in radiation-induced inflammation. These immune cells are widely distributed, participating in immune defense, homeostasis, and surveillance. Macrophages can differentiate into different phenotypes depending on the environment, playing various roles in maintaining tissue homeostasis and immune defense. Classically activated M1 macrophages participate in positive immune responses by secreting pro-inflammatory cytokines (e.g., IL-6, TNFα) and chemokines (e.g., monocyte chemoattractant protein-1, MCP-1, and inducible nitric oxide synthase) and presenting antigens [124]. Alternatively activated M2 macrophages play an important role in immune regulation by secreting inhibitory cytokines such as IL-10 or TGFβ to downregulate the immune response. Recent research has identified defective efferocytosis of macrophages as a factor in radiation-induced inflammation [125]. Accumulation of alveolar and interstitial macrophages is a histopathological characteristic of normal tissue inflammation after radiation [126]. Macrophage accumulation and activation stimulate the production of reactive oxygen species and reactive nitrogen species, proinflammatory, profibrogenic, and proangiogenic cytokines, perpetuating a non-healing tissue response after radiation injury [125]. Additionally, radiation-induced macrophages can secrete factors that limit pinocytotic effects, aggravating inflammation [127].

The gene expression signatures of mammary glands of mice irradiated with 10 cGy showed that radiation significantly enriched genes associated with macrophages and chemotropism [101]. Subsequent analysis of these tissues confirmed a significant increase in the number of F4/80-labeled mature macrophages adjacent to mammary epithelial ducts at 12 weeks [12]. Inflammatory-activated macrophages are involved in modulating the morphological changes of mammary acini after irradiation through IFNγ by showing that blocking IFNγ signaling using an IFNγ monoclonal antibody remodels the normal morphology of mammary acini [12].

Our experiments over the last decade indicate that host irradiation indirectly promotes the development of an immunosuppressive tumor microenvironment [12,105,107]. Strikingly, we found that only irradiated hosts gave rise to tumors lacking cytotoxic CD8+ lymphocytes (i.e., immune deserts), moreover, that these tumors grow faster, and their TME is high in COX-2 and TGFβ [12,107]. More immunosuppressive myeloid cells but fewer apoptotic cells were present in tumors from irradiated hosts compared to tumors from sham mice [12,107]. Tumor growth rate was correlated with the lymphocytic infiltrate, i.e., highly infiltrated tumors grow more slowly, consistent with an active yet insufficient immune response [107]. Moreover, we found that the markedly immunosuppressive TME was also evident in human breast cancers from women who had prior therapeutic radiation for childhood cancers [12]. This correspondence suggests that host response to radiation, rather than mutations, mediates the development of aggressive cancers with a highly immunosuppressive TME.

To test this idea, we asked whether the cold tumor immune phenotype arising in the radiation-genetic chimeric model could be rescued post-irradiation. Reasoning that adaptive immunity was key, we repeated the radiation-chimera experiment in Ncr nude mice, which lack an effective cytotoxic T-cell response, irradiated with 10 cGy because these mice are genetically radiation sensitive [12]. Neither tumor number nor latency was affected by host irradiation, but surprisingly, the growth rate of tumors arising in irradiated nude mice was still significantly increased compared to those in sham-irradiated nude mice. Consistent with increased growth rate, apoptotic cells were decreased in tumors from irradiated hosts compared with tumors from sham hosts even though cytotoxic T cells do not function in nude mice. Increased cytotoxic activity of natural killer cells compensates for T lymphocyte dysfunction in immunodeficient mice [128]. Indeed, compared to tumors arising in sham nude mice, tumors from irradiated hosts had fewer NK cells, consistent with decreased immunosurveillance.

Nonetheless, transcriptomic signatures of tumors arising in irradiated mice invoked inflammation; hence, we postulated that the pro-inflammatory pathways and immunosuppressive TME reflected radiation-induced, low-grade systemic inflammation. Markers of systemic inflammation are increased in atomic bomb survivors decades after exposure [129,130]. A chow supplemented with an anti-inflammatory and immunomodulatory compound, caffeic acid phenol ester (CAPE), was fed to mice after irradiation, preventing the development of rapidly growing lymphocytic desert tumors [107]. Tumors arising in irradiated mice treated with CAPE were transcriptomically re-wired, showing a reduction of pathways involved in inflammation. CAPE has been shown to exhibit its anti-inflammatory effects by being the most potent modulator of the arachidonic acid cascade through the inhibition of leukotriene production and prostaglandin formation by inhibiting COX and lipoxygenase pathways.

COX-2 is a critical factor that allows cancer cells to escape host immune defenses by modulation of cytokine production [131]. In a recent study, the production of prostaglandin E2 (PGE2) COX-2-expressing fibroblasts in lung drives dysfunctional dendritic cells and suppressive monocytes, thus remodeling an immunosuppressive preneoplastic [132].PGE2 is a known negative regulator of immune response in the TME by inhibiting the expansion of tumor-infiltrating lymphocytes and disrupting IL-2 signaling [133]. PGE2 also impairs the inflammatory monocyte state and intratumoral T cell stimulation [134]. COX-2 inhibition accelerates lymphocyte infiltration of mouse tumors, which in turn slows tumor growth [135]. Tumor-infiltrating lymphocytes are also a favorable prognostic factor in certain breast cancer subtypes [136]. Given the robust evidence that COX-2 can modulate early events in cancer and the high risk of breast cancer for women treated with radiotherapy for childhood cancers [137], we tested a common anti-inflammatory, aspirin, in the radiation-genetic chimera [12]. Low-dose aspirin (0.1 mg/ml), equivalent to a baby aspirin, given in drinking water for 6 months after irradiation, well before tumors developed reset the TME and decreased the growth rate of tumors arising in irradiated hosts. These data are consistent with the concept that systemic inflammation during carcinogenesis creates the context for aggressive cancers characterized by an immunosuppressive TME, and provides a feasible target to reduce risk in women treated with radiation as children [12].

TGFβ signaling mediates development of immune cold tumors

Cold tumors arising in irradiated mice are also rich in TGFβ [12]. TGFβ plays myriad deleterious roles in cancer [138] and has long been considered an important target in cancer therapy because autocrine TGFβ promotes malignant phenotypes, such as invasion, and paracrine TGFβ has pro-tumorigenic effects on the tumor microenvironment (reviewed in [139]) yet the context in which TGFβ activity is clinically actionable has yet to be established. In the context of immunotherapy, TGFβ signaling is immunosuppressive via multi-faceted mechanisms of immune evasion via the generation of immunosuppressive stromal fibroblasts [73,140], myeloid cells [141], T regulatory cells [142], as well as mediating cell interactions [143].

We discovered another aspect of TGFβ biology is its significant role in genomic stability and DNA repair. TGFβ regulates the expression or function of crucial DNA repair proteins, including ATM, BRCA1, and LIG4, that are necessary for maintenance of genomic integrity (reviewed in [144]). Loss of TGFβ signaling compromises the canonical DNA double-strand break repair pathways homologous recombination and non-homologous end-joining. Faulty DNA repair is a hallmark of cancer,

and specific repair defects can provide the basis for response to specific therapies, including immunotherapy [145]. When classical DSB repair is defective, backup is provided by alternative end-joining (alt-EJ) [146]. Repair by alt-EJ is highly error-prone because the use of microhomologies at processed ends generates frequent genomic deletions and insertions [147,148]. Even though alt-EJ is a survival mechanism that backs up canonical repair, cells using it are more sensitive to genotoxic chemotherapy or radiotherapy [149,150]. Hence, loss of TGFβ signaling in cancer leads to reliance on alt-EJ via negative feedback.

We used this information to describe the functional relationship between TGFβ signaling competency and DNA damage in terms of a transcriptomic signature called βAlt, which is a measure of the negative correlation of TGFβ targets and genes necessary for alt-EJ. Because cancer cells have both genetic and epigenetic means to down-regulate TGFβ signaling, βAlt varies across the range of solid cancers [151, 152]. Cancers that are low βAlt maintain TGFβ signaling that endorses effective DNA repair, making them resistant to agents that cause DNA damage. In contrast, high βAlt cancers, in which intrinsic TGFβ signaling is compromised by mutation or epigenetic mechanisms, shift to error-prone DNA repair and are markedly more responsive to standard genotoxic therapies. High βAlt reports poor DNA repair, which is reflected by its significant pan-cancer correlation with increased genomic alterations and an indel flanked by microhomologies. Indeed, indels are thought to be highly immunogenic [153]. Hence, we predicted that high βAlt cancers would have activated cytosolic DNA sensing that promotes T cell recruitment and thus be infiltrated ('hot'), whereas low βAlt, indicative of competent DNA repair and high TGFβ signaling, which is immunosuppressive and therefore would be immunologically 'cold.'

Contrary to our expectation that high βAlt cancers that exhibit defective DNA repair and low TGFβ signaling would be 'hot,' like those with defective mismatch repair [88], these data show that high βAlt is characteristic of cancers with immune cold TME and unexpectedly, high βAlt predicts response to ICI, even though the tumors lack lymphocytes [154].

This puzzling result is clarified by considering that the process by which the TME is constructed, including immune composition, is a result of dynamic evolution [1]. TGFβ is subject to feedback control such that loss of cell-intrinsic TGFβ signaling in cancer cells can lead to increased TGFβ activity. This well-established feedback was recently demonstrated by Brown and colleagues in a tumor-specific CRISPR screen that included knockdown of *TGBR2* in the KRAS lung tumor model [155], in which loss of TGFβ intrinsic signaling resulted in lung tumors devoid of lymphocytes due to high levels of TGFβ activity. Radiation locally increases TGFβ that systemic inflammation can sustain, which together profoundly suppresses lymphocyte infiltration and promotes pro-tumorigenic myeloid cells. Hence, cancers arising in irradiated hosts have a strong selective pressure for cancer cells to lose TGFβ signaling. The loss of feedback increases TGFβ insensitive cancer cells to produce more TGFβ that drives the genesis of cold tumors. These tumors respond to ICI by increasing the activation of natural killer cells that recruit lymphocytes [154].

Conclusions

Our series of radiation-genetic chimera experiments over the last two decades describe radiation effects independent of its mutational capacity to show that systemic and tissue responses to radiation affect the occurrence, phenotype, and composition of tumors. The radiation-genetic chimera, introduced in 2000, has led to the exploration of how radiation promotes immunosuppressive tumorigenesis by acting on the host. Studying radiation as a carcinogen in terms of cancer evolution provides a framework for the relatively understudied role of systemic, rather than local, inflammation in the genesis of the immunosuppressive microenvironment. Our experiments using anti-inflammatory treatments after radiation exposure [12,107] provide functional evidence that systemic inflammation significantly impacts how cancer evolves [1]. Unexpectedly, the observation that blocking inflammation can prevent the occurrence of immunosuppressed TME provided new insights into how a cold immune tumor phenotype arises, which may have implications for treating such cancers with radiation in combination with immunotherapy to improve outcomes [154].

Several outstanding questions remain unresolved: What determines how cancers exploit physiologically essential immune homeostatic processes to evade immune surveillance? Does the mechanism depend on the organ, for example, in immune-privileged sites like the eye and placenta, or how early exposures educate the immune system? Can we predict which mechanism of immune evasion will predominate in a population or, even more importantly, in an individual? Understanding the role of systemic inflammation in cancer evolution may lead to more personalized treatment strategies if we identify biomarkers that predict a patient's response to anti-inflammatory treatments, allowing for tailored risk prediction and hence, prevention approaches.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used Microsoft Co-Pilot and Grammerly in order to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Mary Helen Barcellos-Hoff reports financial support was provided by National Institutes of Health. Mary Helen Barcellos-Hoff reports a relationship with Genentech Inc that includes: funding grants and travel reimbursement. Mary Helen Barcellos-Hoff has patent #18/009,885 and 18/602,978, pending to University of California, San Francisco. Personal fees and non-financial support from Innovation Pathways, Inc.; personal fees from Scholar Rock and Vericyte; and non-financial support from Bicara If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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