REVIEW

Pleiotropic effects of cell competition between normal and transformed cells in mammalian cancers

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Abstract

Purpose In the course of tumor progression, cancer clones interact with host normal cells, and these interactions make them under selection pressure all the time. Cell competition, which can eliminate suboptimal cells and optimize organ development via comparison of cell fitness information, is found to take place between host cells and transformed cells in mammals and play important roles in different phases of tumor progression. The aim of this study is to summarize the current knowledge about the roles and corresponding mechanisms of different cell competition interactions between host normal cells and transformed cells involved in mammalian tumor development.

Methods We reviewed the published relevant articles in the Pubmed.

Results So far, the role of several cell competition interactions have been well described in the different phases of mammalian tumor genesis and development. While cell competitions for trophic factors and epithelial defense against cancer (EDAC) prevent the emergence of transformed cells and suppress carcinogenesis, fitness-fingerprints-comparison system and Myc supercompetitors promote the local expansion of transformed cells after the early tumor lesion is formatted. In addition, various preclinical tumor-suppression models which based on the molecular mechanisms of these competition interactions show potential clinical value of boosting the fitness of host normal cells.

Conclusion Cell competition between host and transformed cells has pleiotropic effects in mammalian tumor genesis and development. The clarification of specific molecular mechanisms shed light on novel ideas for the prevention and treatment of cancer.

Keywords Cell competition · Cancer development · Fitness fingerprint · EDAC · Myc

Introduction

In the multicellular organisms, coordination of development among large amounts of cells is an underlying requirement for homeostasis. However, for better survival and development of the body, not only cooperation but also conflicts are needed between individual cells. The concept, which is similar with Darwinian selection (Moreno and Rhiner 2014), that cells can compete with each other for survival is illustrated by "cell competition", a process that eliminates suboptimal cells from growing tissues by apoptosis or any other patterns in various conditions. Cells which finally occupied the clonal dominance in the microenvironment are referred to as winners, while those eliminated are losers.

Cell competition was first described in fly imaginal discs of Drosophila (Morata and Ripoll 1975). Minute heterozygous ($M^{-/+}$) cells, whose proliferation rate was at a competitive disadvantage compared to wild-type (WT, $M^{+/+}$) cells, were finally eliminated by nearby WT cells through apoptosis (Moreno et al. 2002a). Later, the phenomenon of cell competition is extended to other scenes in Drosophila. The different local expression level of Myc elicited cell competition during the development of wing discs. Myc-high cells outcompeted the surrounding Myc-low cells and the latter cells died via the induction of the proapoptotic gene hid (de la Cova et al. 2004). Thereby, the wing could reach to an appropriate and reproducible size, the normal growth of Drosophila was ensured. According to the original

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researches, the occurrence of cell competition follows two fundamental principles. One principle is that the elimination of loser cells requires their being surrounded by winner cells. In other words, the loser cells can survive in a homogenous context. The other principle is that both winner cells and loser cells should be originated from the same identity group. For example, the anterior (A) and posterior (P) compartments are two major developmental compartments formed in the Drosophila wing discs. Cell competition was only observed in the cells belonging to the A compartment, even though P cells were just beside Myc-high A cells (de la Cova et al. 2004).

While the original effect of cell competition in Drosophila was referred to as maintaining homeostasis and controlling the growth and development by eliminating suboptimal cells, increased evidence informs us that cell competition also exists in mammals and acts as a doubled-edged-sword. On the one hand, cell competition selects cells with Myc-high levels, which are comparatively more metabolically active for the epiblast of mouse without perturbing development, indicating positive roles of competition in the early mammalian embryo (Claveria et al. 2013; Sancho et al. 2013).On the other hand, since most oncogene mutations can increase the survival capacity of the transformed cells, cell competition could be hijacked by transformed cells to gain growth advantages, making transformed cells "supercompetitors", thereby the malignant tumor cells could win the competition and exclude the neighboring normal cells at the early expansion stage of cancer (Madan et al. 2019). For example, in the murine colorectal cancer model, APC-mutant cells achieved their own expansion by inhibiting the proliferation of surrounding WT cells through cell competition (Flanagan et al. 2021).

As we all know, the occurrence of tumor is a continuous process, including oncogenic mutations in normal cells due to the disruption of homeostasis, emergence of a single phenotypic precancerous cell, local clonal expansion of tumor cells, regional lymph node metastasis and distant metastasis of aggressive tumor cells. In the course of tumor progression, cancerous clones interact and compete with host normal cells all the time. So far, increased studies revealed that these cell competition interactions make transformed cells under selective pressure and play contradictory roles in different phases of tumor progression. Herein, we discussed cell competitive interactions which have been verified in mammalian cancer development and reviewed recent advances of the specific mechanisms and regulators of these competitive interactions, as well as the potential therapeutic implications.

Different modes of cell competition between cancer cells and host normal cells

Competition for trophic factors

The basic idea of this theory is that winner and loser cells compete for the limited survival signal factors in the microenvironment and the winner cells possess a stronger ability to take up the trophic factors compared to the loser cells. As a result, the loser cells divided more slowly than the winners and finally undergo apoptosis. In the Drosophila wing disc, Decapentaplegic (Dpp) is a trophic factor that promote cell proliferation and growth, and ligand internalization of Dpp is need to be done through endocytosis before survival signal transduction. Since M−/+ cells are metabolically less active than WT cells, the ability of M−/+ cells to capture Dpp is weaker than WT cells, thus brk, the downstream molecular of Dpp signal pathway, in M−/+ cells is upregulated. Consequently, the increased expression of brk elicited JNK activity and M−/+ cells are apoptosis in a JNK-induced way (Moreno et al. 2002b). The trophic factor theory is first established as a surveillance mechanism which maintains cell density homeostasis and controls organ size.

Consistent with the original definition, natural cell competition for survival factors also selects fitter cells and suppresses carcinogenesis in mammals. For example, as the most frequent childhood malignancies, acute lymphoblastic leukemia (ALL) is originated from abnormal transformation and proliferation of lymphocytes which is partly attributable to disorder in thymus. In order to keep thymus functioning normally, a continuous supply of T cell progenitors migrating from the bone marrow is necessary to prevent resident old thymocyte self-renew, otherwise malignant transformation of intrathymic progenitors and T cell acute lymphoblastic leukemia (T-ALL) would be observed in murine models. The substitution of thymus-resident old progenitors would not happen unless the bone-marrow-derived young progenitors were present, which indicates cell competition enabled this turnover and suppressed the generation of T-ALL. The superior ability of young progenitors to utilize IL-7 induces the decreased expression of Bcl2, the IL-7 downstream anti-apoptotic regulator, in old progenitors, thereby eliminating the thymus-resident loser cells. (Martins et al. 2014). It is noteworthy that the disrupted ability of bone-marrow progenitors to synthetic IL-7 receptor reversed the result of competition, which associate points between cell anabolism and cell competition. What is more, the crosstalk between cell metabolism and cell competition is supported by the fact that difference in protein synthesis could elicit cell competition (Nagata et al. 2019) (Fig. 1a).

As we all known, metabolic reprogramming has been considered as a hallmark of cancer considering its pivotal
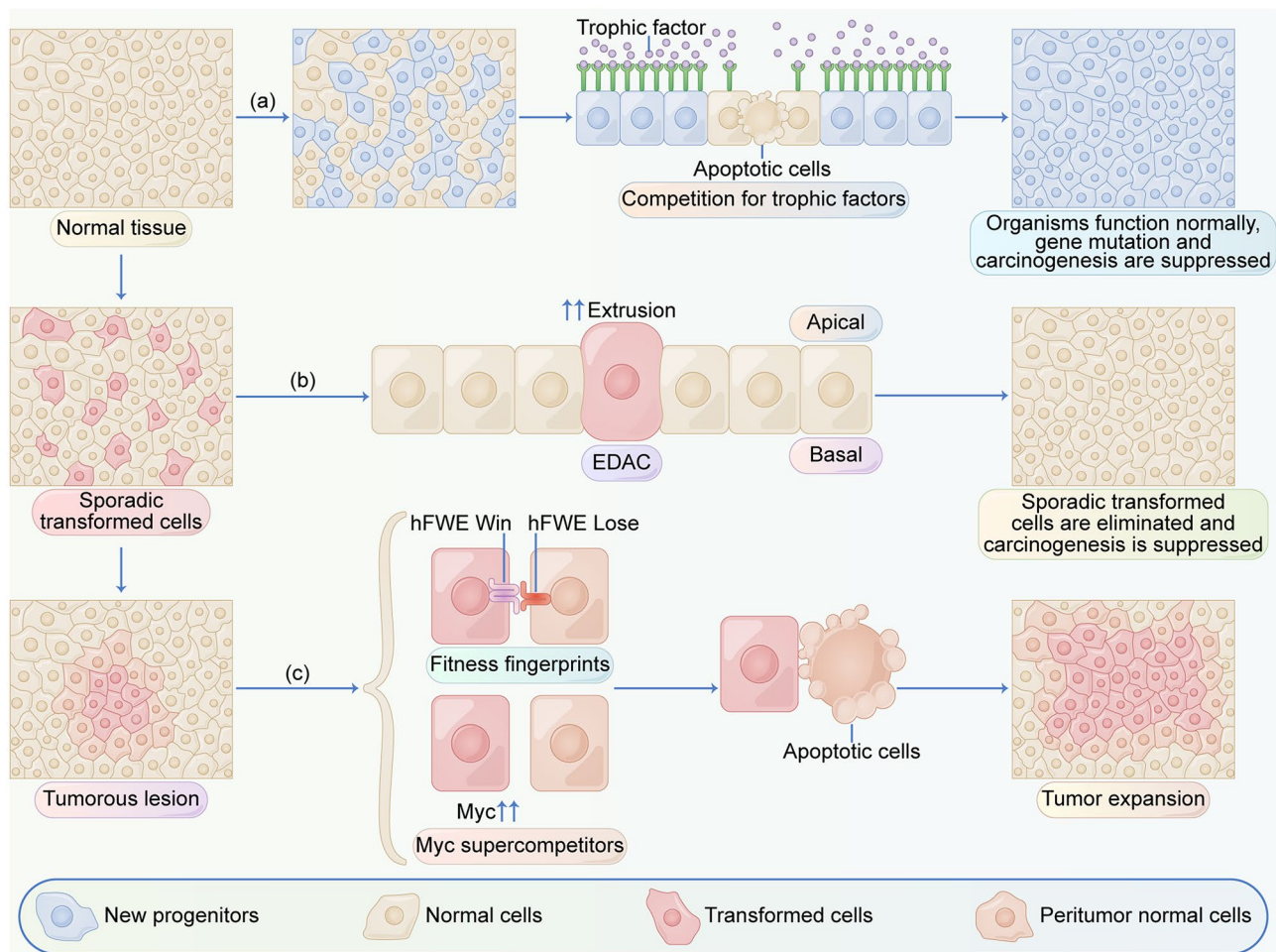
Fig. 1 Distinct modes of cell competition between transformed and normal cells in different stages of cancer in mammals. **a** Cell competition before oncogenic mutation: The superior abilities of new progenitors to synthetic trophic factor receptors and utilize trophic factors make them become winners, while old progenitors lose and undergo apoptosis due to the deprivation of trophic factors. **b** Cell competition that occurs when sporadic transformed cells emerge: when sporadic transformed cells are surrounded by neighboring normal cells, they are extruded apically within the epithelial monolayer. This process is termed as epithelial defense against cancer (EDAC). **c** Cell competitions in early tumor lesion expansion: if the sporadic transformed cells cannot be eliminated, the early small tumor lesion consequently forms. Cell competition is hijacked to improve tumor development in this stage in mammals. Tumor cells expressing the fitness fingerprint human Flower (hFWE) Win can sense and eliminate the neighboring hFwe-Lose-expressing normal cells via apoptosis. Moreover, Myc-high cancer cells can eliminate the weaker Myc-low peritumor normal cells

role in maintaining the balance between considerable biomass production, which is needed for the rapid proliferation, and limited nutrient and energy (Vander Heiden and DeBerardinis 2017). The expanding metabolic repertoire of transformed cells makes neighboring untransformed cells at a disadvantage in biosynthesis, which may induce cell competition and promote the development of tumor. Though the direct evidence supporting that competition for the trophic factor could improve tumor growth in mammals remains elusive, there is another research showing that the APC-mutant cells outcompete wild-type cells and promote their expanding by secreting WNT antagonists in tumor microenvironment (TME), which suggests impaired ability of untransformed cells to transduce WNT signals

makes them loser cells (Flanagan et al. 2021). It implies that the transformed winner cells could restrain neighboring normal cells from binding the trophic factor in a novel paracrine inhibitor way, which to some extent is in accordance with the relatively strong biosynthetic capacity of the winners.

Moreover, the increased metabolic activity of tumor cells promotes cancer development from another aspect. The metabolic reprogramming enhanced the tumor cell's ability to obtain nutrient, for example, transformed cells express more glucose transporters (GLUT) to satisfy their increased demand for glucose (Wang et al. 2018). As nutrient in TME is limited, the function and survival of other cells in TME is impaired due to glucose deprivation, especially T cells (Shao

et al. 2021; Siska et al. 2017). In the murine sarcoma model, enhanced glucose acquisition of transformed cells restricts T cells metabolism, thus dampening their anti-tumor activity, allowing immune evasion and tumor expanding (Chang et al. 2015). Though the nutrient competition does not comply with the principles of typical cell competition, as they are not originated from the same identity group, it suggests the important role of cell metabolism in mammalian tumor development.

Collectively, natural trophic factor competition between transformed cells and normal cells is a surveillance and tumor suppressor mechanism, while it also may be hijacked to promote tumor development. Furthermore, cell metabolism may play a vital role in this mode of cell competition which does not require winner–loser direct contact.

Epithelial defense against cancer

Apical cell extrusion is a biological process that could remove apoptotic cells and maintain homeostasis in epithelia (Eisenhoffer et al. 2012; Rosenblatt et al. 2001). During the extrusion, the apoptotic cell signals its neighboring cells, via secreting sphingosine-1-phosphate (S1P) (Gu et al. 2011) and enhancing its contractility (Nanavati et al. 2020; Sebbagh et al. 2001) which is sensed by neighbors through E-cadherin (Acharya et al. 2018), to form a ring of actin and myosin with increased contractile tension specifically at its junction with the apoptotic cell. Then, the actomyosin network within the neighbor cell effectively applies compressive forces to extrude the apoptotic cells apically.

Recent studies show that the extrusion also can be elicited in an apoptosis-independent fashion in mammals. It is first reported in cell culture systems. When RasV12-transformed Madin–Darby canine kidney (MDCK) epithelial cells are surrounded by normal cells within the epithelial monolayer, they are extruded from the apical surface (Hogan et al. 2009). The similar extrusion also can be observed in Src- (Kajita et al. 2010; Moitrier et al. 2019), YAP- (Ishihara et al. 2020), Cdc42- (Grieve and Rabouille 2014) transformed MDCK cells and ErbB2-transformed human mammary epithelial cells (Leung and Brugge 2012). Importantly, the extrusion is diminished while transformed cells are in a humongous environment, which means it occurs in a cell-context-dependent manner. In addition, the recognition and elimination of the single, sporadic precancerous cells at the initial stage of cancer suppresses the malignant clonal expansion at the most beginning, so it is considered to be a novel mode of cell competition involved in cancer (Tanimura and Fujita 2020). This suggests normal epithelia have anti-tumor activity at the early stage of tumor initiation that does not need the participation of immune cells, which is termed epithelial defense against cancer (EDAC) (Fig. 1b).

Actually, cell-competition-associated apical cell extrusion is first observed in transformed cells mutant for the cell polarity gene scribble in Drosophila to suppress neoplastic tumor development (Brumby and Richardson 2003). This epithelial defense require the cell-surface ligand-receptor system, the ligand standard at second (SAS) on the neighboring normal cells and the receptor-type tyrosine phosphatase PTP10D on the transformed cells, to initiate the cell removeotion (Yamamoto et al. 2017). However, the recognition mechanism of transformed loser cells by surrounding winner cells that elicits mammalian EDAC remains to be elucidated. Under the premise that normal and transformed cells contact with each other, distinct detection mechanisms have been proposed. The interaction between leukocyte immunoglobulin-like receptor B3 (LILRB3), a PirB family protein which is expressed on wild-type cells, and major histocompatibility complex class I (MHC class I), which is highly expressed on the transformed cells, is identified to trigger EDAC via an SHP2-ROCK2 pathway (Ayukawa et al. 2021). Alternatively, the different mechanical properties between normal and mutant cells membrane which caused by the modulation of cytoskeletal regulatory proteins are always believed to induce apical cell elimination. Differential EphA2-ephrin signaling which drives cell repulsion and contractility is thought to be the mechanism by which RasV12 cells are detected in epithelial cell sheets, thus leads to RasV12 separation (Porazinski et al. 2016). In addition, "protrusion to protrusion response" between normal and transformed cells which is mediated by Cdc42 and FBP17 is presumed to trigger cell competition, as the protrusion could evoke physical stimuli which might be recognized by mechanosensors on the opposite cells (Kamasaki et al. 2021).

Unlike the recognition mechanism, cell shape change and cytoskeleton proteins involved in the extrusion seem to be a consensus. Prior to the extrusion, calcium wave arises from the transformed cell and propagates across the surrounding cells (Takeuchi et al. 2020), consistent with the critical role of calcium signaling in controlling cytoskeleton protein (Wales et al. 2016). Upregulation of calcium levels induces the F-actin accumulation in the cytosol and perinuclear region in the surrounding normal cells. As an actin-filament cross-linking protein, filamin within normal cells accumulated specifically at the interface with transformed cells and vimentin, which is one of the intermediate filament proteins that modulates cell adhesion or migration (Helfand et al. 2011; Ivaska et al. 2007; Kajita et al. 2014), are also recruited at the same place. Filamin acts upstream of vimentin, then the surrounding normal cells generate the holding arm-like vimentin filaments which could apply contractile forces and squeeze out the transformed cells (Kajita et al. 2014). S1P-S1PR2 interaction not only plays a role in apoptotic-apical-extrusion, but also promotes accumulation of filamin in cell-competition-extrusion (Yamamoto et al.

2016). ADAM-like Decysin-1 (ADAMDEC1), an intrinsic soluble factor, also facilitates the accumulation of filamin in neighboring normal cells (Yako et al. 2018). In addition, caveolin-1 in normal cells maintains cell ductility by influencing contractile tension in epithelial (Teo et al. 2020). Under the regulation of these molecules, normal cells elongate and extend lamellipodial extensions underneath the extruded cell (Kocgozlu et al. 2016), while the extruding cells become round and tall through the cytoskeleton protein rearrangement. Several researches showed that myosin-II are activated in transformed cells via distinct ways including EphA2-ephrin signaling (Porazinski et al. 2016) and Src activation (Kajita et al. 2010). Moreover, accumulated paxillin-plectin-EPLIN (epithelial protein lost in neoplasm) complex in the apical region of RasV12 cells (Kadeer et al. 2017; Kasai et al. 2018; Ohoka et al. 2015)

and myosin-II-β-spectrin complex in Src-transformed cells (Takagi et al. 2018) also contribute to the cell shape change. In a word, the cytoskeleton protein recruitment within both transformed cells and neighbor normal cells cooperate to promote the apical elimination of transformed cells (Fig. 2).

However, the fate of the extruded transformed cells in vivo remains so far elusive. While many researchers hold the view that transformed cells would suffer from physically and chemically harsh environments after apical extrusion, consequently undergo elimination (Ayukawa et al. 2021; Kajita et al. 2010; Leung and Brugge 2012), various parameters including accumulation of oncogenic mutations and the number of extruded transformed cells may affect the final result. Combined mutations of RasV12 and tricellular junction protein M6 facilitates migration and invasion of extruding cells (Dunn et al. 2018), and sequential mutations of
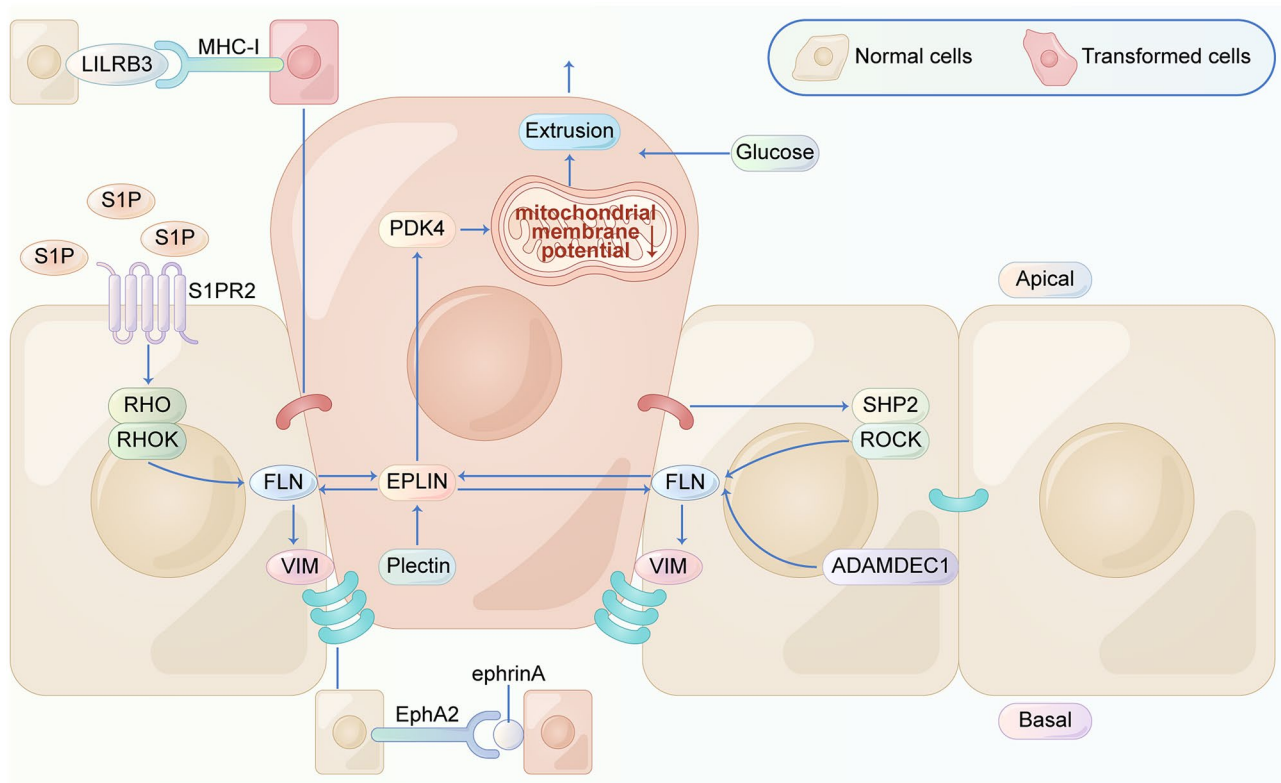

Fig. 2 Molecular mechanisms of epithelial defense against cancer (EDAC) in RasV12-transformed cells and neighboring normal cells. Normal cells recognize transformed cells via the cell–surface interaction between leukocyte immunoglobulin-like receptor B3 (LILRB3) and major histocompatibility complex class I (MHC class I), where MHC class-I is highly expressed on transformed cells and LILRB3 is on neighboring normal cells. Differential ephrin type A receptor 2 (EphA2)–ephrin A signaling is also thought to contribute to the detection of RasV12-transformed cells in epithelial cell sheets. The MHC-I-LILRB3 interaction triggers the accumulation of cytoskeletal protein filamin (FLN) and the intermediate filament protein vimentin (VIM) in neighboring normal cells at the interface of two types of cells. In addition, there are other molecules which also promote the accumulation of filamin, including exogenous sphingosine-1-phosphate (S1P) and intrinsic ADAMDEC1. Exogenous S1P mediates filamin accumulation through the activation of Rho/Rhok pathway via its interaction with S1PR2. In the transformed cells, epithelial protein lost in neoplasm (EPLIN) is recruited, and the accumulation of filamin and EPLIN is mutually influenced, while plectin just promote accumulation of EPLIN. These collective cytoskeletal rearrangements in both cells facilitate the apical extrusion of transformed cells. Signaling downstream of EPLIN accumulation leads to the suppression of mitochondrial membrane potential, which is required for extrusion. Increased glucose uptake is also observed in the transformed cells, indicating the possible role of metabolic alteration in EDAC

RasV12 and Scribble not only diminishes the apical extrusion, but also make transformed cells supercompetitors which engulf the neighboring single-mutant cells (Kohashi et al. 2021). What is more, small population of extruded Src-mutant cells remain alive and display hallmarks of the epithelial-to-mesenchymal transition (EMT) (Moitrier et al. 2019), consistent with the collective effect of multicellular tumors. Collectively, the fate of the extruded mutant cells to some extent determines the development of cancer at the initial stage, as cell elimination suppresses cancer, otherwise promotes expansion of cancerous cells.

Noteworthy, chronic inflammation and metabolic alternations which play important roles (Vander Heiden and DeBerardinis 2017) in cancer are found to be environmental factors that regulate the extrusion of transformed cells. Increased glucose uptake and decreased mitochondrial potential are observed in extruding cells via increased expression of PDK4 (pyruvate dehydrogenase kinase 4) (Kon et al. 2017), while upregulation of PDK4 and cytoskeleton complex may play crucial roles in EDAC as a whole. EPLIN plays a positive role in upregulation of PDK4 and either knockdown of cytoskeleton protein, including EPLIN and filamin or inhibition of PDK4 finally disturbed the apical extrusion of transformed cells. Lipid metabolism is also involved in the regulation of contractile tension (Teo et al. 2020), consequently influences the apical extrusion (Sunaga et al. 2021). Extrinsically inflammation mediated by modulated lipid metabolism and intrinsically inflammation mediated by COX-2/PGE(2) pathway (Sato et al. 2020) both suppress EDAC.

Fitness fingerprints

According to the original definition, cell competition recognized and selected fitter cells based on the fitness status of cells. To elaborate the cell fitness detective mechanism, Merino (Merino et al. 2013; Moreno et al. 2015) put forward the concept of "fitness fingerprints". Each cell has its own fitness marker on the membrane, which displays its fitness status and allows a relative comparison between each other. When winner and loser cells contact (Levayer et al. 2015) or approach (Tamori and Deng 2013), markers recognize and compare with each other. Finally, the suboptimal ones are excluded because of suboptimal fitness marker. That marker is defined as "fitness fingerprint". The transmembrane protein Flower (FWE) is the most studied representative of such cell fitness indicators (Madan et al. 2018; Rhiner et al. 2010), which is a highly conserved sequence between Drosophila and human.

Similar as cell competition, the Flower code is first found and proposed in Drosophila (Rhiner et al. 2010). The researchers established a cell competition model in the imaginal disc of Drosophila by controlling the expression level of MYC in the cell population. Using genomic and functional assays, they identify FWE to be a necessary molecular which labels cells as "winners" or "losers". FWE is a transmembrane protein with an intracellular N-terminus and an extracellular C-terminal part, it has three isoforms including FWE^{Ubi}, FWE^{Lose-A} and FWE^{Lose-B}, which differ in their exposed C-terminal parts. FWE^{Lose} isoforms do not express in loser cells at the detectable level unless they are under competitive stress, while FWE^{Ubi} is expressed ubiquitously in the imaginal discs. In line with the principle of cell competition, loser cells with high FWE^{Lose} isoforms cannot be eliminated in a caspase-3-dependent way only when they are surrounded by FWE^{Ubi} neighbors. As Flower is proposed to be a Ca^{2+} channel in neurons, the first report of a physiological role for the Flower code is found in the creation of the optimal neuron network in Drosophila (Merino et al. 2013; Moreno et al. 2015). Azot and secreted protein acidic and cysteine-rich protein (SPARC) are two key regulators of cell competition in loser cells. The early upregulation of SPARC provides a transient protection and performs as means against unnecessary elimination by inhibiting caspase activation in outcompeted cells (Portela et al. 2010), whereas the expression of Azot ensured fitness-cased cell culling and maintain tissue healthy (Merino et al. 2015).

Overall, this "fitness fingerprints"-based molecular mechanism is naturally used to suppress malformation and extend lifespan in Drosophila. In mammals, this cell fitness comparison mechanism is also found to play a role in the early expansion stage of cancer. Cellular fitness can be defined as the capacity of a cell to survive and proliferate in a particular environment (Merino et al. 2016). As cancer cells can survive and proliferate in the special tumor environment while the neighboring normal cells cannot (Hinshaw and Shevde 2019), this mechanism is hijacked to promote cancer development (Parker et al. 2020). The Flower sequence encodes two main groups of isoforms including FWE^{Win} and FWE^{Lose} through the alternative splicing of mRNA in human. Lose isoforms which consist of hFWE1 (human Flower protein 1) and hFWE3 indicate reduced fitness and label "loser cells", when win isoforms include hFWE2 and hFWE4 (Madan et al. 2019). Human cancer cells express higher level of Win isoforms and proliferate more aggressively (Fujita 2019) when surrounded with Lose-expressing stroma cells which result to be eliminated in a caspase-dependent way via cell competition (Fig. 1c). In addition, as a result of several human xenograft models in mice, it has been concluded that Win isoforms in the tumor could upregulate the expression level of Lose isoforms nonautonomously in the surrounding cells then help tumor grow bigger. This suggests the synergistic effect between stromal Lose and tumoral Win isoforms (Madan et al. 2019) in mammalian cancer progression, which means simultaneous inhibition of both isoforms is required to suppress cancer.

Consistent with this deduction, flower gene knockdown with anti-hFWE shRNA in combination with chemotherapy significantly reduces tumor growth in the preclinical cancer models, suggesting the good therapeutic potential of Flower protein.

Interestingly, the fact that both types of hFWE isoforms expressing level is founded to be very low in human's healthy tissue highlights the difference of the Flower code in human and Drosophila, as Win isoform in Drosophila, which is FWE[ubi], is constitutively expressed in the healthy wing disc. Even so, this fitness comparison system is considered to be a general biological process in multicellular organisms that regulates pathological and physiological activities based on the cellular fitness status, because the Flower code not only plays a key role in generating optimal neural network as well as competition of Dpp morphogen signaling in Drosophila, but also promotes cancer growth and predicts COVID-19 prognosis (Yekelchyk et al. 2021) in human.

Other mechanisms

In addition to the modes described as above, there are several other gene pathways involved in cell competitions at the early stage of mammalian cancer development, whose mechanisms remain to be elucidated or fit none of the above.

Cell competition induced by the differential expressing of Myc, a transcription factor regulating genes involved in cell metabolism, cell cycle and protein synthesis (Tu et al. 2018), has been relatively better studied. With regard to the large target network of Myc, overexpression of Myc in cells always correlates with accelerated biosynthesis and proliferation rate, consequently Myc-high cells eliminated the weaker Myc-low cells and overproliferate to compensate for tissue loss (Claveria et al. 2013). This competition interaction is first found to select fittest cells for mammalian embryo development and always play crucial roles in physiological development. As Myc upregulation and activation frequently promotes tumorigenesis (Choi et al. 2018; Hua et al. 2019; Sheng et al. 2019), it is proposed that Myc-mediated cell competition is involved in the human cancer biology (Paglia et al. 2020). This hypothesis is verified both in cell culture system (Patel et al. 2017) and human cancer tissue samples (Anura et al. 2018; Di Giacomo et al. 2017). MCF7 breast cancer cells with low Myc level were observed to be eliminated and undergo engulfment when they are co-cultured with cells with higher Myc expressing level (Patel et al. 2017), and this result can be subverted if Myc expression in the prospective winner cells is inhibited (Di Giacomo et al. 2017). Moreover, Myc-high cells and apoptotic Myc-low cells are observed via immunohistochemistry at the tumor–stroma interface in various human cancers including colon cancer, breast cancer and lung cancer (Di Giacomo

et al. 2017). Collectively, Myc protein levels may represent the fitness status of cell-competition-associated cells. Furthermore, a recent study demonstrated that Myc-mediated-cell-competition is involved in the progression from oral submucous fibrosis to squamous cell carcinoma (Anura et al. 2018), suggesting its positive role in the initiation stage of cancer (Sollazzo et al. 2018). Though the specific mechanism of Myc-mediated-cell-competition has not yet been clarified, the cell competition elicits by different YAP expressing levels (Liu et al. 2019; Moya et al. 2019) may provide some clues, as YAP is observed to be an important downstream molecular of Myc to promote tumorigenesis in several cancers (Choi et al. 2018; Wang et al. 2022).

Furthermore, sporadic researches, respectively, support that differential expression or activity of the following gene pathways generates competitive interactions between the neighboring cells which influence the early progression of tumors in mammals. These include Notch (Alcolea and Jones 2015), YAP (Liu et al. 2019; Moya et al. 2019), KrasG12D (Hill et al. 2021) and P53 (Watanabe et al. 2018), the details of cell competition mediated by these genes are shown in Table 1.

Therapeutic implications of cell competition

So far, the study of cell competition demonstrated that tumorigenesis not only depend on the complex alterations in the transformed cells, but also is the consequence of competition interactions between tumor cells and normal host cells at the early stage, where whether neighboring normal cells win the competition determines whether tumor can expand. Cell competition highlights the tumor-suppressive influence of the neighboring host tissue, thus harnessing its ability to constrain cancer expansion shed light on innovative therapies to fight cancer, which can be complementary to traditional killing-cancer cell therapies.

In patients with familial adenomatous polyposis (FAP), heterozygous mutations in APCs put them at a 100% predisposition to developing colorectal cancer (Roncucci and Mariani 2015). As described above, APC-mutant intestinal stem cells act as "supercompetitors" by impairing the ability of WT cells to transduce WNT signals (Flanagan et al. 2021). For those patients, boosting the fitness of normal cells to inhibit the tumor-host competition could be an efficient non-surgical method to constrain cancerous progression, which can greatly reduce the suffering of patients. A study based on a preclinical murine model of intestinal tumor shows us feasibility of this method (van Neerven et al. 2021), where oral Lithium chloride treatment rescues WNT inhibition in WT cells through downstream activation of WNT by inhibition of GSK3β, thus prevents the formation of adenomas.

Table 1 Cell competition pathways between normal and transformed cells which are involved in cancer development in mammals

Gene	Mode	Phenotype	Regulators for cell competition		Experimental model	The role in tumor progression	Reference
			In transformed cells	In normal cells			
IL-7	Competition for trophic factors	The superior ability of young progenitors to utilize IL-7 induces the decreased expression of Bcl2 in old progenitors, thereby eliminating the thymus-resident loser cells	IL-7, Bcl2	IL-7	In vivo (mice)	Suppress	(Martins et al. 2014)
APC	Competition for trophic factors	APC-mutant intestinal cells secreted WNT antagonists to neigh WT cells and inhibited WT cells' proliferation and drove their differentiation	Notum		In vivo (mice)	Promote	(Flanagan et al. 2021)
hFWE	Fitness fingerprints	Neighboring normal cells was eliminated in a caspase-dependent way and tumor grown bigger	hFWE2, hFWE4	hFWE1, hFWE3	In vivo (mice)	Promote	(Madan et al. 2019)
Src	EDAC	Apical extrusion of src-transformed cells	Myosin-II, FAK, γ-spectrin, Anillin, p120-catenin	Filamin, vimentin	In vitro (MDCK) and in vivo (zebrafish)	Suppress	(Anton et al. 2018; Kajita et al. 2010; Kajita et al. 2014)
RasV12	EDAC	Apical extrusion of Ras-transformed cells	PDK4, pVASP, EphA2, EPLIN, myosin-II, PKA, paxillin, plectin, Rab5, E-cadherin, MHC class I, FBP17, ZAK	Caveolin-1, COX2-PGE₂, filamin A, S1P–S1PR2, ADAMDEC1, LILRB3, FBP17	In vitro (MDCK) and in vivo (zebrafish, mice)	Suppress	(Anton et al. 2014; Ayukawa et al. 2021; Kamasaki et al. 2021; Kasai et al. 2018; Kon et al. 2017; Maruyama et al. 2020; Ohoka et al. 2015; Porazinski et al. 2016; Saitoh et al. 2017; Sato et al. 2020; Teo et al. 2020; Yamamoto et al. 2016)
YAP	EDAC	Apical extrusion of cells expressing constitutively active YAP	COX-2, EP2, GPCPD1, LCAT	COX-2, EP2	In vitro (MDCK)	Suppress	(Chiba et al. 2016; Ishihara et al. 2020; Sunaga et al. 2021)
ErbB2	EDAC	Translocation of ErbB2-mutant cells from the epithelial layer to the lumen lead to its luminal outgrowth	MAPK, MMPs		In vitro (MCF10A, 3D organotypic culture)	Promote	(Leung and Brugge 2012)

Table 1 (continued)

Cdc42	EDAC	Apical extrusion of cells expressing constitutively active cdc42	MMP, E-cadherin, MEK	In vitro (MDCK)	Suppress	(Grieve and Rabouille, 2014)
Myc	Unknown	MYC-high cells eliminate neighbor MYC-low stromal cells through apoptosis		Human tissue samples	Promote	(Di Giacomo et al. 2017)
Myc	Unknown	MYC-high cells eliminate neighbor MYC-low cells through apoptosis and engulfment	JNK	In vitro (MCF7)	Promote	(Patel et al. 2017)
YAP	Unknown	YAP-high glioma cells eliminated YAP-high glioma cells through apoptosis and occupied the clonal dominance in the tumor		In vivo (mice)	Promote	(Liu et al. 2019)
YAP	Unknown	Peritumoral hepatocytes with high YAP/TAZ activation induce apoptosis in liver tumor cells with relatively less YAP/TAZ to suppress tumor outgrowth	Bcl2	In vivo (mice)	Suppress	(Moya et al. 2019)
KrasG12D	Unknown	KrasG12D-expressing cells are outcompeted from adult pancreas tissues by normal neighbors	EphA2	In vivo (mice)	Suppress	(Hill et al. 2021)
Notch	Unknown	Cells with loss of NOTCH signaling outcompete their WT neighbors		In vivo (mice)	Promote	(Alcolea and Jones, 2015)
P53	Unknown	Mutant p53 cells undergo necroptosis and are basally delaminated by WT epithelial cells		In vivo (mice)	Suppress	(Watanabe, et al., 2018)

Similarly, finding ways to enhance EDAC and thus eliminate nascent cancers may be likewise novel therapies to prevent tumors before they become more unstable and aggressive. As the key molecules mediating EDAC, manipulating the cytoskeleton proteins is a reasonable method to promoting EDAC. PLX4720 which is a ZAK (also called MLTK, MLK-like mitogen-activated protein triple kinase) inhibitor could facilitate accumulation of myosin in transformed cells and filamin in normal cells by inhibiting the negative effect of ZAK on cytoskeleton proteins, consequently promote apical extrusion of RasV12-transformed cells and suppress carcinogenesis. This promotion effect of PLX4720 was identified to restrain the formation of pancreatic ductal adenocarcinoma in the murine model (Maruyama et al. 2020). In addition to regulate EDAC directly via cytoskeleton proteins, targeting certain soluble regulators, such as ADAMDEC1 (Yako et al. 2018), may also be good indirect approaches, though experimental evidence supporting this assumption still lacks. A cell-competition-based high-throughput molecule screen can contribute to the detection of novel compounds involved in the tumor-suppression process (Tadele et al. 2021).

Moreover, though the specific mechanisms of several competition modes have not been clarified, the initiating molecule itself could be an ideal new therapeutic target, such as hFWE, which only highly expresses in tumor cells and the neighboring normal cells, as well as Myc, which has been already extensively studied as an excellent target of cancer therapy (Masso-Valles et al. 2020).

Future perspective

Since cell competition was first described in Drosophila, most of the cell competition-related studies are performed in Drosophila instead of mammals. Considering that the ultimate goal of researches is to achieve clinical application in humans, it is necessary to extend the study of cell competition to mammals. Recent studies revealed analogous interactions are conserved from Drosophila to mammals under various physiological and pathological conditions including cancer. So far, increased experimental evidence supports the view that cell competitions between host and cancer cells play crucial roles in different phases of tumor progression, where neighboring normal host cells can either eliminate nascent cancer cells or be outcompeted for the transformed cells to clonal expansion.

Since several tumor–host cell competition models have been established recently, more studies, especially those in vivo, are required to elucidate the complete and detailed mechanism. In spite of a set of studies providing us with surprising discoveries, there are still many remaining questions which would will reveal more potential target for anticancer

therapy in cell competition. The dominant recognition mechanism in EDAC is needed to be confirmed, as different physical properties (Kamasaki et al. 2021), soluble factors (Yako et al. 2018), and specific receptor–ligand reactions (Ayukawa et al. 2021) are all involved in the initiation of EDAC. In addition, further study to elucidate factors and mechanisms influencing the fates of extruded cells in EDAC is necessary. Any upstream regulators that initiate the differential expressing of hFWE isoforms or downstream molecule influencing the outcome of fitness-fingerprints-comparison-system in mammals, like SPARC and Azot in Drosophila, should be identified. Whether metabolic alterations or other environment factors are involved in all competitive interactions is also an interesting question deserved to be studied since it is the hallmark of cancer. Focusing on its crosstalk with cell competition can provide us a better understanding of cancer biology from a macroscopic perspective. Advanced experimental technologies, including genetic screening, may lead the way. Further work should be done to clarify the specific mechanism behind this competitive process which may open the door to the unexplored world of clinical cancer prevention and treatment.

Data availability All data generated or analyzed during this study are included in this article.

Declarations

Competing interests The authors declare no competing interests.

Competing interest The authors 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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