Cell competition in mammals —novel homeostatic machinery for embryonic development and cancer prevention

(Short title: Cell competition in mammals)

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Abstract

In the multi-cellular community, cells with different properties often compete with each other for survival and space. This process is named cell competition that was originally discovered in *Drosophila*. Recent studies have revealed that comparable phenomena also occur in mammals under various physiological and pathological conditions. Within the epithelium, normal cells often recognize the presence of the neighboring transformed cells and actively eliminate them from the epithelium; a process termed EDAC (Epithelial Defense Against Cancer). Furthermore, physical forces can play a crucial role in the intercellular recognition and elimination of loser cells during cell competition. Further studies are expected to reveal a variety of roles of cell competition in embryonic development and human diseases.

Introduction

In the multicellular organisms, cells communicate with each other and form a peaceful and cooperative society. But, when cells with (chemically or physically) different properties appear in the community, the harmonious status can be disrupted, often leading to a battle between the aberrant cells and the surrounding normal neighbors. Cell competition is a process by which two different cell populations, upon interaction, compete with each other for survival and space; consequently, the loser cells are eliminated from the tissues, while the winner cells occupy the vacant spaces. Such competitive cellular interaction was originally discovered in the imaginal disc epithelium of *Drosophila* [1]. Since then, a number of *Drosophila* studies have revealed that cell competition can occur between normal and various types of transformed cells in epithelial tissues [2-6]. Furthermore, recent studies demonstrate that comparable phenomena also occur in mammals. Cell competition was previously thought to be a phenomenon whereby fast-growing cells compete out slow-growing cells via induction of apoptosis. However, it has become evident that cell growth speed is not the absolute determinant for the consequence of cell competition; rather, the interaction between winner and loser cells induces non-cell-autonomous changes that profoundly influence the behavior of both cells. In addition, the loser cells can present a variety of phenotypes: not only cell death, but also cell senescence, autophagy, and cell death-independent extrusion. Hence, it is now the time to redefine cell competition as more diverse and complex cellular processes than previously envisioned. In this review, we will mainly introduce recent advances on mammalian cell competition and discuss the remaining questions and future perspectives. For

more extensive reviews on cell competition, especially in *Drosophila*, please refer to the review by N. Baker in this issue and other excellent review articles [7-15].

Cell competition *in vitro* and *in vivo*

Using mammalian cell culture systems, cell competition has been observed between normal and various types of transformed epithelial cells (Table 1). For example, when Ras-, Src-, or ErbB2-transformed cells are surrounded by normal cells, the transformed cells are extruded into the apical lumen of the epithelial layer in a cell death-independent manner [16-18]; this process is called apical extrusion. It can be regarded as cancer preventive mechanism because the direction is opposite from basal invasion that is required for cancer metastasis. In addition, cells expressing constitutively active Yes-associated protein (YAP) are also apically eliminated from the epithelium [19]. Furthermore, when tumor suppressor protein scribble- or mahjong-knockdown cells are surrounded by normal cells, the knockdown cells undergo apoptosis and are eliminated from the epithelial layer [4,20]. Importantly, when transformed cells alone are present, neither apical extrusion nor apoptosis occurs, indicating that the presence of surrounding normal cells profoundly influences signaling pathways and behavior of transformed cells. It has also been shown that cell competition can occur not only between epithelial cells, but also between fibroblasts [21].

Recent studies using mouse *in vivo* systems have convincingly demonstrated that cell competition is involved in embryonic development [22,23]. The epiblast is the embryonic tissue that contains the pluripotent stem cells. Up to E6.75, the Myc

protein is expressed in the epiblast where the expression levels are rather variable between cells in an apparently random fashion. At this stage, apoptosis actively occurs, and Myc levels in apoptotic cells are generally lower than those in non-apoptotic cells, indicating correlation between intrinsically low levels of Myc and incidence of apoptosis. Several lines of evidence from the mouse epiblast and cultured ES cells demonstrate that cell competition occurs between cells with different Myc expression levels and that the relative difference in the Myc expression levels, rather than the absolute level of Myc, triggers cell death; low-Myc-expressing cells undergo apoptosis and are eliminated, whereas the neighboring high-Myc-expressing cells proliferate and compensate for the loss of spaces. The functional significance of this cell competition-mediated phenomenon still remains elusive, but it may act as a homeostatic monitoring system that eliminates defective cells and selects fitter cells with higher anabolic activity.

In addition, cell competition can also occur in the mouse fetal and adult myocardium [24]. When Myc-overexpression is induced in a mosaic manner in the cardiomyocytes of the myocardium, Myc-overexpressing cell population expands and dominates the myocardial tissue, which is accompanied by the elimination of wild-type cells. Intriguingly, the phenotype of the loser cells is different between the embryo and adult: apoptotic and autophagic cell death, respectively. In both cases, nonetheless, winner cells proliferate in a compensatory manner for the loss of loser cells; this phenomenon is thus phenotypically silent and does not affect heart function or structure. These results suggest that cell competition can be potentially applied to a cardiomyocyte replacement strategy.

Furthermore, cell competition is also involved in oncogenesis [25]. In the thymus, T lymphocyte precursors are constantly replaced by bone-marrow-derived progenitors. This replacement process is mediated by cell competition between ‘young’ bone-marrow-derived and ‘old’ thymus-resident cells, resulting in the elimination of old cells by apoptosis. Importantly, when cell competition is disrupted by blocking the supply of progenitors from the bone marrow, thymus-resident cells self-renew and continue to remain in the thymus, but eventually leading to T-cell acute lymphoblastic leukemia. This result indicates that cell competition can be a tumor suppressor mechanism in the thymus by replenishing new cells with higher fitness.

Epithelial Defense Against Cancer (EDAC)

It has become clear that at the boundary between normal and transformed epithelial cells, they mutually influence each other, resulting in various non-cell-autonomous changes in both cells. In particular, recent studies have revealed the molecular mechanisms of how normal and RasV12-transformed cells respond to each other (Figure 2). When normal cells are adjacent to RasV12-transformed cells, a versatile cytoskeletal protein filamin is accumulated in normal cells at the interface with RasV12 cells [26]. Accumulated filamin further recruits the intermediate filament protein vimentin at the basal side of the cell-cell contact sites, and the vimentin filaments generate contractile forces that could possibly squeeze out the transformed cells into the apical lumen. These results suggest that normal epithelial cells are able to sense the presence of the neighboring transformed cells and to actively eliminate

them from the epithelium. This implies a notion that at the early stage of carcinogenesis, normal epithelial cells have anti-tumor activity that does not involve immune cells; this process is termed EDAC (Epithelial Defense Against Cancer).

By contrast, in RasV12-transformed cells that are surrounded by normal cells, an actin-binding protein Epithelial Protein Lost In Neoplasm (EPLIN) is accumulated [27]. When RasV12 cells alone are present, the accumulation of EPLIN is not observed, indicating that the presence of the neighboring normal cells influences transformed cells in a non-cell-autonomous fashion. EPLIN then activates downstream protein kinase A (PKA) and myosin-II and induces enrichment of caveolae-containing microdomains, which collectively facilitate apical extrusion of RasV12-transformed cells. In addition, EPLIN depletion in RasV12 cells diminishes filamin accumulation in the surrounding normal cells, whereas filamin-knockdown in normal cells suppresses EPLIN accumulation in the neighboring RasV12 cells. Thus, there are mutual regulatory mechanisms between RasV12-transformed cells and the surrounding normal cells. Furthermore, a recent study demonstrates that Ephrin-Eph signaling also plays a role in cell competition between normal and RasV12-transformed cells [28]. The expression of EphA2 is elevated in RasV12 cells in a cell-autonomous manner, and the interaction between EphA2 in RasV12 cells and Ephrin-A in the neighboring normal cells induces a cell repulsion response, which promotes apical extrusion of the transformed cells. It needs to be clarified in future studies whether filamin-EPLIN and Ephrin-Eph function in the same or independent pathway(s).

In addition to epithelial intrinsic mechanisms, extrinsic factors from the outer-environment can also influence cell competition within epithelia. Sphingosine-1-phosphate (S1P) is a lipid mediator that is secreted from a variety of cell types including endothelial and immune cells in the underlying matrix tissues [29,30]. Not intrinsic but extrinsic S1P binds to S1P receptor 2 (S1PR2) in normal cells neighboring RasV12-transformed cells. S1PR2 then mediates Rho activation, thereby promoting accumulation of filamin and driving apical extrusion of RasV12 cells [31]. This result indicates that S1P is a key extrinsic factor that affects the outcome of cell competition between normal and transformed epithelial cells and that the S1P level in epithelial tissues can affect the frequency of apical elimination of transformed cells.

Mechanical cell competition

In the epithelial cell community, cells are pushed and pulled with their neighbors, and various physical forces are dynamically fine-tuned to maintain the physically homeostatic condition. But, when cells with different membrane tension or elasticity arise within the epithelial layer, the physical equilibrium could be greatly disturbed. Indeed, recent studies have revealed that physical forces are also involved in cell competition.

When scribble-knockdown cells are surrounded by wild-type cells, scribble-knockdown cells become a loser of cell competition and undergo apoptosis [20]. During this process, at least in mammalian cell culture systems, physical forces play a crucial role. Scribble-knockdown cells are hypersensitive to compaction and become apoptotic at high cell density, which is due to the high, basal expression level of p53

[32]. Interestingly, when surrounded by normal cells, scribble-knockdown cells become compacted and form a high-density cell cluster by unknown mechanisms. The cell compaction then further elevates the p53 level through ROCK and p38 mitogen-activating protein kinase (MAPK), leading to apoptosis of scribble-knockdown cells. Thus, the high p53 level and compaction sensitivity could be a property of loser cells. This result suggests that physical forces imposed from winner cells or produced inside loser cells can cause cell death of loser cells, rather than exchange of cell death-related molecules; this type of cell competition is named mechanical cell competition [32].

Physical properties are involved in cell competition between normal and RasV12-transformed cells as well. When RasV12-transformed cells are surrounded by normal cells, myosin-II activity is enhanced and the transformed cells become round and tall with the elevated tensile forces and membrane elasticity [16,26]. The increased myosin-II activity in the transformed cells also induces the pulling forces at the interface with normal cells that could physically drive the apical extrusion process. In addition, as described above, normal cells sense the presence of transformed cells and accumulate filamin at the interface [26]. Filamin crosslinks actin filament to form orthogonal actin-meshworks [33] and acts as mechanosensor/transducer [34]. Indeed, suppression of myosin-II activity in RasV12-transformed cells diminishes filamin accumulation in the surrounding normal cells. Collectively, these data indicate that, by accumulating filamin at the interface, normal cells sense and respond to mechanical environments that are modulated by myosin-II-driven forces in the neighbouring transformed cells. In addition, the redistribution of N-WASP also occurs

during apical extrusion of RasV12-transformed cells [35]. At the steady status, N-WASP is accumulated at adherens junctions and enhances apical junctional tension by stabilizing local F-actin networks. By contrast, at the interface between normal and RasV12 cells, N-WASP is reduced at the apical junctions and increased at the lateral membrane, thereby enhancing lateral tension and promoting the process of apical extrusion.

Remaining questions and future perspectives

One of the biggest challenges in the field is to identify cell competition marker(s) that indicate the occurrence of cell competition, as activated caspase for apoptosis and LC3 for autophagy. Although the previous studies have found several proteins that accumulate at the interface between winner and loser cells such as filamin and EPLIN [26,27], they also play a role in other cellular processes and are thus not suitable as a specific indicator for cell competition. But, if there were a molecule of which expression or activity is specifically upregulated during cell competition, it would become possible to detect phenomena or diseases that involve cell competition. At present, it is not known whether such marker proteins are present or not, but once identified, they will tremendously develop this research field.

Another important issue is to elucidate the initial trigger of cell competition: the difference between winner and loser cells. The initial step of cell competition should be cell-autonomous alteration(s) in winner or loser cells, and several lines of evidence suggest that both winner and loser cells can sense the difference between them. Then, which differences do cells recognize and respond to? It is plausible that cells are able

to sense a variety of changes occurring at their neighbors: plasma membrane composition, soluble factors, physical properties (*e.g.* membrane surface tension or elasticity), and small molecules through gap junction. In general, genetic mutation or transformation affects various molecules and cellular processes, and the neighboring cells may sense some of the changes and respond to them accordingly. But, in the field there is another theory that there is a single and absolute parameter, 'a fitness factor', which triggers competition and determines the winner. Thus, at present how cells sense the difference in the neighbors remains enigmatic, but is the most intriguing and fundamental question to be addressed.

Transformed cells with a single oncogenic mutation are often eliminated from epithelia through cell competition with the neighboring normal cells. This cancer preventive phenomenon reflects the events occurring at the initial stage of carcinogenesis, a black box in cancer biology. Thus, the cell competition study would potentially open the door to the unexplored world of cancer preventive medicine. Indeed, a cell competition-based high-throughput screening platform has been recently established, which has identified small chemical compounds that promote cell competition, leading to the elimination of transformed cells from epithelia [36]. In addition, once cell competition markers are identified, they can be used as boundary biomarkers to detect the interface between precancerous lesions and normal tissues. Furthermore, as cell competition can also occur against non-oncogenic, unhealthy or suboptimal cells [37,38], it is plausible that cell competition is involved in not only cancer but also under other pathological conditions such as metabolic disorder and degenerative disease where fitness of cells is heterogeneously impaired in tissues.

Future studies are expected to reveal more physiological and pathological significance of cell competition in biology and medicine.

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In this study, the authors demonstrate that physical forces imposed from winner cells can cause cell death of loser cells, rather than exchange of cell death-related molecules. In this process, the high p53 level and compaction sensitivity could be a property of loser cells. This type of cell competition is named mechanical cell competition.

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In this study, using cultured cell lines, the cell competition-based high-throughput screening platform is established. Using this system, the authors have identified small chemical compounds that promote the apical elimination of RasV12-transformed cells from epithelia. These results imply that the cell competition study would potentially lead to a novel type of cancer preventive drugs.

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Figure legends

Table 1 Cell competition in mammals

Fig. 1 (a) The multi-step process of cell competition. i) Intercellular recognition of the difference between winner and loser cells. ii) Non-cell-autonomous changes in winner and loser cells. iii) Elimination of the loser cells from the cell community. (b) Cell competition *in vitro*. The oncoprotein-overexpressing cells are extruded from the epithelial monolayer in a cell death-independent manner. The tumor-suppressor protein-knockdown cells undergo apoptosis and are eliminated from the epithelial layer. (c) Cell competition *in vivo*. Recent studies using mouse *in vivo* systems have demonstrated that cell competition is involved in embryonic development in the epiblast, elimination of transformed cells in the intestinal epithelium, and T cell replacement in the thymus.

Fig. 2 Molecular mechanisms of cell competition between normal and RasV12-transformed cells. At the interface between normal and RasV12-transformed cells, a variety of non-cell-autonomous changes occur in both cells.

Figure 1

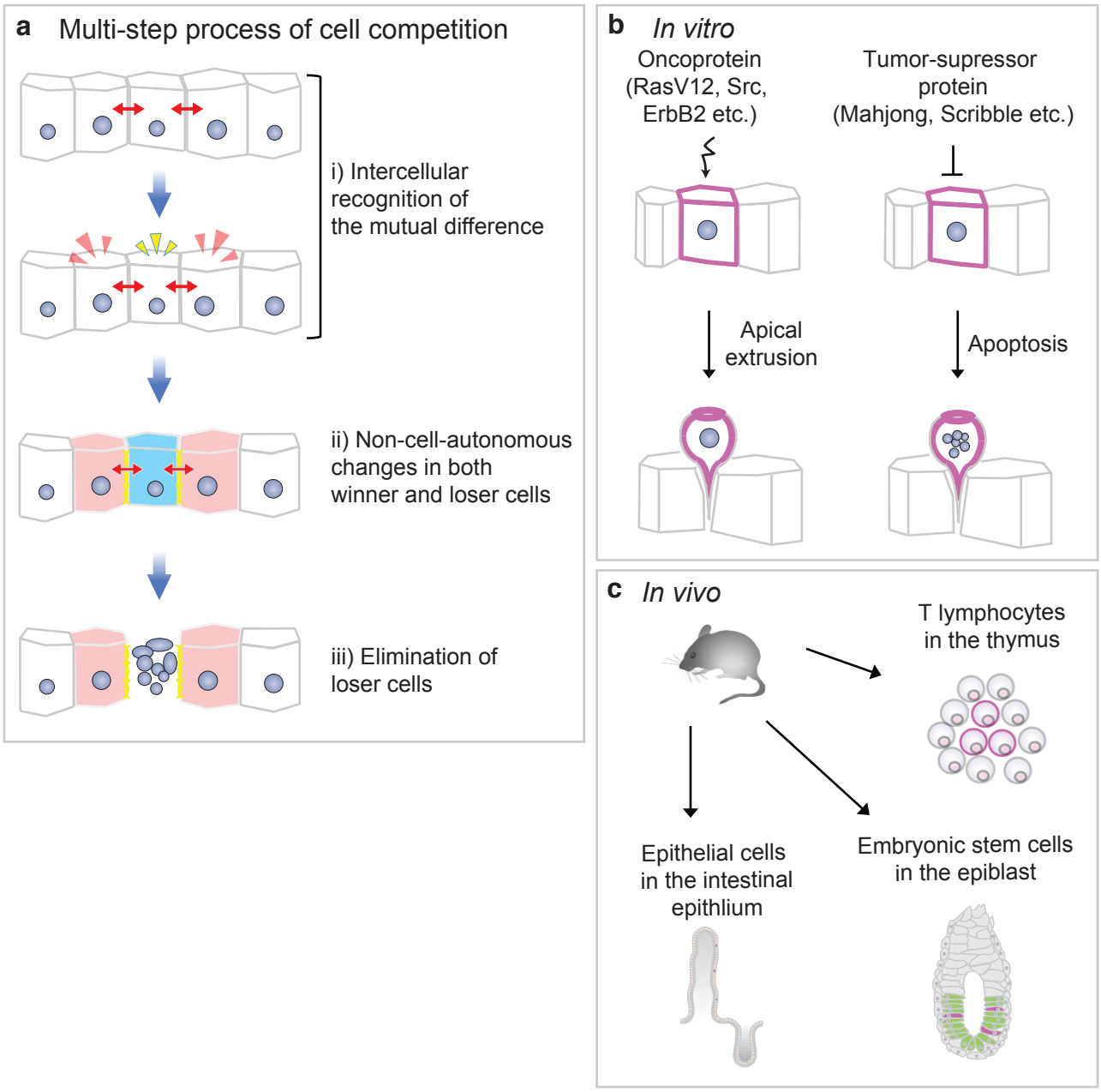

Figure 2

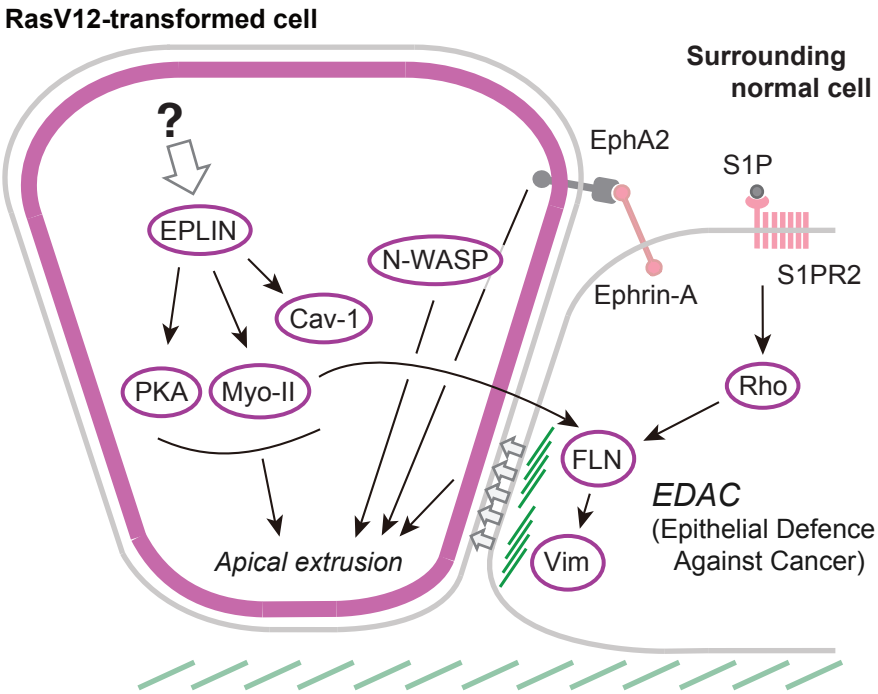

Table 1 Cell competition in mammals

	Mutation	Phenotype	Regulators for cell competition		References
			In mutant cells	In normal cells	
In vitro					
	Ras	Apical extrusion or basal protrusion of Ras-transformed cells	MAPK, Myosin-II, Cdc42, Eph-Ephrin, N-WASP, Caveolin-1, EPLIN	Filamin	16, 26, 27, 31, 35
	Src	Apical extrusion of Src-transformed cells	MAPK, Myosin-II, FAK	Filamin, Vimentin	17, 26
	Mahjong	Apoptosis of Mahjong-knockdown cells	JNK	ND	4
	Scribble	Apoptosis of Scribble-knockdown cells	p38 MAPK, p53	ND	20, 32
	Cdc42	Apical extrusion by expression of the constitutively active form	MAPK, MMPs	ND	39
	ErbB2	Translocation and clonal expansion of ErbB2-overexpressing cells	MAPK, MT1-MMP	ND	18
	Yap	Apical extrusion by expression of the constitutively active form	ND	Filamin, Vimentin	19
In vivo					
Mouse	Minute	Elimination of Minute-knockout cells in the liver	ND	ND	37
	p53	Loss of wild-type cells by senescence-like pheontype in the hematopoietic system	ND	ND	40
	Myc	Cell death of low myc-expressing cells in the epiblast and myocardium	ND	ND	22, 23, 24

ND, not determined