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Competitive Interactions Between Cells: Death, Growth, and Geography

Laura A. Johnston

Department of Genetics and Development, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA. E-mail: lj180@columbia.edu

Abstract

Competitive interactions between cells are the basis of many homeostatic processes in biology. Some of the best-described cases of competition between cells occur in *Drosophila*: cell competition, whereby somatic cells within a growing epithelium compete with one another for contribution to the adult, and stem cell competition, in which germline or somatic stem cells vie for residency in the niche. Both types of competition are conserved physiological processes, with much to tell us about how cellular neighborhoods influence cell behavior, and have importance to stem cell biology, regeneration and transplantation, and cancer.

Competition is pervasive at every level of life—in ecology, economics, between countries and states, and in families—and helps to determine order, status, and survival. Competition also occurs at a cellular level, where it plays roles in tissue homeostasis, organ size control, and stem cell maintenance. In this Review, I focus on two examples of competition currently under intense study: cell competition, which occurs between somatic cells within a growing epithelium, and niche competition, between either germline or somatic stem cells. Although the ultimate fate of the “winners” and “losers” of each type of competition differs, both competitive processes are local and both can alter a cell’s contribution to the adult. Competitive interactions provide a subtle yet powerful mechanism that senses and eliminates vulnerable, mispatterned, or potentially dangerous cells during normal tissue growth. Much of the work I discuss is carried out in *Drosophila* because of the genetic advantages this organism provides. However, both cell competition and niche competition appear to be ancient processes, occurring in diverse animals, and are relevant to regeneration and transplantation biology and to cancer.

Cell Competition: A Homeostatic Mechanism

Cell competition occurs when, within a growing tissue, two cell populations with different metabolic properties or growth rates confront each other, and results in growth of the stronger population at the expense of the weaker. It was discovered in the early 1970s when researchers used dominant, viable, slow-growing mutants, deficient in a ribosomal protein (Rp)-encoding gene [collectively known as *Minutes* (1)], to study cell lineages in *Drosophila*. Using mitotic recombination and genetic tricks to follow growth of marked cells, they generated mosaics where clones of wild-type (+/+) cells grew in a background of *Minute* (M/+) cells and unexpectedly found that the wild-type cells could overtake half (but never more than half) of the wing (2). Two aspects of this discovery were remarkable: First, the wild-type cells colonized areas of the wing that would have been filled by the M/+ cells, which suggests that the two cell populations—born from the same mother—competed for space in the wing; second, that expansion of the wild-type population was limited by an invisible but bona fide boundary dividing the wing into two “compartments” of cells with different developmental ancestry. Discovery of the boundary was of enormous importance for understanding development (3), but the realization that sibling cells compete for contribution to the adult had implications of

great consequence to tissue growth. Cell competition was thus defined as a struggle between slow-growing *M/+* cells (termed “losers”) and faster-growing wild-type cells (“winners”) for territory in the adult.

These experiments were possible because of the genetic tools in *Drosophila* and the simple architecture of the wing imaginal disc, the organ from which the wing develops. The wing disc is a proliferating epithelium that grows in the larva and differentiates adult wing structures during metamorphosis. Early in wing development, disc cells are multipotent, and cell division is stochastic and indeterminate. These properties provide a high degree of flexibility, so that cells lost through damage are rapidly replaced by proliferation of surviving cells. Early work from Morata and Simpson established key features of cell competition: It occurs locally, between clonal populations of wild-type and *M/+* cells, and its severity is proximity-dependent (4,5). Elimination of the *M/+* cells is accompanied by compensatory proliferation of wild-type cells, and a large clone of wild-type cells in a *M/+* disc can fill an entire compartment. Remarkably, despite large territories of cells growing at different rates, the size and shape of the adult wing remains normal (5). These elegant genetic experiments established that a cell’s potential for proliferation and survival—and ultimately its contribution to a fully developed tissue—is determined by its interactions with its neighbors. That cells sense and respond to each other’s growth rate suggested that the sensing mechanism contributes to control of tissue and organ size (6), an idea that was recently confirmed (7).

Group dynamics yield winners and losers

Apoptosis is the principal cause of the growth disadvantage of loser cells: Loser cells die and are eliminated from the epithelium (Fig. 1) (7–12). Inactivation of many genes can lead to death and cell loss during development, often due to a cell-autonomous requirement for the gene for survival or a particular developmental process. However, cell competition is not an intrinsic property of cells: It relies completely on cell-cell interactions. It is these interactions that establish one cell as relatively weaker or stronger than another. Competition is identified by strict experimental criteria, and thus far, only two genetic contexts are legitimately so defined: differences in *Rp* gene dosage, as in mosaics of *M/+* flies and in chimeric *Belly spot and tail* (*Bst*) mice, a mouse “Minute” (13); or in *Myc*, the transcription factor and well-known oncogene (7,9). Several hallmarks distinguish cell competition from other processes that involve cell death and compensatory proliferation. First, competition is context-dependent—cells acquire “winner” or “loser” identity only when in confrontation; each is viable in a homotypic environment. Second, loser apoptosis is triggered by interactions with winner cells. This contrasts cell competition with compensatory proliferation occurring during regeneration, where cells are killed by physical damage or surgery. Finally, competition does not cross the boundaries of developmental compartments (Fig. 2). *Rp*- and *Myc*-induced competition share all of the traits that define cell competition, with minor variations. An interesting difference is that *Myc*-induced competition occurs over a greater distance—up to 10 cells—than *M/+*-induced competition, which occurs extremely locally (7,12).

The cell-intrinsic signaling pathways leading to apoptosis are highly conserved and use prodeath regulatory factors to overcome inhibition of caspases by IAP (inhibitor of apoptosis) proteins. Hid, a *Drosophila* prodeath protein, is a dose-dependent effector of loser-cell death during competition between cells that differ in *Myc* expression and is required for competition to occur (7,10). What signals Hid induction in loser cells is unknown but may be partially due to activation of the Jun N-terminal kinase (JNK) stress-response pathway (7–9). However, JNK’s role is not entirely clear, because Hid expression and competition-induced apoptosis occur even in its absence (7,11). Although losers of cell competition die, winner cells survive and proliferate more, and these two processes are precisely balanced so that wing size is maintained. Expression of the caspase inhibitor, P35, in *M/+* loser cells prevents their death

and simultaneously reduces growth of wild-type winner cells (12), suggesting that the two processes are mechanistically tightly linked. Even without overt competition, preventing apoptosis—particularly that induced by Hid—alters wing growth and causes fluctuating asymmetry, an indicator of developmental instability (7,14,15). These are strong indicators that competition, with its growth and death outcomes, is an essential part of the homeostatic mechanism that stabilizes wing size.

Cell fitness surveillance

The basis of cell competition is that within a field of growing cells, the contribution of a cell and its progeny to a tissue is altered by neighboring cells that possess different growth or metabolic properties. However, such differences do not always lead to competition, indicating an intriguing level of discrimination (7). How do cells sense, compare, and relay their growth or metabolic status to their neighbors? This sensing requires that cells monitor their own metabolic state vis-à-vis their neighbors; thus, molecular sensors of cell competition presumably report cellular fitness. A common denominator in the two characterized examples of cell competition is a local difference in ribosome biogenesis or function. *Minute* mutations directly reduce Rp expression, impairing ribosome synthesis (1). Myc controls expression of numerous genes that contribute to ribosome synthesis, including Rps and rRNA (16,17). An inadequate supply of functional ribosomes is dangerous to cells by interfering with their ability to rapidly regulate translation in response to environmental changes. The nucleolus is a ribosome assembly factory but also contains cell cycle regulators, stress sensors (p53), tumor suppressors (Arf), stem cell factors (Nucleostemin), and transcription factors (Myc), many of which play roles in sensing cellular stress (18). Ribosome vigor may therefore be continually monitored and perhaps reported by a dedicated signaling pathway.

A paucity of ribosomes is potentially stressful, but not necessarily lethal. Both *M/+* flies and *Bst/+* mice grow slowly but develop into adults (1,13). However, confrontation between two populations that differ in ribosomal vigor could be perceived as stress. Our understanding of the requirements for sensors of competition is still limited, and no molecular sensors of cell competition have been unequivocally identified. However, several recent advances shed light on the process.

Ligand-capture-mediated cell competition

As a determinant of a cell's contribution to the adult, cell competition is closely tied to organ growth (7). Initially, it was suspected that cells in imaginal discs compete for growth or survival factors, as postulated for neurons (19). One such factor, the bone morphogenetic protein and transforming growth factor- β family member Dpp, is a secreted protein critical for pattern formation, cell survival, and growth of imaginal discs (20). High Dpp activity stimulates growth (21), whereas low levels activate JNK signaling and apoptosis (22); thus, if potential loser cells were ineffective at capturing Dpp, their survival and growth might be impaired. Some experiments supported this view (8,9), but the selectivity associated with competition argues against it (7). Furthermore, suppressors of *M/+* and *+/+* cell competition isolated in a genetic screen do not require Dpp activity to prevent it (11). Some of these suppressors augmented Dpp activity in loser cells and increased their proliferation, but death was not reduced, so Dpp-stimulated proliferation might just outpace their death (11). However, loser cells are protected from competition by overexpression of the endocytosis-promoting, small guanosine triphosphatase (GTPase) Rab 5 (9). Since numerous cell survival- and growth-promoting factors rely on receptor-mediated endocytosis, further investigation of this intriguing finding should be informative.

Mutual sensing mediated by soluble factors

Recent work suggests that cells recognize competitive status using a mutual sensing mechanism involving production of diffusible factors. In the wing disc, wild-type cells can sense Myc-expressing winner cells up to 10 cell diameters away, suggesting that signaling between the cells is short-range (7). In a cell culture model of competition with *Drosophila* S2 cells engineered to express different levels of Myc, cocultures induced apoptosis specifically in cells with less Myc (10). This did not require cell-cell contact, which suggests mediation by soluble factors. Medium conditioned from competing cocultures was found to contain two activities: One caused Hid-dependent death of naïve, wild-type cells, turning them into “losers,” whereas a second activity turned naïve Myc-expressing cells into “winners” that proliferated faster than normal. A cell’s potential to be a winner or loser was determined by its ability to deregulate Myc expression (10), and production of both activities required reciprocal recognition by each cell type—potential winners and potential losers—suggesting that each activates a sensor that reports the other’s metabolic status (Fig. 1).

Winners eat losers

Cell competition generates dead cells. In the fly, engulfment of dying or dead cells is typically carried out by hemocytes, migratory macrophage-like cells that are dedicated phagocytes. During competition, however, dying *M/+* loser cells are engulfed by nearby wild-type cells (Fig. 2C), possibly driving *M/+* cell death to completion (12). The death tendency of *M/+* cells is overcome if neighboring winner cells lack factors that regulate cell engulfment (including Draper, a *ced-1* homolog and scavenger receptor), WASp (Wiscott-Aldrich Syndrome protein), PSR (phosphatidylserine receptor), RAC (a small GTPase required for cytoskeletal rearrangements) and MBC (myoblast city, a SH3-domain-containing protein) (12). Perhaps the weak metabolic status of *M/+* cells triggers apoptosis, flagging them as “garbage.” The sensing mechanism is unclear, though, because PSR, which recognizes PS exposure on the outer membrane of apoptotic cells, does not drive engulfment in *Drosophila* but inhibits apoptosis by suppressing Hid function and JNK signaling (23). Intriguingly, forced WASp activation stimulates engulfment without prior signaling from dying cells (12). Blocking loser engulfment by winner cells also prevented extra winner growth, adding to the evidence that loser death stimulates the growth of winner cells (Fig. 2) (12). Interestingly, loss of Croquemort, the *Drosophila* homolog of the CD36 macrophage receptor for dying cells, did not prevent engulfment nor prevent cell competition (12), suggesting that stimulation of competition-induced engulfment is qualitatively different from that induced in hemocytes. Still, *M/+* cells are not all engulfed by winners, as many delaminate from the epithelium for phagocytosis by hemocytes, and the importance of neighbor cell engulfment in Myc-induced competition is unclear (7,8,12). Nonetheless, loser cells are clearly perceived as dangerous to the tissue, and a local mechanism is deployed for their removal. The misregulation of wing size that can occur when loser cells cannot die (7) implies that engulfment is critical to the homeostatic function of cell competition.

“Danger Signals” and cell competition

Cell competition appears to proceed through a series of discrete steps: local sensing and recognition of cellular differences, production of diffusible factors, signaling that activates stress pathways and apoptotic suicide of loser cells, deployment of an engulfment program, and growth stimulation of winner cells (Fig. 2). This process is conceptually similar to the innate immune system’s recognition of infectious pathogens, which activates a defensive cellular response that destroys invaders and restores homeostasis (24). Interestingly, the cohort of receptors and signaling modules of the innate immune system are also stimulated by endogenous “danger” signals, released upon tissue damage (24,25). Does cell competition

contribute to an organism's ability to sense and respond to danger derived from itself? The answer to this question awaits further research.

Niche Occupancy: Competition Among Stem Cells

Competition of a different flavor occurs in the *Drosophila* gonad, where both somatic stem cells and germline stem cells (GSCs) vie for occupancy of their particular niche, or microenvironment (26,27). Like cell competition in somatic epithelia, stem cell competition pits cells against each other, but cells are displaced from the niche rather than killed. In the end, competing stem cells both contribute to formation of the ovary, although to different processes.

The GSC niche: Adhesion-based residency

In *Drosophila*, egg chambers arise within the germarium, a structure at the anterior end of the developing ovary. The germarium contains many different cell types in relatively close proximity, including stem cells and their accompanying support cells, the differentiating daughters of stem cells, follicle cells (FCs), and an egg chamber. The GSC niche, at the anterior-most end of the germarium, consists of three somatic cell types: cells in the terminal filament, escort cells, and cap cells (Fig. 3A). GSCs associate directly with cap cells via adherens junctions and are anchored firmly with E-cadherin-dependent interactions (28,29). This association is dependent upon E-cadherin, and loss of E-cadherin leads to a deficit of GSCs. The tight GSC-cap cell association ensures that the GSC receives proximity-dependent signals from the niche: For example, Dpp signal transduction is very high in the GSC but quite low even one cell diameter away (30,31). This high Dpp activity is required to repress expression of two differentiation-promoting genes, *bam* (*bag of marbles*) and *bgn* (*benign gonial cell neoplasm*), in the GSC. GSCs divide asymmetrically, allowing one daughter to remain in the niche while the other moves away from the niche, derepresses *bam* expression, and differentiates into a cystoblast. Niche residency is imperative for a functional GSC and for continued production of new daughter cells (32).

GSCs lacking *bam* or *bgn* cannot differentiate, and the germarium fills with extra GSCs. *bam* mutant GSCs out-compete wild-type GSCs for niche residency; possibly, loss of Bam increases E-cadherin expression, tightening the association between the mutant GSC and the cap cell. After GSC division, daughters are pushed from the niche (Fig. 3B); because *bam* mutant GSCs divide faster than wild-type GSCs, a larger pool of mutant daughters could increase the chance of their niche occupancy. Competition may also be enhanced because, unable to differentiate, mutant GSCs retain stem cell identity. *bam* mutant GSCs require neither Dpp or Myc to compete with wild-type GSCs, although too much Myc leads to GSC loss (27); however, Myc expression may facilitate competition between wild-type GSCs (33). GSCs appear to compete primarily based on their ability to adhere to cap cells, which, perhaps as a proxy for "fitness" and stem cell identity, ensures that they receive signals for their continual renewal (27).

FSC competition: Dynamic niches, migratory stem cells

Niche space for somatic follicle stem cells (FSCs), the progenitors of the follicular epithelium that surrounds the germline cysts, is also subject to competition. Each of two FSCs in the germarium resides in a small niche on opposite sides of the ovariole (Fig. 3, A and C). This niche is ill-defined, but quite different from the GSC niche because it lacks permanent, nondividing stromal cells that anchor the FSC in place. It appears to consist of an FSC, a 2a cyst, and an underlying basement membrane (Fig. 3C). After asymmetric division of the FSC, the daughter moves to the proximate posterior position or sometimes migrates laterally toward the opposite side of the ovariole. Although the niche is not a fixed entity, it is always established

in the same general location, which apparently provides the necessary microenvironment to maintain stem cell identity and activity (26).

One component of the microenvironment might be signals that direct the cross-migration of FSC daughter cells. Laterally migrating FSC daughters move toward the opposite niche and can compete with the resident FSC (26). Displacement of a resident FSC by an incoming daughter is rare, however. Potential barriers to niche competition include E-cadherin- and Beta-catenin-mediated anchoring mechanisms between FSCs and differentiated FCs (29), ring canal bridges between FSCs and their daughters, and attachments with basement membrane (26). The fact that stem cell displacement and replacement is rare despite regular cross-migration of FSC daughters suggests that these mechanisms are quite robust, and occasional displacement by essentially equivalent FSCs may represent opportunistic, rather than competitive, behavior. However, the mechanisms that secure niche residency could encourage competition if one FSC acquired a mutation altering its anchoring ability or its ability to differentiate. In this case, FSC competition could lead to expansion of mutant FSCs and potentially to cancer (26).

Themes and Perspectives

The existence of cell competition tells us that decisions that cells make to grow, die, or differentiate are local and can be communal. Competition between stem cells and their daughters may ensure that functional stem cells reside in the niche (26,32), whereas competition between disc epithelial cells weeds out the relatively weak, including cells carrying a potentially harmful mutation. Whether destructive and leading to cell death, or instructive, determining order and status, both types of competition serve as subtle but important policing mechanisms that promote homeostasis.

Competition allows plasticity during growth, but this plasticity is not without limits. The stem cell niche strictly regulates stem cell numbers by restricting housing space, providing a geographic limitation that protects against deregulated stem cell proliferation. In epithelia such as the wing disc, mutual sensing of cellular status keeps both growth and death in check: In the absence of recognized differences, death is minimal and proliferation proceeds at the normal rate. Cell competition is also restrained in disc epithelia by specific insulating mechanisms. Cells in one developmental compartment are completely insulated from ongoing competition across its boundary (Fig. 2) (4,7), protecting each territory and the disc as a whole from unrestrained competition and unrestrained growth. Nutrient deprivation and cell cycle exit also protect against competition (14,34). How these protective mechanisms operate is unknown, but they limit competition geographically and stabilize organ size, preventing both detrimental overgrowth of winner cells and excessive loss of loser cells.

A fundamental difference distinguishes stem cell competition from cell competition. The goal in both types of competition is to acquire prime real estate, but competition for niche occupancy is adhesion-based, whereas competition between disc epithelial cells is established by a direct cell-cell comparison of metabolic status. In the latter, we still lack information about what molecules are measured, but the mechanism may well be conserved. Competitive-like interactions have been noted between transplanted wild-type cells and diseased host liver cells during liver regeneration in rats (35), highlighting its potential utility in therapeutic transplantations. In diverse animals, the expansion of one cell population at the expense of another is a common outcome in chimeras, and is also a hallmark of cancer (36–38). Indeed, both stem cell competition and cell competition are emerging models for tumorigenesis. A few rogue, mutant cells in a tissue or organ could enhance their own growth by killing off their neighbors (39–41). Likewise, mutations that increase adhesiveness or “stemness” of winner stem cells could out-compete wild-type stem cells and lead to tumors. Study of cell and stem cell competition offers a novel route to identify genes that report winner (precancerous) cells

and loser (noncancerous) status in tissues harboring an incipient tumor. The continued use of *Drosophila* to discover such genes and the development of models of competition in vertebrate systems promise to reveal new and fascinating ways whereby cell fitness is sensed and communicated and homeostasis is maintained in local cellular communities.

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Fig. 1.

A model of cell competition. **(A)** Neighboring epithelial cells recognize relative differences in ribosome function through a sensing mechanism that may involve the production of secreted factors by each cell (orange and green dots). **(B)** Once a difference is sensed, cells acquire “winner” or “loser” status, determined by their relative ribosome function. Loser cells sense stress and activate the JNK signaling pathway and expression of the proapoptotic factor, Hid. Hid induces apoptosis and leads to loser-cell death. Winner cells, with optimal ribosome function, are stimulated to proliferate faster. They also can activate genes required for cell engulfment, leading them to engulf dying loser cells (asterisk). Arrows depict genetic relationships rather than direct biochemical interactions.

Fig. 2.

Cells are insulated from competition by compartment boundaries. **(A)** Cell competition occurring on one side (left) of a compartment boundary (dotted line) does not affect cells on the other side (right). Gray cells, losers; orange cells, winners. **(B)** Local interactions between cells identify relative metabolic status, triggering apoptosis in losers. Signals from dying cells (arrowheads) may stimulate the growth of winner cells. Cells to the right of the compartment boundary are completely protected. **(C)** Loser cells can be engulfed by winner cells. This process promotes winner-cell proliferation. **(D)** Winner cells expand their territory at the expense of loser cells. However, this expansion is limited to one compartment, because cells in the opposite compartment (right of the dotted line) remain insulated. The geographic limits of competition help stabilize organ size.

Fig. 3.

Stem cells compete for their niche. (A) Depiction of the germarium (adapted from 26). (B) GSC competition. GSCs (blue and yellow) adhere to cap cells (green) in the niche via strong E-cadherin interactions. *bam*-mutant GSCs (blue) cannot differentiate, and they retain strong adherens junction (AJ) connections that can displace wild-type GSCs from the niche. (C) FSC competition. FSCs occupy a niche composed of the lateral edge of a 2a cyst encased in an escort cell (EC), the basement membrane (magenta line), and the FSC (red). Green circles are ring canal bridges. Arrows show direction of movement of the newly born FSC. The FSC can move posteriorly (bottom arrow) or toward the opposite niche (top arrows), where it can displace the resident FSC.