Cell Competition and Its Possible Relation to Cancer

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Abstract

Cell competition can occur when cells of different genotypes share the same developing compartment, with one genotype displacing the other as a result of a proliferative advantage. Studies of cell competition in Drosophila have identified an active process of cell assassination and corpse engulfment, and also roles for Myc and the Warts/Hippo tumor suppressor pathway. Here, we discuss the possible relevance of cell competition to cancer. [Cancer Res 2008;68(14):5505–7]

Background

This primer will review current knowledge of cell competition, mostly gleaned from *Drosophila melanogaster* studies, and briefly outline possible roles cell competition might play in cancer, where no role has yet been shown.

The relative contribution of two cell populations to an organ will always be affected by their respective growth rates. "Cell competition" refers more specifically to a phenomenon in which the growth rate is altered by having different neighbors (1). It turns out that the growth properties of cells can depend on who their neighbors are, with cell competition defined by reciprocal increases and decreases in growth on the part of cells juxtaposed in a chimera (Fig. 1). Cell competition occurs in certain tissues and between cells differing in certain growth pathways but not others (Fig. 1; ref. 2). Cancer is an obvious situation where the mammalian body is a chimera of distinct genotypes that probably grow differently. Thus, cell competition might occur in cancer (3).

Competition Genes

There are two clear examples where cellular growth rates in chimeras and nonchimeras have been measured and found different. Genetically normal "wild-type" cells grow faster when sharing a compartment with cells heterozygous for a mutation in a ribosomal protein gene. Conversely, the ribosomal protein mutant cells grow even more poorly and are eliminated, although they would be viable if wild-type cells were not present (4); see (1) for review. Similar interactions are seen when cells differ in Myc levels (2, 5). Wild-type cells grow faster in the presence of cells lacking one copy of the *Dmyc* gene, and the haplo-*myc* cells are progressively lost, although they would be viable if wild-type cells were not present. Triplo-*myc* cells are "supercompetitors" that will out-compete wild-type (diplo-*myc*) cells but are themselves out-competed by tetraplo-*myc* cells. Mechanisms of competition due to altered Myc and ribosomal protein gene dose might be similar, given that Myc activity promotes ribosome biogenesis (6), although this is not the only possibility. Mosaic ribosomal protein gene dose may also lead to competition in mammals, as there is evidence that heterozygous cells are disproportionately disadvantaged in chimeric embryos (7). Myc mosaic mice also exhibit competition-like effects. When c-*myc* is conditionally deleted from intestinal cells, a normal intestine can be rapidly regenerated from even a small proportion of unrecombined, wild-type cells that proliferate and eliminate c-*myc* mutant regions (8).

Another pathway that seems related to cell competition is the Warts (or Hippo) tumor suppressor pathway (9). The serine/threonine kinase Warts was the first component of this pathway identified as a tumor suppressor in flies; knockouts of the mouse homologue (called Lats1) are associated with soft tissue sarcomas and ovarian tumors (10). The pathway is now known to extend from the cell membrane to the nucleus, acting to phosphorylate and inactivate the transcriptional cofactor Yorkie that regulates cell proliferation and survival genes (mammalian homologue: Yap; ref. 10). Cells that are mutated for Warts pathway tumor suppressors kill neighboring wild-type cells, and so mimic cell competition (9). It has not yet been possible to determine whether growth of *yki* mutant cells is enhanced by the death of their neighbors, as would be the case for true cell competition, because of the difficulty of obtaining entirely mutant territory for comparison.

There is a second relationship between the Warts pathway and cell competition. Mutating Warts Pathway genes in cells that have reduced ribosomal protein gene dose prevents this cell population being lost by cell competition, as would otherwise occur. Although the mechanism of protection is not clear, it seems to be quite specific (9).

In contrast to these examples, activities of Cyclin D/Cdk 4, or of the Insulin/insulin-like growth factor (IGF) receptor pathway, do not cause cell competition. When juxtaposed with wild-type cells, these cells grow according to the same, intrinsically higher, growth rate that they would always show, and the neighboring wild-type cells are similarly unaffected. These disparities distort organ growth and shape (Fig. 1). By contrast, competition makes chimeric organs seem more normal, as elimination of slower-growing cells makes room for the others (Fig. 1; ref. 2).

Cellular Mechanisms

Cell competition depends on apoptotic death of out-competed cells (3). A surprising finding is that the cell death also depends nonautonomously on genes functioning in the winning cells, showing that these cells are active assassins (Fig. 1). Five genes that are required for wild-type cells to kill and engulf ribosomal protein-mutant neighbors are *draper, Wiskott-Aldrich Syndrome protein, rac, myoblast city*, and *phosphatidylserine receptor* (11). These genes are familiar as components of the apoptotic corpse engulfment pathway, They indicate that cells are killed actively during competition. Corpse engulfment also occurs when cells compete on the basis of Myc levels, although it is not certain that the extent to which engulfment drives the competition is the same (11).

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Recent tissue culture studies strongly suggest that cells with more Myc become active assassins in the presence of less favored cells, however, and produce signals that kill such cells (12). Because genetically normal cells can be the assassins, both in the myc and ribosomal protein gene examples, cell competition is a process induced by interaction between cells in certain specific growth states, not a direct effect of mutations on individual cells.

It is unusual for corpse engulfment to be required for apoptosis, and to define where it takes place, as occurs during cell competition. Corpse engulfment has more usually been considered a process that follows apoptosis rather than causes it. This has been much studied in the nematode *C. elegans*. The molecular mechanism by which cells are killed by being engulfed is not yet clear (1). Active contributions of engulfment to death has also seen in other circumstances, such as in the assassination of Purkinje neurons by microglia and in certain circumstances in *C. elegans* (13).

Competition in Cancer

There are several reasons for wondering whether cell competition could be involved in cancer and could discriminate between cancer cells and normal cells. One is that cell competition seems to provide an additional selection for some kinds of rapidly growing cells. The *myc* and Warts pathways, and changes in growth regulation by translation are all implicated in human cancer as well as in cell competition in *Drosophila*. Myc has been studied intensely (14). In the intestine, c-*myc* seems to be the only important target of the *APC* mutations that characterize the inherited cancer syndrome familial adenomatous polyposis (15). Recent work indicates that the entire Warts/Hippo pathway has a conserved role in growth control in mammals, and is mutated in many cancers, where it seems to affect contact inhibition in particular (16, 17). Phagocytosed or engulfed cells are seen in tumors and not only within immune cells (18). They could indicate cell competition, but there are alternative explanations, including the recently recognized cell-invasion process, entosis (19).

Hundreds of mutations are selected during tumor development, mostly for unknown reasons (20, 21). Selection must reflect interactions among tumor and normal cells during the development and progression of cancer. Some of the genes may be selected through effects on cell competition. They might not be strictly required for tumorigenesis but still affect the probability or rate of

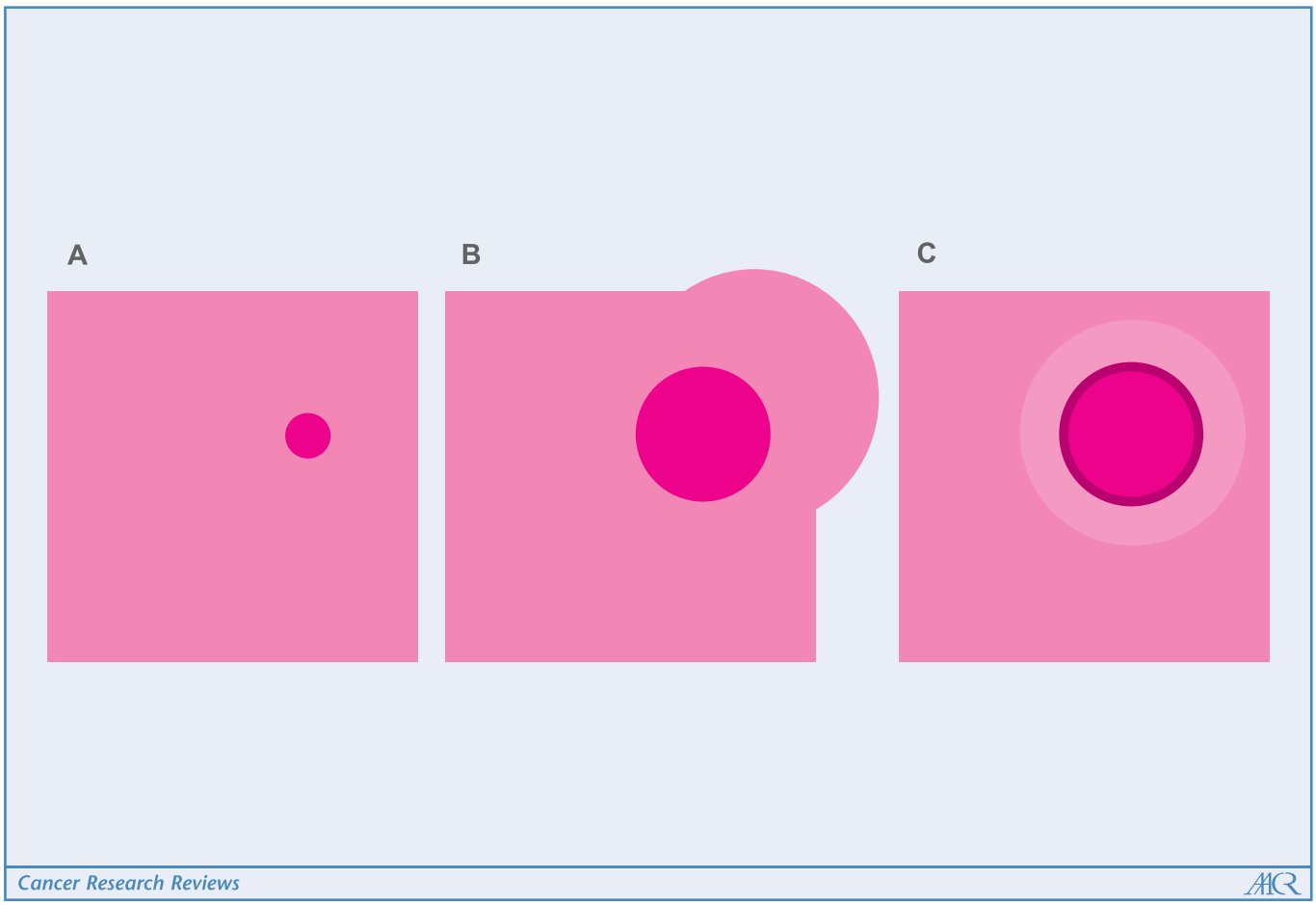

Figure 1. *A,* the clonal descendants of a single normal cell are darkly shaded in this cartoon of a growing organ. These cells are growing at a similar rate to their neighbors. *B,* without competition, a hyperplastic clone distorts organ growth. The darkly shaded, hyperplastic clone creates a bulge in the organ. In *Drosophila*, cells with elevated CyclinD/Cdk4 or Insulin/IGF activities have this effect (2). *C,* the defining features of cell competition are the reduction in growth rate of the out-competed cells, indicated here by a lighter, out-competed zone around the clone, and enhanced growth rate of the winners, shown by still darker shading around the boundary of the hyperplatic clone. That is, the supercompetitor cells in *C* grow even more than the hyperplastic cells in *B*, and the surrounding cells in *C* are being eliminated, unlike those in *B*. One consequence of cell competition is that overall organ size can be remarkably unaffected by the diverse growth rates of its constituent cell populations. In *Drosophila*, cells with higher Myc gene dose out-compete those with lower, and wild-type cells out-compete those with reduced ribosomal protein gene dose (2, 5).

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tumor progression. It is also possible that genes that are *not* mutated in tumor cells could still be required for their growth and survival (22), such as assassin genes that are required for cell competition to occur in *Drosophila* (11).

One obvious possibility is that that tumors may out-compete normal cells, such as supercompetitors that out-compete wild-type cells. If tumors benefit from consuming normal cells, this would be one mechanism by which microenvironment could contribute to tumor growth. Other scenarios are also possible. Normal cells may compete with tumor cells, which would need secondary mutations for protection from competition. For example, mutations in Warts/Hippo pathway genes can rescue clones of cells with mutations in a ribosomal protein gene; such cells would otherwise be eliminated by cell competition (9). Some anticancer therapies might discriminate against cancer cells by making them targets for cell competition. Tumors can be genetically heterogenous, so it is plausible that cell competition might occur between subpopulations of tumor cells. Finally, cell competition involves elimination of certain cells followed by compensatory proliferation, and it has been argued that compensatory proliferation of itself provides opportunities for tumor promotion, by virtue of the increased cellular turnover and potential mutation fixation that are involved (23).

These possibilities should be considered as more genes are identified in *Drosophila* and elsewhere because such genes might be suitable drug targets with selectivity for tumors over normal cells. It would be especially interesting to discover genes involved in apoptotic corpse engulfment, or in susceptibility to such engulfment, that are selected during cancer development. It would also seem worthwhile to better understand the functional consequences of phagocytic engulfment of tumor cells, or of normal cells by tumor cells, should such engulfment occur.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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