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Socializing with MYC: Cell Competition in Development and as a Model for Premalignant Cancer

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Studies in *Drosophila* and mammals have made it clear that genetic mutations that arise in somatic tissues are rapidly recognized and eliminated, suggesting that cellular fitness is tightly monitored. During development, damaged, mutant, or otherwise unfit cells are prevented from contributing to the tissue and are instructed to die, whereas healthy cells benefit and populate the animal. This cell selection process, known as cell competition, eliminates somatic genetic heterogeneity and promotes tissue fitness during development. Yet cell competition also has a dark side. Super competition can be exploited by incipient cancers to subvert cellular cooperation and promote selfish behavior. Evidence is accumulating that MYC plays a key role in regulation of social behavior within tissues. Given the high number of tumors with deregulated MYC, studies of cell competition promise to yield insight into how the local environment yields to and participates in the early stages of tumor formation.

In multicellular animals, cells reside within structured communities—tissues and organs—and rely on signals and interactions between them to communally oversee each cell's identity, survival, and rate of growth. Tissues and organs can therefore be considered social groups that are governed by societal rules. According to kin-selection theory the identical genetic relatedness of somatic cells fosters cooperative behavior (Hamilton 1964; West et al. 2002), which will promote development of organs as functional units and thereby the reproductive success of the animal as a whole. However, somatic mutations that allow cells to cheat or ignore communal rules can lead to pathologies such as cancer. Evolution has provided a variety of mechanisms of enforcing cooperation including those that safeguard the genome, ensure normal tissue architecture, and uphold developmental boundaries. In this review I discuss a process known as "cell competition" that is receiving new attention because of its relevance to development and cancer. Cell competition is initiated upon the recognition of cells perceived as weak by their more robust neighbors. The recognition elicits interactions that prevent the weaker cells from contributing to the animal. However, competitive behavior is also exploited by cells with deregulated oncogenes or tumor suppressors, to expand their territory at the expense of—and with assistance from—their cooperating, wild-type neighbors. A recent surge

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of interest in understanding competitive interactions between cells has fueled work to research to identify the genes and pathways involved. In this review, my primary aim is to discuss what is known about competitive interactions that are regulated by cell-to-cell differences in MYC activity.

COMPETITION: A MECHANISM OF ELIMINATING GENETIC HETEROGENEITY

Although organ development demands cooperation between cells, the introduction of a population of genetically dissimilar cells can promote interactions that are competitive.

This first caught the eye of *Drosophila* researchers during the generation of mosaics in imaginal discs, the primordial cells of the adult appendages. Mosaic discs composed of wild-type cells and cells with haploinsufficient mutations in genes that encode ribosomal proteins (called *Minutes* [*M*]) led to strong competitive interactions. On their own, *M*/+ cells are viable but slow growing because their ribosome deficiency makes them inherently weaker, but they produce phenotypically normal flies. However, when surrounded by wild-type cells, *M*/+ cells are actively eliminated and the wild-type cells overtake the tissue (Morata and Ripoll 1975; Simpson 1979; Simpson and Morata 1981). It was later shown that the elimination of the *M*/+ cells are eliminated by apoptosis, which requires the presence of nearby wild-type neighbors (Moreno et al. 2002). Thus, interactions between the weaker *M*/+ cells and relatively stronger wild-type cells cause loss of the *M*/+ cells. The cellular interactions that mediate cell competition are local, and competition between wild-type and *M*/+ cells is most intense at clone borders. The sharp increase in cell death at the clone edges has allowed competition between wild-type and M/+ cells to be followed by staining for the apoptosis marker, activated caspase-3 (Simpson and Morata 1981; Li and Baker 2007; Li et al. 2009). Cell competition is thus a mechanism that promotes cooperation among cells by eliminating genetic heterogeneity in tissues.

Social interactions of any kind have consequences for the actor and the recipient, and in cell competition the *M*/+ cells die and the wild-type cells proliferate to compensate for their loss. There is debate over whether the compensatory proliferation of "winner" cells is accelerated over normal rates in *M*/+ backgrounds (Martin et al. 2009; de la Cova et al. 2014), but it is well documented in other genetic backgrounds (Neto-Silva et al. 2010; Wu and Johnston 2010). The consequence of the additional growth is that the tissue has a larger than normal fraction of the "winner" cells at the expense of the weaker cells (in the vernacular of cell competition, the "losers"); however, normal overall tissue size is maintained. Defining characteristics of cell competition are listed in Table 1.

CELL COMPETITION IS CONSERVED AND COMES IN DIFFERENT FLAVORS

Since the discovery of cell competition using *Minutes*, a handful of other genes has been shown to induce cell competition when activated, and mutations in several signaling pathways have been shown to be subject to cell competition in wild-type mosaics (Tables 2 and 3). The first documentation of competition in a mouse *Minute* mutant came when the Belly Spot and Tail (Bst) mutant was found to carry a mutation in RpL24 (Oliver et al. 2004). Linkage of the mutation to coat color showed a clear competitive underrepresentation of *RpL24*/+ cells, indicating loser status, in chimeras. In *Drosophila* the outcome of the loser population is apopto-

Table 1. Hallmarks of cell competition

Context dependent: occurs only in mixed cell populations
Triggered by local differences in growth or cellular metabolism
Proliferation of winner cells is stimulated by loss of loser cells
Short range effect, stronger at the interface between loser and winner cells
Restricted by boundaries of developmental compartments
Tissue maintains appropriate size and pattern

Table 2. Mutations that lead to cell competition in mosaics

Gene name	Function	Allele type	Species	Outcome	Involve Myc?	Phenotype
RpL/+, *RpS*/+	Ribosome biogenesis	Loss of function (LOF)	*Drosophila melanogaster*, *Mus musculus*	Loser	N	Apoptosis
$myc^{-/-}$	Growth regulation	LOF	*D. melanogaster*, *M. musculus*	Loser	Y	Apoptosis
$stat^{-/-}$	Growth, immune regulator	LOF	*D. melanogaster*	Loser	N	Apoptosis
$yki^{-/-}$	Hippo signaling	LOF	*D. melanogaster*	Loser	Y	Apoptosis
$tkv/Bmpr1a^{-/-}$	Dpp/BMP signaling	LOF	*D. melanogaster*, *M. musculus*	Loser	Y	Extrusion, apoptosis
$scrib^{-/-}$	Epithelial polarity/integrity	LOF	*D. melanogaster*	Loser	Y	Apoptosis
$Igl^{-/-}$	Epithelial polarity/integrity	LOF	*D. melanogaster*	Loser	Y	Apoptosis
$mahj^{-/-}$	Epithelial polarity/integrity	LOF	*D. melanogaster*	Loser	ND	Apoptosis
$csk^{-/-}$	Src inhibitory kinase	LOF	*D. melanogaster*, MDCK cells	Loser	ND	Extrusion, apoptosis
p53	Transcription factor	Gain of function (GOF)	*M. musculus*	Loser	ND	Sensescence

Y, yes; N, no; ND, no data.

Table 3. Super competitors

Gene name	Function	Species	Outcome	Involve Myc?	Phenotype
Myc GOF	Growth regulation	*D. mel*, *M. musculus*	Winner	Y	Proliferation
Stat GOF	Growth, immune regulator	*D. melanogaster*	Winner	N	Proliferation
$APC^{-/-}$	Wnt signaling	*D. melanogaster*	Winner	N	Proliferation
$axin^{-/-}$	Wnt signaling	*D. melanogaster*	Winner	N	Proliferation
$hippo^{-/-}$	Hippo signaling	*D. melanogaster*	Winner	Y	Proliferation
$warts^{-/-}$	Hippo signaling	*D. melanogaster*	Winner	Y	Proliferation
Yki GOF	Hippo signaling	*D. melanogaster*	Winner	Y	Proliferation
RasV12 GOF	GTPase	MDCK cells	Loser	Y	Extrusion
Mahj GOF	Epithelial integrity	*D. melanogaster*, MDCK cells	Winner	ND	

Y, yes; N, no; ND, no data.

sis, but this may not be a general rule. When mildly stressed mouse hematopoietic stem cell precursors (HSCPs) compete with nonstressed HSPCs in mixed bone marrow repopulation experiments, the loser cells initiate a program of senescence rather than apoptosis (Bondar and Medzhitov 2010). Here, the relative cellular level of the tumor suppressor p53 dictates the direction of competition, and this is dependent on the presence of both HSPC populations. Cells with higher p53 activity induce the senescence program only when in mixed company with low-p53 cells (Bondar and Medzhitov 2010).

Repopulation experiments provide good examples of competitive behavior, and such experiments have shown that competition for antigen contributes to homeostatic size regulation of the immune system in vertebrates (Freitas et al. 1995). In these experiments irradiated mice were repopulated with equal mixtures of B lymphocyte precursors of different antibody diversity (McLean et al. 1997). The cell populations expanded equally well when seeded in hosts on their own but when mixed the cells with limited antibody diversity contributed significantly less to the final population size. Interestingly, the populations initially grew at the same rate, but competition altered their growth dynamics as the tissue reached its appropriate size (McLean et al. 1997). Whether this process is the same as cell competition is not clear, but other suggestive cases in vertebrates include the reconstitution of diseased rat liver with healthy fetal liver progenitor cells, where repopulation was competitive and was accompanied by increased apoptosis of host cells adjacent to donor cells (Oertel et al. 2006). Some of the first evidence for competitive interactions between genetically different cell populations was actually provided by mammalian embryologists using the creation of chimeric or mosaic embryos to generate cellular heterogeneity in studies of developmental potential (McLaren 1976; Rossant and Spence 1998; Tarkowski 1998).

An important caveat to studies of competition is that although an inability of mutant cells to populate an organ is often observed in mosaics, it may not always result from competitive interactions. Mutations in genes involved in regulation of growth, pattern formation, and cell fate specification can weaken cells or make them subviable. Such mutations may prevent proliferation through defects such as cell lethality, a block in the cell cycle or growth machinery, or loss of integrity leading to delamination. Although these cells are disadvantaged they are not "competed" from the tissue, rather they have an inherent defect that prevents their survival or proliferation. Competition can be distinguished from an inherent defect through a variety of experiments. Commonly, mutant cells are introduced into a genetic background, such as a strong M/+, that gives them a relative advantage. Viability and proliferation of mutant cells in the context of surrounding $M/+$ cells indicates that their demise in wild-type mosaics is owing to competitive interactions; if the mutant cells still die (or cannot proliferate) in a $M/+$

background, it is assumed that the mutation confers an inherent inability to populate the tissue.

Of all genes found to be involved in cell competition (Table 2), *Drosophila* MYC is the most extensively studied. MYC is encoded by the *diminutive* (*dm*) gene and is the sole homolog of c-MYC (see Gallant 2013). It was noticed that hypomorphic alleles of MYC led to flies that were smaller than normal with thin thoracic bristles, a phenotype usually associated with severe *Minute* mutations (Johnston et al. 1999). This raised the possibility that *dm* mutants would be subject to cell competition like $M/+$ cells. Clonal analysis confirmed that *dm* mutant cells were rarely recovered in mosaic tissues, and it was determined that these cells were eliminated through apoptosis (Johnston et al. 1999). Subsequent studies have shown that the intensity of competition by wild-type cells is determined by the level of MYC in the mutant cells: Competition is strongest against cells carrying the dm^4 null allele, whereas for cells with the hypomorphic dm^{P0} allele, in which MYC is still expressed at approximately 15% of wild type, competition is less severe (Wu and Johnston 2010; de la Cova et al. 2014). Very recently, two groups reported convincing evidence for MYC-regulated cell competition in mouse embryos (discussed below) (Clavería et al. 2013; Sancho et al. 2013).

MYC AND SUPER COMPETITION

In 2004 two groups reported that elevating the cellular level of *Drosophila* MYC less than twofold above normal in mosaic tissues had the striking effect of causing the death of nearby wild-type cells (de la Cova et al. 2004; Moreno and Basler 2004). Both groups engineered systems to heritably express MYC in marked clones of cells and followed the fate of the MYC-expressing cells and that of their neighbors. As reported previously (Johnston et al. 1999), MYC-expressing clones grew larger than controls; however, the surprise was that marked sister clones composed of wild-type cells actually grew less than controls (de la Cova et al. 2004). These experiments defined the phenomenon of "super competition" (Abrams 2002) as robustly growing cells that are able to not only outgrow but also actively trigger the elimination of nearby wild-type cells from the tissue.

Super competition by MYC obeys the rules of cell competition defined in the original $M/+$ experiments (Table 1) (Morata and Ripoll 1975; Simpson 1979; Simpson and Morata 1981). There are some interesting differences, however. For example, apoptosis of wild-type loser cells competing with high-MYC cells occurs diffusely over short range in vivo (de la Cova et al. 2004), whereas in $M/+$ loser cells apoptosis is detected specifically at the boundary of the cell populations (Li and Baker 2007; Li et al. 2009). The range over which wild-type loser cells die in response to MYC super-competitor cells suggested that cell–cell contact was not necessary, and this was confirmed in cell culture experiments. Cocultures of wild-type *Drosophila* S2 cells and S2 cells that expressed MYC led to competitive interactions identical to the experiments in vivo (Senoo-Matsuda and Johnston 2007). By using a transwell assay, it was shown that physical contact between the two cell populations was not necessary. Furthermore, conditioned medium (CM) from cocultures of these cells was sufficient to cause naive S2 cells to behave as if in competition: Apoptosis was induced in wild-type S2 cells when cultured in the CM, whereas the S2 cells that expressed extra MYC proliferated at an accelerated rate (Senoo-Matsuda and Johnston 2007). These results indicate that the competitive interactions are mediated by secreted factors, which appear to be produced by both cell populations (Senoo-Matsuda and Johnston 2007).

Since the realization of these properties of MYC, the list of super-competitor genes has expanded rapidly. The list includes the genes encoding APC and Axin, regulators of the Wingless/Wnt pathway (Vincent et al. 2011), the signal transducer and activator of transcription (STAT) (Rodrigues et al. 2012), and Yorkie (Yki) (Tyler et al. 2007; Neto-Silva et al. 2010; Ziosi et al. 2010), the *Drosophila* homolog of the Yes-associated protein (Yap) transcriptional

coactivator (Table 3). In addition, certain tumor suppressor genes act as "anti-super-competitors," as cells carrying mutations in these genes are converted into super competitors. Anti-super-competitors include the Warts/Lats and Hippo/Mst kinases (Tyler et al. 2007; Neto-Silva et al. 2010; Ziosi et al. 2010), the cell polarity determinants Scribbled (Scrib) and Lethal giant large (Lgl) (Froldi et al. 2010; Menendez et al. 2010; Chen et al. 2012; Schroeder et al. 2012), and the Lgl-associated protein Mahjong/VprBP (Tamori et al. 2010), among others (Table 3). Of interest here, the super-competitor function of several of the genes is due partially to increased MYC expression.

ROLES FOR CELLULAR BIOSYNTHESIS AND METABOLISM IN CELL COMPETITION

Cell competition requires mechanisms that alert cells to the presence of suboptimal or damaged cells, and implies that cells "know" themselves and can recognize other cells as similar or different. Because somatic cells are essentially all related, genetic differences that arise through mutation are probably immediately recognizable—for example, a mutation that causes differences in cell adhesion. How are more subtle changes like heritable alterations in gene expression recognized? Because cell competition is context dependent (so clearly illustrated by the opposite response of wild-type cells to simple changes in MYC expression) (Fig. 1A,B) alterations that change growth or metabolism are obvious considerations.

Ribosome Biogenesis and Protein Synthesis

The slow growth of $M/+$ mutants suggested that rates of cell growth or division could be important determinants in competition. MYC's conserved role in regulation of a number of genes involved in protein synthesis and ribosome biogenesis, including ribosomal protein (Rp) genes, which when mutant are classified as *Minutes* (Grandori et al. 2005; Grewal et al. 2005; see also Campbell and White 2014), also suggests a role in cell competition. Moreover, cells that overexpress MYC but also carry a heterozygous $M/+$ mutation no longer function as super competitors (Moreno and Basler 2004), and c-MYC's oncogenic behavior in a mouse model is abolished in the background of an Rp mutation (Barna et al. 2008).

However, several other reports indicate that local differences in rates of cell division or protein synthesis are not sufficient to induce competitive interactions. Increased activation of Dp110, the *Drosophila* PI3K and a potent growth regulator that increases protein synthesis does not lead to cell competition (Weinkove et al. 1999; de la Cova et al. 2004). Neither do cell-to-cell differences in the activity of Cyclin D/CDK4, another regulator of growth, cell division, and metabolism (Datar et al. 2000; de la Cova et al. 2004; Frei and Edgar 2004). In addition, an increase of the growth-promoting JAK/STAT pathway in cells in mosaic imaginal discs leads to competition with wild-type cells without increasing ribosome activity or MYC expression (Rodrigues et al. 2012). Similarly, *APC* or *axin* mutant cells, which have increased Wnt/Wingless signaling, compete effectively against wild-type cells in the absence of increased MYC or changes in ribosomal activity (Vincent et al. 2011).

These studies argue that although alterations in cell division, cell growth, or ribosome function are commonly associated with cell competition they are not sufficient to induce it. It is possible that these processes act as sensing devices in some cases, however. One way this could occur is if alterations in protein synthesis affected translation of key mRNAs that then modulated a process common to all competitive contexts.

Cellular Metabolism

A defining aspect of cell competition is the compensatory growth of winner cells. As described above, wild-type cells proliferate faster when mutant loser cells are eliminated (Neto-Silva et al. 2010; Wu and Johnston 2010; de la Cova et al. 2014), and in competitive coculture experiments MYC-expressing cells proliferate faster than they do in monocultures (Senoo-Matsuda

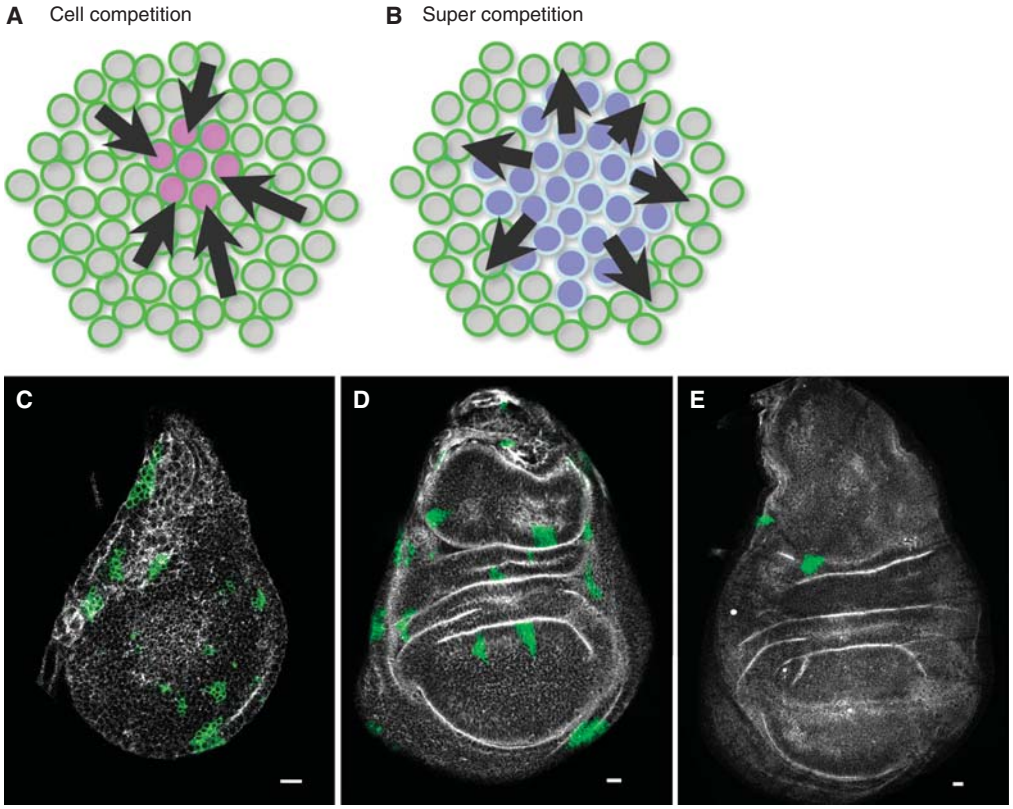

Figure 1. Cell competition and super competition. (*A*) Wild-type cells (gray and green) become "winners" when a population of relatively less fit cells (pink and green) appears. The wild-type cells instruct (arrows) the less fit cells to induce apoptosis, thereby eliminating them from the tissue. (*B*) In super-competition, wild-type cells (gray and green) become "losers" and undergo apoptosis owing to signals (arrows) from super-competitor cells (blue). The switch of wild-type cells from "winners" to "losers" illustrates the context-dependent nature of the competitive interactions. (*C–E*) MYC super-competition assay in *Drosophila* wing imaginal discs. All cells are wild-type but express a transgene (*tub* > *MYC* > *Gal4;UAS-GFP*, in which ">" denotes Flp recognition target (FRT) sequences) that imparts approximately a 1.5-fold increase in MYC expression above endogenous levels. Excision of the >MYC> cassette by heat-shock-driven Flp recombination yields green fluorescent protein (GFP)-positive clones of cells that no longer express extra MYC. These cells become "losers" owing to a relatively lower level of MYC and are competed away over time by surrounding cells that retain the MYC cassette. (*C*) Wing imaginal disc with GFP-positive "loser" clones 24 hours after clone induction. (*D*) Fewer clones remain in the wing disc after 48 hours because of competition from GFP-negative cells. (*E*) By 72 hours after clone induction, almost all GFP-positive clones are eliminated from the tissue.

and Johnston 2007). These observations indicate that acquiring "winner" status leads to growth stimulation, and implies that metabolism may need to be revved up for this to occur. Much evidence documents the powerful effect of increased MYC expression on cellular metabolism (see Dang 2013). Increased c-MYC stimulates glycolysis and lactate production even in an oxygen-rich environment, a symptom of the "Warburg effect," that is also observed in *Drosophila* (de la Cova et al. 2014). Glucose uptake and consumption increases, accompanied by up-regulation of genes such as glucose transporter *glut 1* and many of the rate-limiting enzymes of glucose metabolism. Production of lactate increases in MYC-expressing cells because of increased expression of the gene encoding lactic acid dehydrogenase (Ldh), which cat-

alyzes the reversible reaction of pyruvate to lactate. This reaction appears to be critical for MYC to promote growth in flies, because null alleles of *ldh* reduce the growth of MYC-expressing clones in imaginal discs (M. Ziosi, J. Tennessen, and L. Johnston, unpubl.). LDH-A is also required to promote c-MYC-mediated oncogenicity in a variety of MYC transformed cells (Shim et al. 1997), thus stimulation of glycolysis leading to extra lactate production appears to be an important event downstream from deregulated MYC. Increased MYC activity also stimulates mitochondrial biogenesis in vertebrates and invertebrates (see Morrish et al. 2008; Graves et al. 2012; Morrish and Hockenbery 2014).

Interestingly, acute changes in cellular metabolism appear to be critical for the "winner" phenotype during Myc super competition in *Drosophila*. New studies indicate that under competitive conditions, MYC-stimulated glycolysis is considerably enhanced, a finding that could be very relevant to progression of incipient tumors (de la Cova et al. 2014). Moreover, this enhancement requires p53, suggesting that p53 and MYC synergize in "winner" cells to promote metabolic regulation over and above what MYC does alone. p53 promotes metabolic homeostasis by regulating expression of genes that dampen glycolysis and increase oxidative phosphorylation, including the *synthesis of cytochrome C oxidase* (*scox*) gene in *Drosophila* (de la Cova et al. 2014) and its homolog *Sco2* in the mouse (Matoba et al. 2006). Remarkably, p53 is dispensable for growth and survival of nonmosaic MYC-expressing cells, but when these cells exist in mosaics with wild-type cells p53 becomes essential for their survival, for their enhanced glycolysis, and for their ability to kill off nearby cells (de la Cova et al. 2013)—in other words, for all aspects of the Myc super-competitor phenotype. The mosaic loss of *p53* in the absence of added stress does not cause competition in the mouse (Bondar and Medzhitov 2010) or in *Drosophila* (Wells and Johnston 2012), implying that p53 activity is induced because of the confrontation between the two cell populations. p53 may therefore function as a sensor of cell competition. This idea is supported by the observation that accelerated proliferation of wild-type "winner" cells competing with $M/+$ cells or *dm* mutant cells is also reduced in *p53* mutants, and suggests that the metabolism-boosting role of p53 could be generally required for the winner phenotype during competition (de la Cova et al. 2014).

SIGNALING PATHWAYS IN SENSING AND RECOGNIZING FITNESS DIFFERENCES

Transforming Growth Factor-β/Bone Morphogenetic Protein/Decapentaplegic Signaling

The conserved transforming growth factor-β/bone morphogenetic protein/decapentaplegic (TGF-β/BMP/Dpp) proteins function in signaling gradients to pattern tissues and control numerous processes during animal development, including cell proliferation, epithelial integrity, and cell fate specification (Perrimon et al. 2012). In *Drosophila* loss of Dpp activity through removal of the Dpp receptor Thickvein (Tkv) in clones of cells leads to their competitive elimination from the imaginal discs (Burke and Basler 1996). The *tkv* mutant cells are eliminated because they derepress the Dpp inhibitor Brinker (Brk), and Brk up-regulation in *tkv* mutant cells activates Jun-amino-terminal kinase activity and leads to apoptosis (Adachi-Yamada and O'Connor 2002; Moreno et al. 2002). Loss of Dpp was subsequently implicated in the competitive elimination of $M/+$ cells in mosaics by a similar mechanism. $M/+$ clones survived better in areas of the wing disc where *brk* expression is at its highest, and removing *brk* from these $M/+$ clones prevented their elimination by effectively increasing Dpp activity in the clones (Moreno et al. 2002). The elimination of wild-type cells by super-competitor activity of MYC-expressing cells can also be partially overcome by increasing Dpp activity (Moreno and Basler 2004). The Brk-Dpp regulatory axis regulates MYC expression (Prober and Edgar 2000; Doumpas et al. 2013), and because increased MYC will boost Rp gene expression, the ability of Dpp to rescue loser cells from com-

petition could partially be attributed to up-regulation of MYC.

Recently, two exciting papers revealed a role for c-MYC in cell competition in the mouse embryo, one deriving from analysis of loss of BMP activity and its effect on c-MYC expression. In cultures of mouse embryonic stem (ES) cells, Sancho et al. (Sancho et al. 2013) found that reduced BMP activity in one population of mixed cultures of ES cells led to cell competition. ES cells mutant for the Tkv homolog BMP receptor1a (BMPR1a) are defective in BMP signaling but retain pluripotency and in monoculture will proliferate at the same rate as wild-type ES cells. However, when mixed with wild-type ES cells, the *Bmpr1a* mutant cells had a significant proliferative disadvantage that was traced to an increase in apoptosis. Quite remarkably, the competition between *Bmpr1a* mutant and wild-type ES cells in coculture followed the same principles as in *Drosophila* cells (Senoo-Matsuda and Johnston 2007): Competition was associated with a difference in c-MYC expression between the two cell populations, competition did not require direct cell–cell contact between the populations, and competition was mediated by secreted factors shed into the culture medium (although in wild-type and MYC-expressing ES cell cocultures direct or close proximity between the two populations was required) (Clavería et al. 2013). As in flies, the growth advantage of the wild-type "winner" ES cell population was dependent on the death of the "losers."

The exit from pluripotency that normally occurs in preimplantation embryos and ES cells is accompanied by a decrease in c-MYC expression and correlates with an increase in apoptosis (Sancho et al. 2013). Although c-MYC down-regulation did not occur in monocultures of *Bmpr1a* mutant ES cells, it did in cocultures of these cells with wild-type ES cells. This prompted examination of whether competition required a pluripotent state. Strikingly, competition was blocked by conditions that maintained pluripotency, and further experiments showed that competition was specific to acquisition of competence to differentiate. An apoptotic fate associated with c-MYC down-regulation also occurred in tetraploid ES cells and *Atg5* mutant ES cells deficient for autophagy that were cocultured with wild-type ES cells, suggesting a common mechanism for cell elimination (Sancho et al. 2013). A second paper (Clavería et al. 2013) observed MYC-driven cell competition in epiblast cells of the mouse embryo. The investigators engineered an inducible recombinase-based system to make heritable, marked patches of cells that expressed different levels of c-MYC in mosaic embryos and found that the cells with higher MYC populated more of the developing embryo at the expense of the cells with lower MYC, which died via apoptosis. The highest level of c-MYC expression allowed otherwise wild-type cells to compete against nonexpressing wild-type cells (as did overexpression of c-MYC in ES cells [Sancho et al. 2013]) documenting c-MYC-mediated super competition in mammals (Clavería et al. 2013; Sancho et al. 2013).

Competition occurred early in development in a restricted window around embryonic day (E) 6.5, coinciding with the increase in endogenous apoptosis also noticed by Sancho et al. (Sancho et al. 2013). In addition, both groups noticed that c-MYC is expressed in the epiblast in a periodic manner (Clavería et al. 2013; Sancho et al. 2013), similar to MYC expression in the developing *Drosophila* wing disc (Johnston et al. 1999; Neto-Silva et al. 2010; Wu and Johnston 2010). In mouse epiblasts low-MYC expression correlated with cell death, potentially reflecting competitive interactions. Clavería and colleagues tested for endogenous cell competition by blocking competition-driven death in one population of mosaic embryos. Consistent with competition, most cells now survived and contributed to the embryo. However, not all cell death was prevented, suggesting that heterogeneity in MYC expression may rid the embryo of weak (but viable) cells, whereas competition-independent mechanisms eliminate nonviable cells that are unable to participate in embryogenesis (Clavería et al. 2013). Thus these two reports provocatively suggest that at early stages of mammalian embryogenesis cells survey their fitness relative to their neighbors and weed out those that are deemed unfit.

MYC and the Hippo Tumor Suppressor Pathway

Recent work in *Drosophila* indicates that MYC and the conserved Hippo growth inhibitory pathway engage in a codependent relationship with implications for growth regulation, cell competition, and neoplasia. In both mammals and in *Drosophila*, the activity of the Hippo signaling pathway regulates the activity of Yki/Yap in control of developmental growth and in neoplastic growth by preventing it from entering the nucleus and activating target genes (Pan 2010). Interestingly, Yki requires MYC function to drive cell proliferation in imaginal discs (Neto-Silva et al. 2010; Ziosi et al. 2010). Furthermore, Yki binds to the *dm* gene in wing discs and regulates its transcription. These proteins are codependent, because in the absence of Yki, expression of MYC is also unable to sustain proliferation. However, MYC remains able to promote cellular biosynthesis in the absence of Yki, suggesting that MYC's primary contribution to Yki-dependent growth is enhancement of cellular biosynthesis (Neto-Silva et al. 2010). Intriguingly, MYC indirectly regulates its own expression by controlling the expression of Yki, through both transcriptional and post-transcriptional mechanisms (Neto-Silva et al. 2010). This finding provides a mechanism for balancing MYC-regulated growth-promoting activity with Hippo pathway-mediated growth-suppressing activity. It also suggests that MYC expression is modulated on a cell-by-cell basis, and perhaps provides a mechanism for the heterogeneity in MYC expression that occurs in wing discs and in mouse embryos, mentioned above.

As would be predicted from the activation of MYC, clones of cells that express Yki acquire super-competitive properties and kill nearby wild-type cells, just as high-MYC cells do (Neto-Silva et al. 2010; Ziosi et al. 2010). Their super-competitive capability is owing to induction of MYC expression, because if the dose of MYC is genetically reduced the competitive advantage of Yki-expressing cells is abolished (Ziosi et al. 2010). Interestingly, coexpression of MYC and Yki leads to significantly more growth than expression of either factor alone, consistent with findings from mouse models that Yap and MYC synergize to accelerate tumor formation (Zender et al. 2006). Amplification of 11q22, the chromosomal region that contains Yap, is observed in several human cancers (Overholtzer et al. 2006), suggesting that deregulation of MYC by amplified Yap could contribute to tumorigenesis. Because c-MYC expression is increased by Yap activity in some mouse tissues, the combination of Yap amplification with the super-competitive properties of MYC could lead to particularly aggressive tumors.

Indeed, the relationship of Yki and MYC acts as a tumor accelerant after cells mutant for the cell polarity determinants Lgl, Dlg, or Scrib gain ground within a tissue. These genes are required to maintain epithelial cell integrity, and their absence in the whole tissue eventually leads to disorganized, rampant growth and loss of normal tissue structure. However, within mosaics, cells that lack one of these genes are eliminated by nearby wild-type cells via cell competition (Agrawal et al. 1995; Brumby and Richardson 2003). Recent work sheds some light on this difference in behavior. Clones of cells that lack *lgl* express MYC at low levels, which helps explain their competitive elimination by wild-type cells. The elimination of *lgl* or *scrib* mutant cell clones can be rescued by expression of MYC, activated Ras (RasV12) or Yki (both of which cause up-regulation of endogenous MYC), but also results in neoplastic transformation of the cells (Froldi et al. 2010; Menendez et al. 2010; Chen et al. 2012). RasV12 stimulates nuclear localization of Yki and activates Yki target genes in *lgl* mutant cells (Menendez et al. 2010); with time, these cells take on super-competitor status and expand their territory, lose normal polarity, and can acquire metastatic ability (Brumby and Richardson 2003; Pagliarini and Xu 2003; Igaki et al. 2006; Menendez et al. 2010).

Remarkably, *lgl* mutant cells can up-regulate MYC and become super competitors simply by being surrounded by a relatively weaker cell population such as $M/+$ cells (Froldi et al. 2010). The context-dependent behavior of

polarity mutant cells thus appears to be completely determined by the fitness status of their neighbors, rather than the *lgl* mutation itself. The cells are competitively eliminated when surrounded by more fit cells, but acquire super-competitor aggressiveness when surrounded by relatively weaker cells (Froldi et al. 2010; Chen et al. 2012).

Other factors also play important roles in the competition of cells deficient for polarity genes in *Drosophila*, including signaling by the c-Jun amino-terminal kinase (JNK) pathway and the tumor necrosis factor Eiger (reviewed in de Beco et al. 2012), and by the JAK/STAT pathway (Schroeder et al. 2012). In terms of MYC, however, an interesting insight into the aggressiveness of polarity mutant neoplastic tumors is that the negative-feedback relationship between MYC and Yki described above is lost in *scrib* mutant tissue (Chen et al. 2012), implying that MYC's ability to down-regulate Yki (Neto-Silva et al. 2010) is critical for restraining the tumorigenic potential of polarity mutant cells. This raises the very interesting prospect that polarity determinants play a role in the feedback mechanism.

The Code of Flower, a Putative Calcium Channel

An integral transmembrane protein thought to be a calcium channel has also been identified as a mediator of cell competition. Flower (Fwe) was first characterized in the nerve terminals of *Drosophila* photoreceptors as an integral membrane protein that associates with and regulates synaptic vesicles (Yao et al. 2009). Subsequently, it was identified in microarrays as a gene up-regulated during competition between wild-type and Myc-expressing wing imaginal disc cells (Portela et al. 2010; Rhiner et al. 2010). Fwe is normally expressed as three different isoforms with one, Fwe^{Ubi}, predominating (Yao et al. 2009; Rhiner et al. 2010). During competition Fwe^{Ubi} is down-regulated in the loser cells, whereas expression of two other isoforms, Fwe^{LoseA} and Fwe^{LoseB}, is increased. Because Fwe^{Ubi} remains expressed in the winner cells, a differential is thus set up (Rhiner et al. 2010). Expression of either Fwe^{Lose} isoform is sufficient to induce apoptosis in cells as long as they reside next to cells expressing Fwe^{Ubi} (Rhiner et al. 2010). This suggests that the different Fwe isoforms serve as flags that communicate cell identity or fitness. How the Fwe^{Lose} forms function mechanistically in the loser cells is not known, but presumably they have a role in regulating *hid* and/or *reaper*, the proapoptotic genes responsible for killing loser cells. Interestingly, another gene found in the microarray, the extracellular matrix protein Sparc, has a temporary protective effect on the loser cells, which might allow some designated loser cells a chance to recover and survive (Portela et al. 2010). Whether the Fwe^{Lose} isoforms have a role in inducing (or repressing) Sparc is not clear, because initial results suggest that expression or inhibition of either one does not affect the other (Portela et al. 2010).

The Fwe^{Lose} isoforms were shown to be expressed in loser cells of several different competitive contexts, including *scrib* mutants, *tkv* mutants, and $M/+$ mutant cells (Rhiner et al. 2010), implying that the Fwe^{Lose} forms play an important role in the loser cell fate. This has led to the proposal of a "Flower code" that acts as a downstream signaling event during competition that labels cells as "losers" and leads to their elimination (Rhiner et al. 2010).

CELL COMPETITION IN PREMALIGNANCY AND IN DEVELOPMENT

As is evident from the work described above, the parallels between super competition and the premalignant stages of cancer are striking. In the fly, a simple twofold increase in MYC expression is enough to render cells the ability to kill off their wild-type neighbors. With the demonstration that MYC expression confers super-competitor status in mouse cells (Clavería et al. 2013; Sancho et al. 2013) it seems clear that this non-cell autonomous function of MYC is conserved. This is troubling, as super competition is essentially a mechanism by which cancer cells could propel their own grim momentum. Both precancerous fields and established tumors could use super competition to kill non-

transformed neighboring cells to expand their territory. Heritable increases in c-MYC expression occur in numerous cancers of all major types and are often an early event (see Huang and Weiss 2013; Roussel and Robinson 2013; Gabay et al. 2014; Schmitz et al. 2014). It has been proposed (Moreno and Basler 2004) that cell competition could explain "field cancerization," a clinical finding in which patches of genetically related mutant cells with no overt phenotype slowly expand and acquire additional mutations that lead to frank tumors (Slaughter et al. 1953; Braakhuis et al. 2003). In humans, cells carrying precancerous mutations that are phenotypically silent for many years are not uncommon (Bissell and Hines 2011). Large patches of p53 mutations in skin cells, for example, can exist for years without causing harm (Zlegler et al. 1994) before eventually erupting into full-blown malignancy. What molecular and cellular events determine whether a tissue responds to the appearance of a cell with cancer potential by eliminating it or promoting its growth? The answer remains a mystery, although there are examples in the literature of tumor inhibition by neighboring stromal cells that prevent a precancerous field of cells from expanding (Stoker et al. 1966; Bissell and Hines 2011).

The evidence also argues that cell competition provides a developmental mechanism for culling tissues of cells perceived as dangerous early after their appearance. Cells found to be unfit are killed by apoptosis and thereby prevented from contributing to the animal. A recent demonstration that cell competition can occur in the follicular epithelium of the *Drosophila* ovary at a stage when the cells are postmitotic suggests that competition can promote homeostasis even in nonproliferating tissues (Tamori and Deng 2013). As pointed out (Clavería et al. 2013), competition may be especially important in animals in which somatic tissues must be functional over long life spans. The mechanisms regulating competitive interactions may have arisen as adaptive traits that promote fitness, first as a developmental cell fitness-monitoring system, and perhaps later as a "gatekeeper" for cancer. In this regard, the identification of an endogenous system of cell competition in mouse embryos and the finding that competition-induced apoptosis contributes to precision in organ size control in *Drosophila* (de la Cova et al. 2004) suggest that competition enhances tissue flexibility while at the same time setting its limits. In light of the restricted time window of competition in mouse embryos, it is also interesting to consider life strategies for which cell competition may be useful. Epiblast cells contribute to many organs, and competition between them can impact all developmental stages, whereas the contribution of cells of each imaginal disc, which grow during a juvenile (larval) stage are restricted to one organ in the adult *Drosophila*. Competition at each point has the potential to significantly impact the physiology, survival, and thus reproductive fitness of the animal, and may have evolved as a general mechanism of tissue optimization that is applied at points in development where cooperative interactions are especially important.

CONCLUDING REMARKS

Many of the genes found to be players in cell competition and super competition have vital physiological roles in animal development. The regulatory roles of MYC and p53 in growth, metabolism, and stress sensing are exceptionally well studied, and their freedom from regulation is central to tumorigenesis. The ECM component Sparc has been reported to have both anticancer and metastasis-promoting roles (Chong et al. 2012), and mice deficient in Fwe are less susceptible to skin papillomas, linking it to cancer (Petrova et al. 2011). How these factors and pathways intersect is an important avenue for study. What is the mechanistic contribution of the fundamental cellular processes like ribosome biogenesis or cellular metabolism to sensing and communicating cellular fitness? How does p53 function as a fitness sensor? The explorations into cell competition described here lay the groundwork for new ways of thinking about how a constructive social order is maintained during development and how it is undermined during tumorigenesis.

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