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REVIEW

Cell competition: the winners and losers of fitness selection

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ABSTRACT

The process of cell competition results in the elimination of cells that are viable but 'less fit' than surrounding cells. Given the highly heterogeneous nature of our tissues, it seems increasingly likely that cells are engaged in a 'survival of the fittest' battle throughout life. The process has a myriad of positive roles in the organism: it selects against mutant cells in developing tissues, prevents the propagation of oncogenic cells and eliminates damaged cells during ageing. However, 'super-fit' cancer cells can exploit cell competition mechanisms to expand and spread. Here, we review the regulation, roles and risks of cell competition in organism development, ageing and disease.

KEY WORDS: Cell competition, Fitness selection, Super-competition

Introduction

We are entering a new era in biology in which we are increasingly recognising that our tissues are composed of a highly heterogeneous collection of cells. Even identical cell types within the same individual show a vast degree of variation in signalling, proliferation, function and genotype. These findings have enhanced our understanding of multiple areas, from how tissues are formed in development to how cancer cells resist treatment. However, another implication of cellular heterogeneity concerns the social interactions between cells, particularly those with different fitness levels. One such type of interaction is cell competition, a 'survival of the fittest' mechanism, which removes viable cells that are less fit than their neighbours. The process has been described across multiple taxa, from flies to mammals, and from early stages of development to ageing organisms. Over the past 50 years, research into cell competition has expanded rapidly as the mechanisms, roles and ways to exploit the process have been probed. As this expansion has occurred, a number of questions have arisen, such as how do cells sense the fitness levels of neighbouring cells? What are the roles of cell competition in development and throughout life? Can we harness cell competition for therapeutic benefit? Here, we summarise key discoveries and discuss what progress has been made towards answering these questions, and outline exciting future directions for the field.

What is cell competition?

During cell competition, cells that would be viable in a homogenous environment are eliminated as a result of being surrounded by cells with increased fitness levels. The process can be divided into at least three stages (Fig. 1A). First, cells with heterogeneous fitness levels arise within a tissue. In the context of cell competition less-fit cells can be termed as 'loser' cells, whereas more-fit cells can be considered to be 'winner' cells. The second step of cell competition involves the loser cells being eliminated from the tissue. The mechanisms through which this elimination occurs are diverse: studies have described elimination through (1) apoptosis/cell death, (2) extrusion from the epithelia, (3) senescence, (4) phagocytosis or (5) cell differentiation. In this Review, we limit our definition of cell competition to examples where the ultimate fate of the less-fit cells is their death or senescence. For more information on cell competition through differentiation in stem cell niches, see the related review by Klein and Simons (2011). Finally, following loser cell elimination, compensation of tissue size occurs through increased proliferation or hypertrophy of surrounding winner cells. Because a key feature of competition is its 'silent' phenotype (despite loser cell elimination, a constant tissue size is maintained), winner cell compensatory proliferation is key to maintaining a constant tissue size. An exception is when cellular overcrowding triggers competition and this will be discussed later.

Historical background of cell competition

In 1881, the philosopher Wilhelm Roux proposed that cells within multicellular organisms are subject to the same evolutionary pressures as animals in the wild, and that this pressure could enhance organismal fitness by selecting against weaker mutations (Roux, 1881). Almost 100 years later, pioneering work from Morata and Ripoll described competitive interactions between wild-type cells and those lacking ribosomal genes (*Minute* mutants) in developing *Drosophila* tissues. Flies with heterozygous *Minute* mutations are viable and fertile, albeit with mild phenotypic abnormalities, including shortened bristles and slowed development. However, when clones of *Minute*$^{+/-}$ cells are formed in a wild-type background, these clones are eliminated by apoptosis and are not recovered in the adult fly wing (Morata and Ripoll, 1975). This observation of cell non-autonomous behaviour was the first to be classed as cell competition. Subsequent research led to the discovery of multiple mutations in developing fly tissues that turn cells into 'losers'. These mutations affect a diverse range of cell functions, including growth and protein translation [by reduction in levels of the transcription factor Myc (de la Cova et al., 2004; Moreno and Basler, 2004)], changes to cell signalling [by altered bone morphogenetic protein (BMP), Wnt, JAK/STAT and Hippo pathway activity (Burke and Basler, 1996; Neto-Silva et al., 2010; Rodrigues et al., 2012; Vincent et al., 2011)] and changes to cell pattering [by altered polarity gene expression (Agrawal et al., 1995; Brumby and Richardson, 2003; Menéndez et al., 2010; Norman et al., 2012; Yamamoto et al., 2017)].

A key discovery in the cell competition field has been that not only is it cells with compromised function that are removed from the tissue, but wild-type cells can also be eliminated by this process (Fig. 1B). Named 'super-competition', the process highlights the relative nature of cell fitness and cell competition triggers. The first example of super-competition was demonstrated through altering

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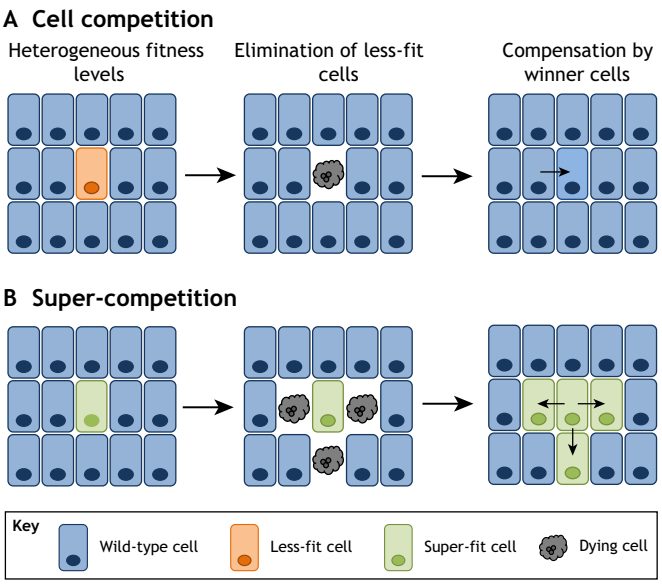

Fig. 1. Cell competition versus super-competition. (A) Less-fit but otherwise viable cells ('losers', orange) are eliminated when surrounded by wild-type cells ('winners', blue). (B) Super-fit cells (green) are capable of outcompeting wild-type cells that have reduced relative fitness.

the levels of transcription factor *Myc:* overexpression of *Myc* is sufficient to convert cells from losers into winners that are capable of outcompeting wild-type cells (de la Cova et al., 2004; Moreno and Basler, 2004). A number of mutations are now known to induce super-competition, many of which, like *Myc*, alter pathways that are also responsible for loser cell elimination, such as *p53*, JAK/STAT, Hippo and Wnt pathway activity (Bondar and Medzhitov, 2010; Neto-Silva et al., 2010; Rodrigues et al., 2012; Tyler et al., 2007; Vincent et al., 2011; Wagstaff et al., 2016; Ziosi et al., 2010).

Also in the early 2000s, an exciting advance in the field was made when cell competition was found to be conserved in developing mouse tissues (Oliver, 2004). Interestingly, some of the same mutations trigger cell competition in the mouse as in *Drosophila*, including in ribosomal subunit genes (Oliver, 2004), *Myc* (Clavería et al., 2013; Sancho et al., 2013), the apicobasal polarity protein scribble (Norman et al., 2012), BMP signalling pathway components (Sancho et al., 2013) and Hippo (Hashimoto and Sasaki, 2018 preprint). This conservation suggests that cell fitness is a quality that can be relayed between cells in tissues from different species.

Cell competition locations

The majority of cell competition work has been described in developing tissues. However, across flies and mammalian models, cell competition has also been described in adult tissues, e.g. between young cell types and their older counterparts in the liver and the blood (Martins et al., 2014; Oertel et al., 2006), and between sub-lethally damaged and wild-type blood stem cells (Bondar and Medzhitov, 2010). Cell competition even occurs in a range of post-mitotic tissues, such as the *Drosophila* follicular epithelium, intestinal epithelium and neuroepithelium, and the adult mouse heart (Kolahgar et al., 2015; Merino et al., 2013; Tamori and Deng, 2013; Villa del Campo et al., 2014). Also of interest are instances where cell competition does not occur. For example, in developing *Drosophila* imaginal wing discs, competition does not occur across compartment boundaries (Garcia-Bellido et al., 1973). During embryonic mouse development, out-competition of some mutant cell types occurs specifically during primed pluripotency but not in naïve pluripotency (Clavería et al., 2013; Sancho et al., 2013), and competition also does not occur in *Drosophila* histoblasts (Simpson, 1981).

What is cell fitness?

Despite its central role in defining the outcome of cell competition, it is still unclear what exactly determines competitive cell fitness. However, potential definitions can be inferred from the mutations that are known to trigger competition. Here, we discuss the different possibilities.

Growth rates

An early hypothesis posited that the parameter of cell fitness measured by cell competition is related to either the regulation of cell growth or proliferation, as various competition-triggering mutations can affect either one or both of these processes. For example, *Myc* over-expression increases cell size (Johnston et al., 1999), while *Minute* mutation primarily decreases proliferation (Morata and Ripoll, 1975). However, the observations that, in *Drosophila*, competition is not triggered through changing cell size via overexpression of cyclin D and CDK4 (de la Cova et al., 2004), by increased insulin signalling (de la Cova et al., 2004) or by decreased growth through reducing insulin signalling (Böhni et al., 1999; Verdu et al., 1999) suggest that relative cell size does not determine the outcome of cell competition. Similarly, although cells with mutations in polarity genes are fast proliferating, they are eliminated by relatively slower proliferating wild-type cells (Brumby and Richardson, 2003; Menéndez et al., 2010). This, together with the finding that cell competition occurs in non-proliferating tissues (Kolahgar et al., 2015; Merino et al., 2013; Tamori and Deng, 2013; Villa del Campo et al., 2014), firmly underlines that proliferation differences are also unlikely to drive competition.

Damage

Another common trigger of competition is differential activation of cell damage pathways. When expression of the damage-response gene *Trp53* (encoding p53) is elevated to non-lethal levels, cells become outcompeted in the blood (Bondar and Medzhitov, 2010), MDCK cells (Wagstaff et al., 2016) and developing mouse embryo (Bowling et al., 2018; Zhang et al., 2017). Although p53 does not seem to play a similar role in fly models of cell competition (De La Cova et al., 2014; Kale et al., 2015), an oxidative stress response is found in *Minute*$^{+/-}$ and *Mahjong* loser cells (Kucinski et al., 2017). Furthermore, overexpression of the oxidative stress response gene *Nrf2* is sufficient to convert cells into losers (Kucinski et al., 2017). This last finding indicates that alteration of the activation level of stress-response pathways is sufficient to lead to competition in the absence of any cellular damage, suggesting that fitness can be defined and communicated by the status of these pathways alone. When considered from an evolutionary perspective, there is a clear advantage in removing cells that have sublethal damage when there are healthier cells in the proximity, as it provides organisms with a mechanism to remove less-fit cells only if they can afford to do so.

Metabolism

The metabolic activity of a cell is another, less investigated, potential measure of cell fitness. Many triggers of cell competition have significant effects on metabolism, including *Myc*, *Trp53* (*p53*) and the mTOR pathway. Indeed, the glycolytic activity of *Myc*-overexpressing cells is crucial for super-competition to take place

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(De La Cova et al., 2014). Similarly, the elimination of oncogenic RasV12 cells in the mouse intestine is dependent on non-cell autonomous metabolic changes involving upregulation of glycolytic activity (Kon et al., 2017). It is not yet clear how metabolic differences can affect the competitive ability of a cell or be read between cells, although differences in the rate at which nutrients and growth factors are taken up or transduced by cells is one attractive possibility (see below).

In summary, there is still no clear consensus on the factors that determine cell fitness and trigger competition, although there is expanding evidence that cellular damage and metabolic activity strongly influence fitness. An important consideration is that cell fitness is a context-specific trait: a cell that acts as 'super-fit' in one context has no advantage in another. For example, overexpression of *Myc* triggers competition in developing *Drosophila* and mouse tissues (de la Cova et al., 2004; Moreno and Basler, 2004), but not in post-mitotic epithelia of the *Drosophila* follicular epithelium (Tamori and Deng, 2013). Similarly, *Trp53*$^{-/-}$ cells act as super-competitors in the developing mouse embryo (Dejosez et al., 2013), but additional damage is required for their selective expansion in the mouse gut (Vermeulen et al., 2013), in mouse hematopoietic stem and progenitor cells (Bondar and Medzhitov, 2010), and in MDCK cells (Wagstaff et al., 2016). These data highlight that fitness is not an absolute universal quality, but instead is heavily context dependent.

Types of cell competition

There is much debate as to whether cell competition operates through one 'universal' mechanism or whether there are several different types of cell competition. To date, no common pathway has been found that explains all the different types of competitive interactions that have been described. For this reason, we broadly categorise cell competition into three types (Fig. 2).

Competition for nutrients or growth factors

In the simplest model of competition, cells compete for limited levels of survival factors such as nutrients or growth factors (Fig. 2A). Most famously, the neurotrophic theory describes the phenomenon whereby neurons compete for limited levels of nerve growth factor, resulting in the culling of nearly half the originally produced cells (Raff, 1992). Similar mechanisms have been proposed to take place during *Drosophila* development. For example, limited levels of EGFR signalling support the survival of only a subset of cells in larval tissues (Parker, 2006), although it is unclear whether competition is fitness dependent in this context. In contrast, some studies also indicate that the elimination of less-fit cells in the developing imaginal wing disc results from competition for bone morphogenetic protein (BMP; Moreno and Basler, 2004; Moreno et al., 2002), although conflicting findings challenge this hypothesis (de la Cova et al., 2004; Martin et al., 2009). Cell competition in the early post-implantation embryo is dependent on reduced activation of the nutrient-sensing mTOR pathway in the outcompeted cell type, also pointing towards a trophic mechanism (Bowling et al., 2018). Finally, competition for interleukin-7 (IL-7) appears to mediate selection of young T cells over old T cells in the thymus (Martins et al., 2014).

Competition for space

Within an epithelium, cell crowding is sufficient to induce cell elimination (Fig. 2B). Mechanical, stress-induced competition was first predicted through computational modelling (Shraiman, 2005) and has now been validated in a range of biological contexts,

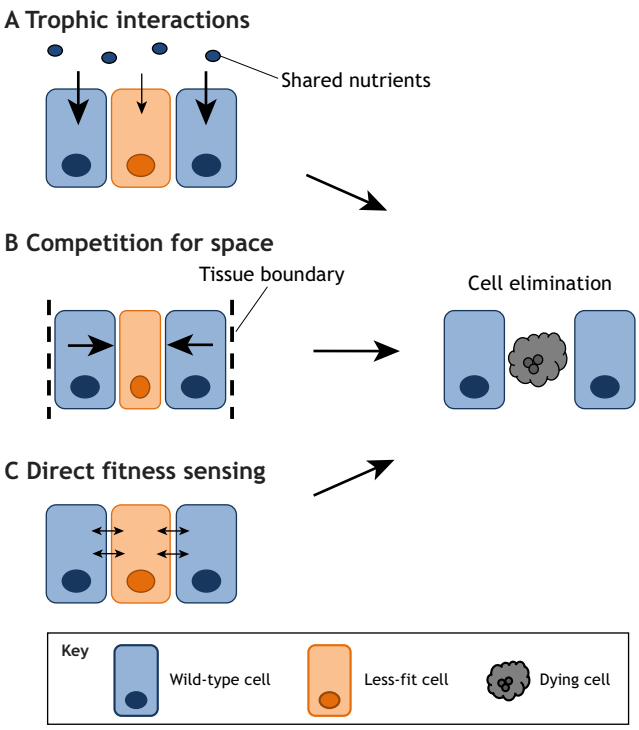

Fig. 2. Multiple mechanisms leading to cell competition. (A) Cells compete for a shared pool of nutrients. Loser cells (orange) may have a competitive disadvantage due to a reduced ability to take up nutrients or reduced signal internalisation/transduction (as indicated by a smaller arrow). (B) Cells compete for limited space in a confined epithelium. (C) Fitness levels are directly compared between cells using a cell fitness recognition code such as those mediated by the Flower genes or by Sas-PTP10D signal recognition.

including the human colon, the zebrafish epidermis, MDCK cell sheets and the *Drosophila* pupal notum (Eisenhoffer et al., 2012; Marinari et al., 2012; Wagstaff et al., 2016). In the pupal notum, slower growing cells are preferentially extruded over fast growing cells (Levayer et al., 2016), while polarity-deficient MDCK cells are eliminated in culture by their wild-type counterparts through mechanical triggers (Wagstaff et al., 2016). The finding that contact-based elimination of MDCK cells is triggered by elevation of p53 alone alludes to the possibility that the activation of cell stress pathways sensitises cells to mechanical stimuli, resulting in the preferential removal of damaged cell types.

Fitness-sensing cell competition

As well as 'passive' competition for limited nutrients or space, 'active' competition has been described, where cells are able to directly compare fitness levels through cell-cell communication (Fig. 2C). This fitness comparison is followed by apoptosis in the loser cells, which is triggered by the winner cells, or by loser cells recognising their own less-fit status, which leads to the activation of death pathways or the repression of survival pathways. A number of such fitness-sensing forms of cell competition have been described in *Drosophila* systems. The first described example is competition mediated by a group of cell membrane proteins encoded by the *Flower* (*fwe*) gene: in competitive environments in *Drosophila*, loser cells upregulate two 'lose' Flower splice isoforms, while surrounding cells express only the 'ubiquitous' isoform. As expression of the 'lose' isoforms is both sufficient and necessary for loser-cell death during competition, the 'FLOWER code' has been proposed to be a cell-surface marker of relative fitness status,

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which allows for the detection and elimination of less-fit cells (Merino et al., 2015; Rhiner et al., 2010).

More recently, a genetic screen identified new molecular components responsible for recognition and elimination of *scribble*$^{-/-}$ cells in *Drosophila* tissues (Yamamoto et al., 2017). Specifically, the cell surface receptor PTP10D in *scribble*$^{-/-}$ cells is recognised by the ligand Sas in wild-type cells. The authors observed that, at the interface between wild-type and *scribble*$^{-/-}$ clones, both PTP10D and Sas are relocalised to the lateral cell surface. Following this relocalisation, PTP10D is activated in loser cells, which sets off a signalling cascade that results in inhibition of pro-survival EGFR-Ras signalling and activation of pro-apoptotic Jun N-terminal kinase (JNK) signalling that induces *scribble*$^{-/-}$ cell death.

Finally, the observation that components of innate immunity pathways are required for the elimination of defective cells in *Drosophila* has led to the hypothesis that this mechanism, which is involved in host defence from foreign or altered-self cells, can be repurposed to eliminate less-fit cells (Alpar et al., 2018; Meyer et al., 2014). The authors of Meyer et al.'s study observed that, during cell competition, there is a repurposing of Toll-related receptors and NFκB factors, and this repurposing is required for the elimination of losers in *Myc*- and *Minute*-induced competition models. Interestingly, Alpar et al. have found that this role for an innate-like immune response is not found in a sterile environment, suggesting that infection needs to be present for this response. In contrast to this, another study has described a protective role for Toll signalling in the elimination of polarity-deficient cells (Katsukawa et al., 2018), with activation of this pathway being sufficient to prevent the elimination of these cells and turn them into winners. Therefore Toll pathway signalling appears to play a cell type- and context-dependent role in determining the outcome of competitive interactions.

In each of the cases above, the interaction between cells with different fitness levels leads to either the recognition of a differential fitness fingerprint (in the case of *Flower*), or the activation of a signalling cascade in the loser cells (in the case of PTP10D/Sas and innate immunity). However, it is important to note that the mechanisms driving the expression of 'low fitness' cell-surface receptors in the loser cells remains unknown, and as such it is unclear how detection of loser cells occurs. Furthermore, it is as yet unclear whether these fitness-sensing pathways have a role in regulating competition in mammalian systems.

The loser cell fate

In most competition models, the elimination of loser cells occurs through activation of apoptosis in the less-fit cell type. This has been described in many *Drosophila* models, where the JNK pathway acts as a key mediator of apoptosis in several studies (Kolahgar et al., 2015; Moreno and Basler, 2004; Moreno et al., 2002; Suijkerbuijk et al., 2016; Tamori and Deng, 2013), but not all (de la Cova et al., 2004; Tyler et al., 2007). In mouse development, competition is dependent on caspase activation and can be blocked through the use of caspase inhibitors (Bowling et al., 2018; Clavería et al., 2013; Hashimoto and Sasaki, 2018 preprint; Sancho et al., 2013). In other models, alternative cell elimination mechanisms have been described. For example, outcompeted hematopoietic stem and progenitor cells are eliminated from the functioning pool of cells through activation of senescence-like programs (Bondar and Medzhitov, 2010). Here, the authors suggest that the senescence-like phenotype permits continued proliferation and function of the loser cells, but marks them as damaged and so acts to facilitate gradual replacement by fitter cells over time.

Another form of loser-cell elimination is extrusion from an epithelium. This has predominantly been described in a subgroup of cell competition named 'epithelial defence against cancer' (EDAC). During this phenomenon, clones of cells with oncogenic mutations, including *RasV12*, *Src* and *Trp53*, are removed specifically when in a wild-type epithelium (Hogan et al., 2009; Kajita et al., 2010; Kon et al., 2017; Watanabe et al., 2018). The outcome of extrusion has both anti- and pro-tumourigenic roles in different circumstances. In some cases, extrusion will result in death of oncogenic cells through anoikis or necroptosis. However, if mutations are present that induce basal extrusion (Hogan et al., 2009; Kajita et al., 2014) or allow the cell to override anoikis (Leung and Brugge, 2012), EDAC can promote cancer outgrowth by removing the cell from the confines of the epithelium and promoting cell metastasis.

Engulfment of loser cells is another described mechanism of loser cell elimination. In *Drosophila* imaginal wing discs, loser cells are eliminated through engulfment by surrounding winner cells (Li and Baker, 2007) and engulfment of loser cells has also been observed in mouse ESCs (Clavería et al., 2013). Similarly, out-competition of wild-type cells by cells overexpressing EGFR and the microRNA miR-8 relies on engulfment proteins (Eichenlaub et al., 2016). However, as the cytoskeleton has many cellular functions, the rescue of competition following alteration of cytoskeletal components may be due to engulfment-independent cytoskeletal roles, such as an involvement in sensing mechanical stress (Wagstaff et al., 2016). Furthermore, other reports have contested a role for engulfment proteins in competition in developing *Drosophila* tissues (Lolo et al., 2012). Cell engulfment has also been implicated in cell competition between breast or pancreatic cancer cell lines and in non-tumourigenic cell lines derived from the equivalent tissue. This process, named 'entosis', is dependent on the cytoskeleton and correlates with mechanical deformability (Sun et al., 2014).

The winner cell fate

Despite the death of cells during competition, overall tissue size is not affected. In some cases, cell competition becomes activated in response to tissue overcrowding and the process itself eliminates surplus less-fit cells. In cases where tissue overcrowding is not a trigger of cell competition, once less-fit cells have been removed from the tissue, surrounding cells respond to fill the cleared space. In these circumstances, fine-tuned tissue compensation mechanisms by winner cells function to maintain tissue size. This aspect of cell competition has been less well investigated, although recent work has started to shed light on specific mechanisms at work.

In most contexts, increased cell proliferation accounts for compensation of cell number following cell competition. In the fly, JNK signalling is activated in apoptotic cells and this promotes the proliferation of surrounding cells through the release of paracrine growth-promoting factors such as Dpp (BMP homolog) and Wingless [Wnt homolog (Ryoo et al., 2004)]. In the fly gut, eliminated loser cells release Unpaired3, which promotes the increased symmetric division of intestinal stem cells through JAK/STAT pathway activation (Kolahgar et al., 2015). Interestingly, compensatory proliferation during elimination of *Minute* clones in *Drosophila* is associated with a re-orientation of cell divisions in wild-type cells adjacent to apoptotic cells in a process dependent on planar cell polarity genes (Li et al., 2009). Another strategy for tissue size control following cell death is compensatory cellular hypertrophy, whereby an in increase in cell size compensates for cell loss. Described in post-mitotic tissues, this process occurs through either endocycling (DNA duplication in the absence of mitosis) or

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cell fusion. These mechanisms have been described in non-dividing *Drosophila* epithelia following the removal of less-fit cells by competition (Tamori and Deng, 2013) and in response to damage (Losick et al., 2013).

Recently, two studies have further characterised the local and systemic compensatory responses to cell apoptosis. The first explores changes occurring in cell-cell contact following cell competition-induced cell death (Tsuboi et al., 2018). Elegant analysis of the cell junctions between outcompeted clones and their neighbours indicates that remodelling of cell contacts promotes the expansion of the winner cells. This compensatory behaviour aids the expansion of oncogenic clones in the fly epithelium. In the second paper, mechanisms orchestrating the regulation of cell number and tissue size following insult were investigated in the mouse (Roselló-Díez et al., 2018). The authors generated a genetic model in which *Cdkn1a* (*p21*) is overexpressed in a mosaic manner specifically in the left-forelimb developing bone, allowing the right-forelimb bone to serve as an internal control. Remarkably, left-right limb symmetry is not affected by this perturbation, indicating the existence of highly effective compensatory mechanisms, which enable catch-up growth in the limb containing *Cdnk1a*-expressing cells. This compensation involves both increased proliferation of wild-type chondrocytes in the bones containing *Cdnk1a*-overexpressing cells, as well as upregulation of growth factor IGF2 secretion from the placenta, pointing to both local and systemic size regulation mechanisms.

Cell competition: the good and the bad

The existence of competitive interactions between cells has a clear benefit in a multicellular organism. By ensuring that those cells best able to function and proliferate are more likely to survive, cell competition helps to maintain tissue integrity and optimise tissue function. However, when the mechanisms of selection employed by cell competition are used by the 'wrong' cell types, the process can act as a potent tumour-promotion mechanism at multiple stages of tumour development. Below, we discuss a range of beneficial and detrimental roles that cell competition may contribute to in the organism (Fig. 3).

Beneficial roles in development

Removal of damaged cells

Many of the cell types eliminated during development by cell competition present hallmarks of damage, such as p53 elevation (Bowling et al., 2018; Zhang et al., 2017) and oxidative stress (Kucinski et al., 2017). There is a clear advantage to removing damaged cell types prior to their propagation within developing tissues or their allocation to the germline, although until recently, the rate at which *de novo* mutations occur during development was

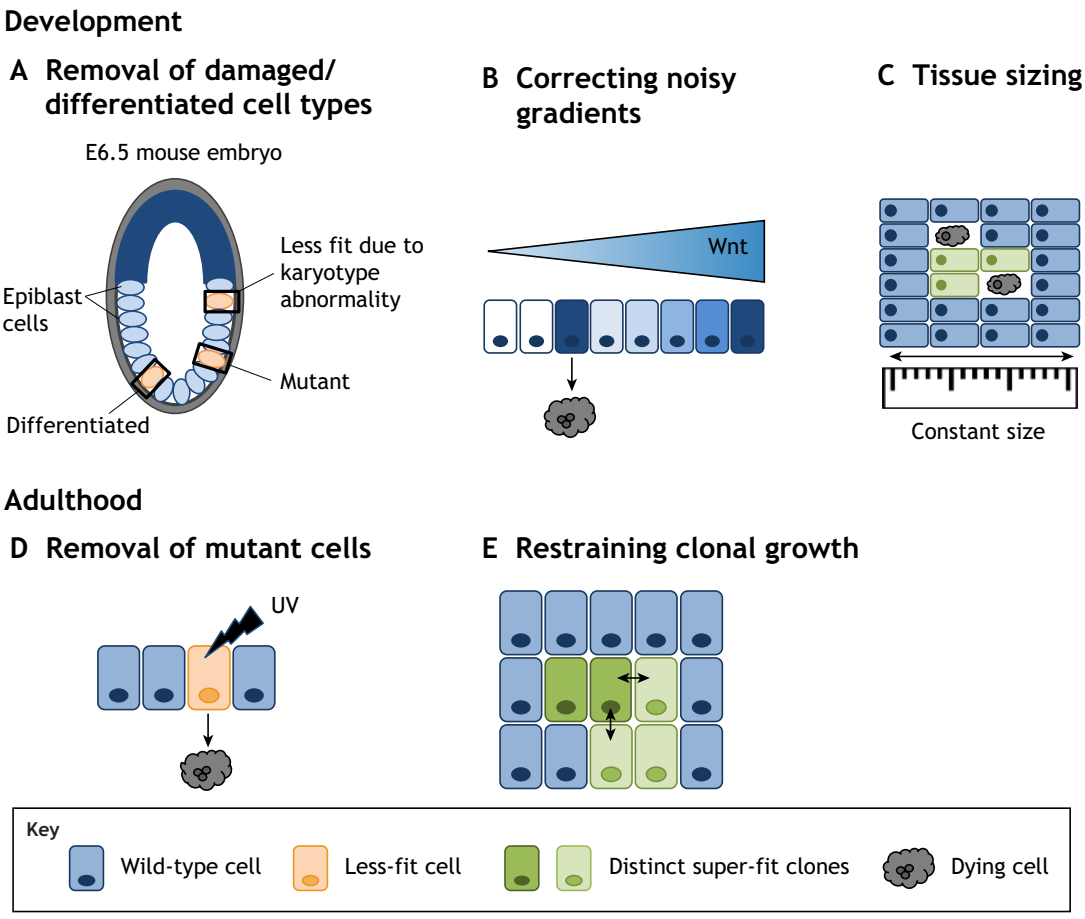

Fig. 3. Roles of cell competition in development and adulthood. (A) Cells that are mis-patterned, mutant or less fit as a result of karyotypically abnormalities (orange) are eliminated from the embryonic day (E) 6.5 mouse embryo. (B) 'Noisy' morphogen gradients are smoothened by elimination of cells with steep differences in signalling compared with neighbours. (C) Cell competition enables tissue sizing in development by adjusting for faster-growing cell populations (green). (D) Cells damaged by UV light (orange) in adulthood are eliminated through competition. (E) Competition between clones of mutant cells (green) restrains overgrowth of certain clones in tissues with high mutational burden. The double-headed arrow indicates mutual restraint.

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unknown. Whole-genome sequencing efforts have now provided average estimates of between one and two mutations per cell per division during human embryogenesis (Bae et al., 2018; Behjati et al., 2014; Ju et al., 2017; Lee-Six et al., 2018a). Although many of these mutations are likely to have a neutral effect on cell fitness, this finding indicates that cells with deleterious mutations could be formed naturally at non-trivial rates in the early stages of development. One possible cause of these mutations could be that in order to fulfil the increasing demands for body mass occurring during embryogenesis, there may be instances where the organism favours rapid expansion over slow but accurate DNA replication. The high cell proliferation rates described during early development (in mouse cell cycling time can be as short as 3 h; Snow, 1977) support this possibility and create a high potential for a cell to acquire mutations that deleteriously affect cellular fitness. Cell competition could then function as a quality-control mechanism to remove mutant cell types that would otherwise have negative impact on the organism at later stages. Given this role, one interesting possibility is that failure of cell competition and the persistence of mutated cells could be the origin of mutant clones that give rise to tumours in postnatal *Trp53*-null mice (Donehower et al., 1992). The new sophisticated DNA sequencing tools together with the insight we are gaining on how cell competition is regulated in the early embryo may help investigate this possibility.

Another example of how cell competition could contribute to the elimination of damaged cells relates to the elimination of aneuploid cells, an aberrant type of cell that is prevalent during early human development. Meta-analysis studies of data derived from chromosomal analysis of human embryos generated through *in vitro* fertilisation demonstrate that up to 80% of embryos contain karyotypically abnormal cells (van Echten-Arends et al., 2011). If similar proportions of these cell types exist in normal embryos, another plausible function of cell competition during early development could be to eliminate these types of cells (Fig. 3A). Supporting this hypothesis, aneuploid and tetraploid cells are eliminated from developing tissues in mice (Bolton et al., 2016; Sancho et al., 2013) and humans (Greco et al., 2015), and in the case of tetraploid cells this elimination has been shown to be through cell competition (Sancho et al., 2013).

Elimination of mis-specified cells

As well as removing cells with intrinsic damage, cell competition has been shown to remove cells that are mis-specified when compared with their neighbours (Fig. 3B). For example, mouse epiblast cells with defective BMP signalling become mis-specified when all the cells in the embryo have defective signalling (Di-Gregorio et al., 2007), but are eliminated by cell competition when surrounded by wild-type cells (Sancho et al., 2013). In addition, embryonic stem cells that have differentiated precociously are eliminated through cell competition when surrounded by cells with a more naïve status (Díaz-Díaz et al., 2017). A further example of the elimination of mis-specified cells can be found in the developing mouse blastocyst, where cell competition functions to remove cells that have not been specified to either the primitive endoderm or the epiblast lineage when their neighbours have (Hashimoto and Sasaki, 2018 preprint).

In all these contexts, cell competition is capable of removing cells that differentiate either too quickly or too slowly, but the question that arises is how do cells recognise that they are mis-patterned? A clue may come from studies in *Drosophila* and zebrafish. In both these systems, steep differences in Wnt signalling levels trigger cell competition (Akieda et al., 2018 preprint; Vincent et al., 2011). This suggests that cells may have an intrinsic mechanism to compare their signalling status with that of their neighbours, and raises the possibility that cell competition may also function to smoothen signalling gradients by removing 'noisy' cells (Fig. 3B) (Akieda et al., 2018 preprint), providing an additional layer of control to morphogenesis.

Tissue sizing

Finally, it is possible that cell competition forms part of a tissue-sizing mechanism (Fig. 3C). How organ size is regulated is a key issue in development, and various studies indicate that cell number is fine-tuned through the culling of over-produced cells. Cell competition has been proposed to regulate organ size by countering the increase in size of one highly proliferating population by inducing death of nearby slower dividing populations (de la Cova et al., 2004). Supporting this, overexpression of *Myc* in all cells of the developing *Drosophila* wing results in an increase in the size of the tissue (de la Cova et al., 2004). In contrast to this, heterogeneous overexpression of *Myc* results in apoptosis of surrounding low-Myc cells, which results in a normal size wing and therefore rescue of the large-size phenotype.

As discussed above when describing the types of cell competition, this process is also involved in the culling of overproduced cells in tissues. For example, developing neurons in the mouse compete for limited levels of nerve growth factor, a process that is thought to ensure the correct number of neurons innervate each cell (Raff, 1992). Similarly, cell survival within *Drosophila* tissues is governed by limiting levels of secreted EGF ligands, and this mechanism ensures correct compartment size is achieved even when cell proliferation rates are perturbed (Gilboa and Lehmann, 2006; Parker, 2006).

High levels of cell death also occur during mouse gastrulation (Manova et al., 1998). Indeed, our recent work demonstrates that inhibiting cell death at this stage leads to both an increase in cell number and an increase in the proportion of cells with low activation levels of the nutrient-sensing mTOR pathway (Bowling et al., 2018). Given that the mTOR pathway is downstream of growth factor and nutrient inputs, one possibility is that, similarly to what occurs with neuronal culling, in the early mouse embryo unwanted cells may be eliminated if they are unable to compete for a limiting pool of growth factors or nutrients. Interestingly, 'double-sized' embryos generated through aggregation of two or more blastocysts remain double-sized until gastrulation, where their size then scales to that of control embryos (Lewis and Rossant, 1982). This indicates that gastrulation is a key stage at which embryo size can be fine-tuned, and raises the possibility that the scaling that occurs with these double-size embryos may be due to this competition for growth factors or nutrients. Although producing excess numbers of cells followed by apoptosis may seem like a wasteful way of generating organs of the correct final size, it has been suggested that this may be the most evolutionarily efficient process, because initially forming the exact number of cells would require dramatically increased genetic complexity (Penaloza et al., 2006). Furthermore, overproducing cells would presumably increase the ability of tissues to recover from perturbation and to tailor cell number according to need.

Beneficial roles in adult tissues

Elimination of damaged cells

An important advance in the field was the demonstration that cell competition takes place not only during development, but can also act in the adult to promote tissue health. Experiments that provide compelling functional evidence supporting this hypothesis have

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been performed in flies, in which cell competition rates can be manipulated by altering the activation levels of a gene named *Azot*. It is currently unclear how *Azot*, a gene encoding a potential calcium-binding protein (Merino et al., 2015), affects cell competition. However, deletion of *Azot* leads to the inhibition of cell competition, which in turn results in reduced lifespan and increased signs of tissue degeneration in fly wings and brains. Furthermore, *Azot* mutant wings have reduced tolerance to UV exposure. These findings indicate that cell competition involving Azot clears damaged cells, enables buffering of tissues following damage, and provides a protective effect against neurodegeneration. Remarkably, increasing cell competition through expression of another copy of *Azot*, or expression of the apoptotic gene *Hid* under the *Azot* promoter, results in an increase in both lifespan and health span, as shown by a decrease in wing aberrations and neurodegenerative vacuoles. A more recent study by the same group has demonstrated that the *Azot* and *Flower* genes play a role in removing cells producing the amyloid-β42 peptide, a protein strongly implicated in Alzheimer's disease pathophysiology, and that this removal improves brain function (Coelho et al., 2018). Although similar findings have yet to be confirmed in mammalian systems, this study provides support for a role for cell competition in the clearance of damaged cells (Fig. 3D), which increases both health- and lifespan.

Anti-tumourigenic roles

Cell competition also has a number of proposed anti-tumourigenic roles (Fig. 4A). As described earlier, EDAC acts as a potent surveillance mechanism to remove small clones of oncogenic cells. Initially described as an *in vitro* phenomenon, the process has now been demonstrated in organoid and *in vivo* settings (Hogan et al., 2009; Kajita et al., 2014; Kon et al., 2017; Sasaki et al., 2018; Watanabe et al., 2018). Other tumour-suppressive roles of cell competition have been described in the immune system, where out-competition of old T cells by young counterparts prevents the development of tumours resembling T cell acute lymphoblastic leukaemia (Martins et al., 2014).

Cell competition has also been suggested to be involved in tumour suppression by mediating the competition between different types of mutant clones in a tissue (Fig. 3E). This is borne out by recent deep sequencing efforts that have revealed a remarkable degree of mutational diversity in tissue from normal, undiseased but aged (60 years+) human subjects, including the skin, oesophagus, intestine, endometrium and blood (Anglesio et al., 2017; Lee-Six et al., 2018b preprint; Martincorena et al., 2015, 2018). Importantly, many of these mutations affect known oncogenes and tumour suppressors. The question that then arises is how can such high mutational burden in non-diseased tissues be consistent with our current understanding of cancer development? Recent work suggests that competition between mutant cells within these epithelia could prevent individual clones from overdeveloping and forming tumours (Murai et al., 2018). This study found that although *Trp53* mutant cells clonally expand in a wild-type background, in a high mutation background, similar to that seen in non-diseased human tissues, *Trp53* mutant cells are less able to colonise tissues over time. One interpretation of these data is that competition with other mutant clones restrains *Trp53*-mutant cell proliferation. It may be possible, therefore, that the accumulation of somatic mutations with age has a role in preventing the clonal

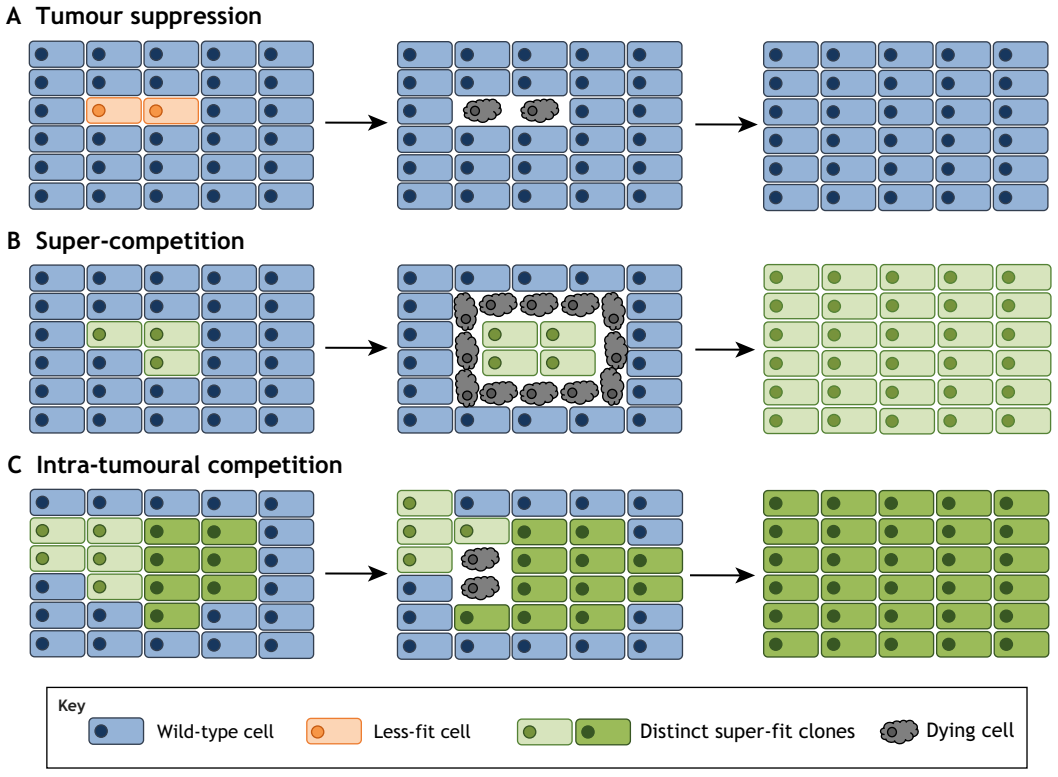

Fig. 4. Roles of competition during tumour progression. (A) Competition acts as a tumour-suppressive mechanism during early tumorigenesis. Cells that acquire detrimental mutations (orange) are removed from the tissue by apoptosis or extrusion. (B) Super-competition allows cells that acquire beneficial mutations (light green) to eliminate surrounding wild-type cells (blue), thus aiding their expansion in the tissue. (C) Intra-tumoural competition acts between distinct clonal populations or cell types within a tumour (light green versus dark green), therefore promoting the survival of subpopulations with increased fitness in later stages of tumourigenesis.

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expansion of cells with increased fitness through tumour-suppressive competition (Higa and DeGregori, 2019).

Detrimental roles: hijacking of cell competition by cancer cells

Tumour promotion through super-competition

As previously described, it is possible for cells to acquire mutations that allow them to eliminate wild-type cells in a process termed super-competition (Fig. 4B). This phenomenon of super-competition has been most convincingly demonstrated in cells that overexpress *Myc*, which outcompetes and eliminates surrounding wild-type cells (Clavería et al., 2013; de la Cova et al., 2004; De La Cova et al., 2014; Froldi et al., 2010; Levayer et al., 2015; Moreno and Basler, 2004; Sancho et al., 2013). Given that *Myc* is frequently upregulated in tumour cells, this observation suggests that tumour cells with high Myc levels may be able to create space for themselves through competitive interactions with adjacent cells. Additionally, if oncogenic Ras^{V12} or *Notch* are overexpressed in *scribble* or *Lgl* mutant cells, their elimination by EDAC is prevented and these clones demonstrate unrestricted growth (Brumby and Richardson, 2003; Menéndez et al., 2010). Thus, it seems likely that cancer cells with other oncogenic mutations may also be able to exploit super-competition to aid their expansion.

Super-competition has also been suggested in a mouse model of intestinal stem cell turnover (Vermeulen et al., 2013). This study showed that stem cells carrying mutations in adenomatous polyposis coli (APC), a negative regulator of WNT signalling, or stem cells that express the Ras oncogene homologue Kras, which promotes proliferation, have a selective advantage over wild-type cells. This selective advantage of mutant clones does not require apoptosis, but instead involves a biasing of the stochastic 'drift' of these stem cells towards the mutant clones and is similar to what has been previously observed in *Drosophila* stem cell niches (Amoyel et al., 2014; Snippert et al., 2014). Intriguingly, *Trp53* mutant stem cells have no selective advantage under normal conditions, but do preferentially replace wild-type cells under conditions that mimic colitis in the mouse (Vermeulen et al., 2013). Given the lack of elimination of loser cells, it is questionable whether these observations fall under the umbrella of the super-competition category. More-direct evidence of super-competition has been demonstrated in the *Drosophila* intestine (Suijkerbuijk et al., 2016). This study showed that $Apc^{-/-}$ clones induced in the *Drosophila* midgut lead to benign hyperplasia. The authors observed an enrichment of apoptotic cells surrounding the $Apc^{-/-}$ clones and wild-type clones surrounding the mutant clones were significantly smaller than in control guts, suggesting that they are being out-competed. Most interestingly, if apoptosis is prevented in the wild-type cells, not only is their clone size restored to that of control guts, but the growth of the $Apc^{-/-}$ clones is constrained (Suijkerbuijk et al., 2016). A similar observation was made by Eichenlaub et al., who examined cells over-expressing EGFR and mir8 in the *Drosophila* imaginal wing disc (Eichenlaub et al., 2016). These mutant cells can eliminate surrounding cells by apoptosis and give rise to metastatic tumours. As in the previous study, inhibition of apoptosis, and thus blockade of cell competition, constrains tumour growth and metastasis (Suijkerbuijk et al., 2016). These initial reports therefore hint at the possibility that manipulating cell competition could be a therapeutic strategy to inhibit tumour expansion. This is an observation that is supported by mathematical modelling of cancer treatment strategies, which demonstrates that boosting the survival and proliferation of wild-type or benign clones within the tumour would be an effective treatment strategy as it reduces the likelihood of resistance to treatment evolving (Maley et al., 2004).

One important consideration is that in many instances the effects of super-competition are only visible after a further insult. For example, cells lacking *Trp53* do not have a growth advantage over wild-type MDCK cells, but do expand through cell competition when the same monolayers are treated with non-lethal levels of Nutlin-3a, a p53 activator (Wagstaff et al., 2016). Similarly, $Trp53^{-/-}$ cells have a competitive growth advantage in colitis-damaged tissues in the mouse, but have no such advantage in non-diseased tissues (Vermeulen et al., 2013). This suggests that super-competition may be activated by an external insult, highlighting that mutant clone behaviour may be very different during tissues homeostasis than during stress. This importance is also implicit in exciting recent evidence demonstrating that the elimination of oncogenic RasV12 cells is attenuated in the guts and pancreas of obese mice, leading to an increased rate of tumour development (Sasaki et al., 2018). These studies open up a new realm of our understanding of cancer development. Could perturbation of cell competition dynamics account for increased cancer risk with age or tissue damage? Similarly, could drugs that affect cell competition mechanisms act as carcinogens by preventing the elimination of damaged cells, or by reducing overall tissue fitness and thereby enhancing the relative fitness of super-competitor cells? Further research in this direction is likely to yield exciting conceptual advances in our understanding of the steps leading to cancer development.

While the reports previously mentioned have relied primarily on *Drosophila* or mouse models of cell competition, some recent studies have provided preliminary evidence that super-competition could also occur in human cancer cells. One such study used the human breast cancer line MCF7 to show that cells transfected with *Myc* shRNA are out-competed by control cells (Patel et al., 2017). Another study examined the tumour-stroma interface in a number of human tumour samples and found a strong correlation between levels of *Myc* expression in the tumour and cleaved caspase 3 levels in the adjacent stroma (Di Giacomo et al., 2017). This study also made use of co-culture assays between paired human cancer cell lines with differing levels of *Myc* expression and showed increased apoptosis in those with lower Myc levels. Human tumour cell lines with active mutant Kras have also been shown to engulf and kill surrounding cells in a process known as entosis (Sun et al., 2014). Finally, it has also been found that SPARC, a protective protein produced in loser cells to delay apoptosis in some *Drosophila* competition models (Portela et al., 2010), is upregulated in stromal cells at the tumour boundary in some human cancers (Petrova et al., 2011). However, the relevance of this protein to competition has been disputed, as a subsequent study failed to detect *SPARC* expression in loser cells in *Drosophila* (Rodrigues et al., 2012).

Clonal competition within tumours

Finally, a further possibility is that competition could play a significant role within tumours to alter the evolution of clonal populations as the tumour progresses (Fig. 4C). It was previously thought that cancer evolution involved the linear acquisition of driver mutations in clones over time, which progressively increased their fitness and therefore gave them a cell-autonomous selective advantage over their predecessors. However, recent deep sequencing and single-cell analyses have revealed a high level of genetic diversity within tumours (Gupta and Somer, 2017). This challenges the model of linear evolution and raises the possibility that more complex interactions between clones, including both cooperative and competitive interactions, are also taking place (Marusyk et al., 2014). For example, as discussed above, it has been

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proposed that clonal diversity can prevent the expansion of certain mutation subtypes (Murai et al., 2018), which has been modelled mathematically and observed in mouse xenograft models of tumour heterogeneity (Marusyk et al., 2014; Testa et al., 2018). In contrast to this, non-cell-autonomous interactions that exaggerate the differences in proliferation rates between clonal populations in a tumour have also been proposed (Waclaw et al., 2015). However, neutral evolution also likely plays a significant role in tumour heterogeneity (Niida, 2018). Indeed, one study found that clonal selection in more than one-third of cancers only occurs at early stages prior to the onset of tumourigenesis and subsequent tumour evolution is neutral (Williams 2016). High intra-tumoural heterogeneity alone therefore does not prove the existence of positive or negative selection pressures. Given the complexity of the range of interactions invoked, and our lack of full understanding of the relative importance of cell-autonomous versus non-cell-autonomous effects of any given mutation, the precise importance of these interactions for tumour growth and heterogeneity will most likely be the subject of a great deal of future work.

Overall, these findings provide evidence that competition plays multiple roles during tumour development, and that, although it may be part of the host defence against cancer, it can also be exploited by tumours to aid their expansion and invasion. It is undeniably the case that the processes described here represent a broad range of non-cell-autonomous interactions that have been captured under the umbrella of cell competition and likely occur through distinct mechanisms. However, the field of competition underscores the importance of not considering cancer cells in isolation and investigating the potential ability of surrounding cells to both constrain and promote tumour growth.

Modelling competitive interactions between cells

Computational and mathematical modelling can be applied to cell competition because quantitative data can be derived from the differential proliferation rates exhibited by loser and winner cells in both non-competitive and competitive environments (Bove et al., 2017). Cell competition dynamics have been accurately modelled using equations borrowed from ecology, such as the Lotka-Volterra model (Nishikawa et al., 2016), which was first used to describe predator-prey interactions between animals in the wild. Use of mathematical models has also shed light on mechanisms of cell competition. For example, modelling cell behaviour in an epithelium indicated that mechanical forces play a role in the elimination of slower-growing cells (Shraiman, 2005), a prediction that was later confirmed *in vitro* and *in vivo* (Levayer et al., 2016; Wagstaff et al., 2016). Similarly, computational data have been used to demonstrate that compensation of cell number following elimination of mutant clones in the *Drosophila* intestine occurs through increased proliferation of surviving intestinal stem cells (Kolahgar et al., 2015). Finally, mathematical and computational modelling has provided insight into the role of cell competition in promoting the growth of mutant clones in non-diseased human tissue (Lynch et al., 2017). Going forward, such multi-disciplinary approaches are likely to be fruitful for understanding cell dynamics in a broader range of cell competition contexts.

Conclusions and future perspectives

The field of cell competition has developed rapidly in recent years. In particular, we are in the early stages of understanding the roles that cell competition plays in enhancing tissue and organismal fitness. Exciting future directions involve the role of cell competition in disease and ageing. In particular, what role does cell competition have in tumour evolution? It is clear from *Drosophila* studies that cell competition promotes expansion of oncogenic clones (Eichenlaub et al., 2016; Suijkerbuijk et al., 2016). Furthermore, the expansion of mutant clones in human skin is suggestive that competition mechanisms promote the selection of fitter clones (Lynch et al., 2017; Martincorena et al., 2015). However, it is still unclear whether this expansion in human tissues is fuelled by death of wild-type cells, as happens in *Drosophila* (Li and Baker, 2007), or occurs through more subtle mechanisms such as differences in stem cell self-renewal. Shedding light on these areas could be used to develop various areas in cancer research. First, new routes for therapeutic intervention could be opened up by targeting the driving forces of cell competition; this has been sufficient to contain tumour growth in *Drosophila* models (Eichenlaub et al., 2016; Suijkerbuijk et al., 2016). Second, further understanding into the tissue-specific nature of cancer driving mutations could be gleaned by exploring the context-dependent nature of fitness drivers (Schneider et al., 2017). Finally, evaluating clonal dynamics in cancers following treatment in the context of cell competition could yield greater insight into how resistance to chemotherapy is achieved.

Other key questions are: what role does cell competition have in physiological ageing? Are cell competition mechanisms maintained with age and, if so, do they provide important anti-tumour functions? Conversely, could cell competition mechanisms deteriorate with age, leading to a rise in age-related pathology? Although there is promising evidence to suggest that cell competition affects ageing in *Drosophila* (Coelho et al., 2018; Merino et al., 2015), opening up the investigation to mammalian systems will be crucial in establishing if altered cell competition dynamics can indeed be added to the hallmarks of ageing (López-Otín et al., 2013), and whether either boosting or blocking cell competition could therefore be a viable prevention strategy for age-associated disease.

Finally, we are at the early stages of establishing the endogenous rates and occurrence of cell competition in both developing and adult tissues. Recent technological advances in our ability to trace cells *in vivo*, through the use of somatic mutations as lineage-tracing markers, will enable clonal behaviour and competitive interactions to be better studied in physiological conditions and in human models (Lee-Six et al., 2018a; Ludwig et al., 2019; Osorio et al., 2018).

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