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Abstract

Cancer has long been regarded and treated as a foreign body appearing by mistake inside a living organism. However, now we know that cancer cells communicate with neighbours, thereby creating modified environments able to support their unusual need for nutrients and space. Understanding the molecular basis of these bi-directional interactions is thus mandatory to approach the complex nature of cancer. Since their discovery, MYC proteins have been showing to regulate a steadily increasing number of processes impacting cell fitness, and are consistently found upregulated in almost all human tumours. Of interest, MYC takes part in cell competition, an evolutionarily conserved fitness comparison strategy aimed at detecting weakened cells, which are then committed to death, removed from the tissue and replaced by fitter neighbours. During physiological development, MYC-mediated cell competition is engaged to eliminate cells with suboptimal MYC levels, so as to guarantee selective growth of the fittest and proper homeostasis, while transformed cells expressing high levels of MYC coopt cell competition to subvert tissue constraints, ultimately disrupting homeostasis. Therefore, the interplay between cells with different MYC levels may result in opposite functional outcomes, depending on the nature of the players. In the present review, we describe the most recent findings on the role of MYC-mediated cell competition in different contexts, with a special emphasis on its impact on cancer initiation and progression. We also discuss the relevance of competition-associated cell death to cancer disease.

Keywords: MYC, Cancer, Cell competition, Cell death

Abbreviations: MMCC: MYC-mediated cell competition; OE: overexpression; nTSGs: neoplastic tumour suppressor genes

1. General introduction

Cancer challenges researchers more than any other human disease, despite the heretofore unmatched effort to decipher its seemingly chaotic biology. While in the past cancer was considered as an autonomous disease, and treatments were mainly focused on hampering its ability to grow, it is becoming ever more clear that cancer cells initiate and maintain important relationships with their relatives and with the host tissue which deeply impact cancer evolution [1, 2]. Moreover, cancer proceeds by genetic and phenotypic diversification that, combined with clone selection, originates a heterogeneous milieu where reciprocal signalling plays remarkable roles in specifying malignant traits [3, 4]. Therefore, it is widely accepted that a better understanding of the molecular basis of cancer's social interactions is essential to devise novel therapeutic approaches [5].

MYC oncoproteins are deregulated in many different ways in a large fraction of human malignancies [6], where they play central roles in cancer initiation and progression by reprogramming a number of cellular processes [7]. In addition to fueling cancer by the promotion of autonomous cell growth and proliferation [8], MYC also impacts disease outcome by modulating tumour-stroma interplay [9, 10]. Another interesting interaction-based process primed by MYC is cell competition, initially discovered in *Drosophila* as a safeguard mechanism assuring organ homeostasis during development [11]. MYC is one of the most powerful activators of cell competition: adjacent cells showing disparity in MYC protein levels initiate a local battle for ground occupancy, with MYC low-expressing cells (called *losers* in the jargon of cell competition) dying from non-autonomous apoptosis induced by MYC high-expressing neighbours (called *winners*), which overproliferate and fill the vacant space [12, 13]. Given the relevance of MYC to cancer biology, MYC-mediated cell competition has immediately raised the interest of the scientific community, fostering a number of studies aimed at characterising the process at the functional and molecular levels in *Drosophila* and mammalian development [14-18]. In the last decade, MYC-mediated cell competition has been emerging to fulfil a primary role in additional aspects of physiology, from organ regeneration [19, 20] to cell stemness [21, 22], but also in pathological conditions such as cancer [23-27]. In this review, we will discuss the current body of research on the role of MYC and cell competition in development and cancer, dwelling upon the most recent findings obtained in *Drosophila* and mammals. In particular, we will discuss how MYC-mediated cell competition participates in different phases of cancer development and how the apoptotic cell death associated with this process can be relevant to cancer history.

2. The fundamentals of a notorious transcription factor

2.1. MYC history

MYC entered the history of biology about 40 years ago, when early studies on chicken fulminating tumours identified *v-MYC* as the transforming gene of avian myelocytomatosis virus [28, 29]. Soon after, the human homologue *c-MYC* was isolated [30, 31] and from those days onwards, *MYC* has become one of the most studied oncogenes, with a lot of information coming from studies in *Drosophila*. *Drosophila c-MYC* homologue is *diminutive* (*dm*), named after the small body size of mutant flies [32] well before its molecular characterisation [33]. Its product, called dMYC, shows poor sequence homology with the mammalian counterpart, but it exerts the same functions in cell growth as those carried out by mammalian c-MYC [34]. The high structural conservation of the regions containing functional domains indeed allows the two genes to substitute each other's function in reciprocal systems [33, 35]. For this reason, while describing consistent findings obtained in flies and mammals, both dMYC and c-MYC proteins will hereafter be referred to as MYC. In mammals, *MYC* gene family includes, besides *c-MYC, MYCN*, with similar functions but tissue-restricted expression [36], and *MYCL*, whose role is less well understood [36, 37]. MYC

proteins are evolutionarily conserved basic helix-loop-helix-leucine zipper (bHLH-LZ) transcription factors [38], whose C-terminal domain is used to dimerise with cognate proteins, forming the so-called MYC network [39]. The major partner of MYC in transcriptional activation is MAX (MYC-Associated protein X) [40], whose structure and function are well conserved in the fly [41], and MYC::MAX complexes bind DNA at short sequences called E-boxes [42]. Highly dynamic interactions among network members shape and refine MYC function in any given cellular condition, from flies to humans [43, 44], and recent work suggests that MYC promotes major changes in chromatin structure, regulating a large fraction of the genome by transcriptional activation or repression [45-48]. This concept is supported by the evidence that MYC network regulates transcription of protein-encoding genes, but also microRNAs-encoding *loci* [49] and long non-coding RNA sequences [50, 51], further to activate transcription of the three RNA polymerases [52-54].

2.2. Regulation of MYC expression

MYC's ability to maintain tissue homeostasis by promoting physiological growth and proliferation is mainly associated with development [34, 55-58]. Indeed, while it contributes to the maintenance of cells with regenerative and proliferative potential in adult organs [59-62], its activity decreases in differentiating progenitors to assure proper organogenesis [63, 64]. MYC is indeed one of the original Yamanaka's factors necessary to reprogramme committed cells into pluripotent stem cells [65].

Given its key roles in cellular physiology, and since even small increases in its levels can drive overgrowth [66], MYC expression is tightly regulated by a number of cellular activities [67]. Among the developmental signals converging on MYC to pattern cell and tissue growth, the fly morphogen Decapentaplegic (Dpp) and its mammalian orthologue Transforming Growth Factor β (TGFβ) have been found to control, directly or indirectly, *MYC* transcription [68, 69]. Another morphogenetic protein, Wingless (Wg), and its mammalian counterpart Wnt, are largely known to regulate *MYC* transcription alone [70, 71] or in combination with Notch [72], which can also regulate *MYC* promoter activity independent of Wg/Wnt [73-75]. The JAK/STAT signalling was also found to modulate MYC expression in the *Drosophila* intestine [62] and in B-cells, where JAK1 promotes lymphomagenesis by epigenetic activation of the *MYC* promoter [76]. Moreover, *MYC* transcription is regulated in *Drosophila* by the Hippo pathway downstream effector Yorkie (Yki) [77, 78] and by the Yki homologues YAP/TAZ proteins in mammals [79]. Of note, all these pathways have been so far implicated in cell competition [80], and their dysregulation contributes to human cancer [81-85].

With regard to MYC post-transcriptional regulation, several miRNAs have been shown to directly or indirectly target MYC mRNA in the fly [86-88] and in mammals [89, 90]. In addition, MYC protein levels are regulated by ubiquitin-mediated proteasomal degradation [91, 92]. The short half-life of the MYC protein [93] can be extended as a consequence of direct phosphorylation by kinases downstream of the Ras/MAPK and PI3K pathways [94-97], or by inhibition of the Glycogen Synthase Kinase 3β (GSK3β, which is known to target MYC for ubiquitination [98, 99]. Point mutations modifying the MYC residues targeted by GSK3β, found in sporadic cancers [100], possibly contribute to cell transformation by interfering with MYC degradation.

2.3. MYC relevance to cancer biology

As mentioned in paragraph 2.1, MYC is considered a global driver of transcription, regulating about 15% of all genes from flies to humans, with genes involved in cell cycle, cell metabolism, ribosome biogenesis, protein synthesis and mitochondrial function over-represented in its target network [47]

(Figure 1). Therefore, MYC deregulation leads to dramatic changes in cellular behaviour as a consequence of aberrant gene expression [101], achieved by inappropriate amplification of transcriptional programmes [102, 103].

The first evidence of MYC involvement in human cancer came from a genetic analysis of the Burkitt lymphoma, in which the high levels of MYC are due to the translocation of its coding regions downstream of a strong endogenous promoter [104]. In this case, overexpression of the wild-type form of MYC was sufficient as to drive tumorigenesis, and this was the first demonstration that MYC oncogenic properties were not due to gene mutations giving rise to activated forms of the protein, as it is for other oncogenes such as *Ras* [105]. Another mechanism increasing the expression of MYC in cancer is gene amplification: *MYCN* amplification is a recurrent and prognostic alteration in neuroblastoma [106, 107], while *MYCL* amplification is frequent in lung cancer [37]. Taking into account the workaholic nature of MYC as a transcription factor, different models have been proposed to explain the functional consequences of its overexpression in tumours, from global transcriptional enhancement [103] to amplification of specific gene expression programmes caused by different promoter affinities [108]. At present, the theories supporting differential gene regulation by tumour-specific MYC levels seem more consistent with all the data so far collected by the cancer community [109].

MYC upregulation elicits several important cellular responses that depend on MYC protein levels [110]; however, extremely high levels of this protein may overcome cell's capability to resist the stressful condition generated by aberrant transcription; excess MYC in normal cells can indeed result in genetic instability [111, 112] and autonomous cell death [113, 114] (Figure 1), whereas cancer cells exploit the extra-dose of MYC to accumulate mass and proliferate faster [115]. Therefore, the outcome of MYC activation seems to depend on whether the cells express a sufficient amount of pro-survival factors as to bypass essential apoptotic checkpoints.

3. MYC in physiological cell competition

3.1. Introduction

The intimate relationship between cell proliferation and cell death is intrinsic to any developmental programme, where a suitable balance between cell addition and cell elimination ensures tissue homeostasis [116]. The principles of competition and compensation lie at the heart of animal design; however, the process is not as elementary as it seems. The inherent characteristics of a given cell may make it fit enough to inhabit a certain tissue area, while totally inadequate to be part of a distinct region of the same tissue, depending on the fitness requirements of the specific context (Figure 2A). Any multicellular organism is indeed finely monitored, from development to death, by quality checking systems aimed at identifying, eliminating or modifying, any component that interferes with the physiological activity of the residents. Among these systems, cell competition detects viable but suboptimal cells in the context (losers) and removes them from the tissue, which is then usually replenished by overproliferation of the fittest (winners) [117]. Cell competition was first observed in the *Drosophila* wing disc (Figure 2A), a larval epithelial organ giving rise to the adult wing and thorax [118], where cells carrying mutations in genes encoding ribosomal proteins behaved as losers when confronted with wild-type cells [11]. In time, the concept of cell competition has been extended to mammalian systems, and several genetic conditions have demonstrated to make cells acquire a loser/winner status when adjacent to wild-type neighbours [119]. Of note, many of these conditions lower/increase MYC protein levels in mutant cells [21, 23, 68, 77, 120], highlighting its prominent role in the phenomenon.

3.2. MYC-mediated cell competition in Drosophila

In early '70s, cell competition was observed in mosaic wing discs containing cells bearing mutations in genes encoding ribosomal proteins, the so-called *Minute* (*M*/+) mutations [121]. While these cells were viable in a homotypic background, though slow-growing compared to wild-type cells [122], when adjacent to wild-type cells they were committed to death, and their loss was compensated by consistent overproliferation of the winners [11]. Cell competition has thus emerged as a mechanism necessary to eliminate viable but suboptimal cells in favour of the fittest, assuring that the developing organ will not undergo morphogenetic alterations due to genetic heterogeneity [123]. The process obeys developmental constraints: cell competition indeed occurs within but not across the borders of a given compartment [124]. MYC entered the still poorly characterised topic of cell competition in 2004, when two parallel studies showed that an equivalent phenomenon took place when cells with different levels of MYC grew juxtaposed in mosaic wing discs [12, 13]. Cells expressing lower levels of MYC behaved as losers and died by apoptosis, while cells with higher levels of MYC behaved as winners and overproliferated at their expense [12, 13]. The modulation of other cell growth inducers was not sufficient to activate cell competition [12, 13], which apparently accounts on additional properties of the MYC protein. In addition, although ribosomal proteins act downstream of MYC in cell competition [12], *Minute*- and MYC-mediated cell competition can use different molecular mechanisms to execute cell competition [125]. Several leading laboratories in the field have used *Minute*, MYC and other paradigms of cell competition to investigate in *Drosophila* mosaic tissues the mechanisms responding to competitive stimuli in loser and winner cells [119]. Here we focus our discussion on the findings derived from studies on MYC-Mediated Cell Competition (MMCC).

Cells bearing hypomorphic *MYC* alleles in mosaic tissues have been found to transduce sub-physiological levels of Dpp and to show a consistent upregulation of the Dpp-repressed gene *brinker* (*brk*) [126], leading to activation of the c-Jun N-terminal Kinase (JNK) pathway [12], known to mediate apoptotic cell death in the wing disc [127]. The overproliferation of the winners relied on losers' death, since inhibition of the JNK pathway or overexpression of anti-apoptotic proteins in the prospective losers blocked MMCC [12]. Moreover, activation in the loser cells of the Dpp pathway by constitutive expression of the Thickveins (Tkv) receptor [12], or knockdown of the repressors Brk or dNAB [128], made them resist untimely death. As Dpp is known to regulate MYC expression in the wing disc through *brk* [68], it is possible that Dpp signalling reactivation in the loser cells rescues them from death partly by increasing MYC levels. The Dpp pathway is also involved in a peculiar form of MMCC observed in the *Drosophila* germline, where stem cells with low MYC levels are physiologically expelled from the niche and undergo differentiation [21]. Niche cells secrete high levels of Dpp, and the empowered metabolism of high-MYC-expressing stem cells may outcompete the low-MYC-expressing neighbours by differential eagerness for the stem factor Dpp [21]. In this case, homeostasis of the stem compartment is guaranteed by simple displacement and differentiation of the weakest cells. Another partner of MYC found necessary to MMCC completion in the *Drosophila* wing disc is the oncosuppressor p53: MYC overexpression (MYC OE) in cells lacking p53 wild-type function indeed impairs their metabolism, reduces their viability and their killing activity, ultimately hampering cell competition [129].

The induction of MMCC in the wing disc has also allowed isolating a series of genes specifically expressed in loser or winner cells in the early stages of competition: the most part of them encode membrane proteins, suggesting this phase mainly depends on cell-cell interactions [130]. Among those, *flower* (*fwe*) has been shown to mark the surface of winner and loser cells with different protein isoforms: full-length $Flower^{Ubi}$ is displayed by the winner cells, whereas the truncated $Flower^{LoseA}$ or $Flower^{LoseB}$ isoforms are expressed by the loser cells [130]. A "Flower code" involving the Ubi and the LoseB forms has also been found to play a role in the physiological

elimination of supernumerary post-mitotic clones in the fly retina [131] and in the regeneration of injured adult fly brains [132], showing that different cell lineages, in physiological or in stressful conditions, have evolved similar strategies to restore organ homeostasis. In addition to Flower, another membrane protein identified as an early marker of MMCC is Sparc, whose upregulation in loser cells in the early phases of cell competition offers them transient protection by setting a higher threshold for caspase activation, so restricting death to the unnecessary cells [133]. The cell-autonomous fitness signals from Flower^{Lose} and Sparc protein levels, together with the levels of Flower^{Lose} isoforms in neighbouring cells, are then integrated into the transcriptional regulation of Azot in the loser cells [134]. Azot has been characterised as a cell-fitness checkpoint protein, active in many different competitive contexts, whose physiological expression in viable but unfit or misspecified cells restricts morphological alterations and tissue degeneration, increasing longevity [134]. Flower^{LoseB} and Azot have also recently been found to be necessary to the neuronal death induced by toxic peptides in a *Drosophila* model of neurodegeneration: neuron culling is also in this case mediated by fitness comparison and, contrariwise to common knowledge, the death of unfit neurons ameliorated motor and cognitive functions, possibly allowing dendritic arborisation of the neighbouring healthy neurons [135].

Besides inducing the expression of "fitness fingerprints" in the confronting cells, MMCC has been found to stimulate a bi-directional signalling composed of still uncharacterised soluble factors [136]; consistent with this view, an *in silico* screening has led to the identification in the *Drosophila* genome of some miRNAs potentially involved in cell competition whose human homologues are involved in different types of cancer [137].

With regard to the clearance of the dying cells, they undergo basal extrusion and apoptotic corpses are engulfed and eliminated by circulating hemocytes, the *Drosophila* macrophages [138]. The question about how circulating hemocytes can identify dying cells has been addressed by a successive study, which has demonstrated that loser cells secrete Tyrosyl-tRNA Synthetase which, following to metalloprotease-dependent cleavage, releases the evolutionarily conserved Endothelial Monocyte-Activating Polypeptide (EMAP) fragment, able to guide the hemocytes towards the dying cells [139].

Finally, different laboratories investigated the possibility that the mechanisms implemented by the innate immune system to detect pathogens may also be used to eliminate potentially dangerous cells in a developing tissue. The innate immune response is governed by the Toll receptors and the immune deficiency signalling pathway [140]. Recent studies have revealed that MYC OE in mosaic wing discs autonomously increases the synthesis of some proteases which process the ligand Spätzle for secretion, allowing its binding to Toll receptors in the adjacent loser cells, whose activation promotes NFkB-mediated apoptosis [125, 141]. This mechanism has however been demonstrated to be infection-dependent, as it does not occur when working in axenic conditions, so the local production of the ligand Spätzle and its proteases may be the result of a systemic response to infection [142]. In a different study, Toll signalling has conversely been found to promote the survival and growth of polarity-deficient cells by activating the Hippo pathway effector Yki in the prospective losers [143], highlighting the essential role of the intrinsic genetic background of the confronting cells in interpreting the signalling activated by the competitive stimulus.

3.3. MYC-mediated cell competition in mammals

About thirty years after the observation of cell competition in *Drosophila* [11], a pioneer study demonstrated that murine cells bearing a mutant form of a gene encoding a ribosomal protein were severely outcompeted by wild-type cells in chimeric blastocysts, with about one half of embryos and adults composed exclusively of wild-type cells [144]. Since then, a number of examples of cell

competition have been observed and characterised in different physiological contexts, from development [145-147] to regeneration [148, 149], confirming that cell competition is a general feature of metazoans, whose impairment can result in pathological tissue aberrations [80]. Also in this case, we will concentrate our attention on relevant findings derived from studies on MMCC, which have brilliantly shown how this phenomenon may conserve its intact essence in different cell histotypes, from development to adulthood.

In 2013, two independent studies investigated the role of cell competition in mammalian Embryonic Stem Cells (ESC) [147, 150]. Rodríguez and colleagues showed that, in mosaic embryos, cells defective for the murine homologue of the Dpp receptor Tkv, BMPR1A, were eliminated at the epiblast stage of development [147]. Mutant ESC were consistently out-competed when co-cultured *in vitro* with wild-type ESC; those competitive interactions were found to be apoptosis-dependent and to occur independent of any cell-cell contact [147], as it was previously shown for *Drosophila* S2 cells overexpressing MYC co-cultured with, but physically separated by, native S2 cells [136]. These findings indicate that some still uncharacterised soluble factors are involved in the process. In addition, wild-type ESC showed higher levels of MYC respect to the *Bmpr1a* mutant cells when in co-culture, and mouse epiblast at day 6.5 showed chimeric MYC expression (Figure 2B), with a coherent pattern of apoptotic death in cells expressing lower MYC levels [147]. Torres and colleagues investigated in deeper detail the role of MMCC in mouse embryogenesis, demonstrating that endogenous MMCC selects for cells with higher metabolic activity (Figure 2B), and engineered MYC high-expressing ESC were able to outcompete wild-type cells either *in vivo* or in *in vitro* co-culture assays [150]. A similar mechanism has not been found to occur in the extraembryonic tissues, indicating that selection of the fittest cells is especially relevant in long-lived somatic tissues. In a successive study, the authors demonstrated that MYC levels in ESC positively correlate with stemness, and MMCC restricts premature differentiation by eliminating MYC low-expressing cells before gastrulation [22]. On the other hand, MYC downregulation during gastrulation, necessary to coordinate exit from pluripotency and differentiation, may prevent inappropriate competitive interactions among different cell lineages.

MMCC has also been found to cause cardiomyocyte replacement both in development and adult life, showing it is not a process restricted to stem cell populations [19]. Although previous studies demonstrated that MYC OE leads to cardiac hyperplasia in developing mice [151] and to hypertrophy in adult organs [152], mosaic hearts composed of cells expressing high *vs* endogenous levels of MYC did not undergo pathological growth [19]. MYC high-expressing cardiomyocytes eliminated and replaced the wild-type neighbours through short-range cell-cell competitive interactions without affecting organ development [19] (Figure 2C). In a successive study, the authors expanded on previous work by investigating the role of MMCC in the epicardial cell lineage, which is known to contribute cells to the developing heart and to the injured adult myocardial tissue [20]. They found that, similar to what happens with myocardial cells, epicardial cells overexpressing MYC are able to colonise the epicardial-derived lineage (Figure 2C) and show increased ability to invade the myocardium [20], confirming the putative relevance of MMCC to the emerging field of regenerative medicine.

The role of MMCC was also assayed in mouse embryo fibroblasts: Sasaki and colleagues established an *in vitro* system based on co-culture assays of TEAD activity-manipulated fibroblasts, showing that cells with increased TEAD activity overcame the wild-type neighbours [120]. TEAD stands for Transcriptional Enhanced Associate Domain proteins, which bind YAP/TAZ co-activators downstream of the Hippo pathway and activate transcription of target genes [153]. In the same study, TEAD was observed to upregulate *MYC* RNA, and the authors demonstrated that MYC OE was *per se* sufficient as to outcompete wild-type counterparts [120]. Altogether, these findings

collected in different experimental models mean that cell competition can be regarded as a fully-fledged process regulated by MYC (Figure 1).

4. MYC in cancer-associated cell competition

4.1. Introduction

The ability of MYC-upregulating cells to supersede the wild-type neighbours within a tissue, referred to as "super-competition" [12], while maintaining the correct homeostasis in developing organs, can allow inappropriate expansion and consistent accumulation of oncogenic mutations in adult somatic tissues. Since its identification as a mechanism coupling the elimination of the weakest cells to the propagation of the fittest genotype, cell competition has thus been speculated to play a role in cancer [16, 154, 155]. In this section, we discuss the up-to-date body of evidence on the involvement of MMCC in cancer initiation and progression obtained in different experimental models, from flies to mammals.

4.2. MYC-mediated cell competition in cancer initiation

Recently, an interesting study found a mechanism by which oncogenic MYC may promote tissue invasion by cell competition. The authors observed that the contact surface shared by winner and loser cells positively correlated with the strength of cell competition, and that cell-cell intercalation, a process occurring throughout animal development by which neighbouring cells exchange places with one other, was necessary to eliminate loser cells [156]. Lower levels of F-actin in the loser cells as compared to the winners favoured the stabilisation of low-tension loser-loser and loser-winner contacts; on the other hand, high-tension winner-winner cell contact stabilisation was restrained, supporting tissue invasion by the winner cells [156]. Moreover, the authors demonstrated that reducing tension at the anterior/posterior (A/P) border of the wing disc, which is known to prevent inappropriate cell mixing [157], was sufficient as to increase winner/loser shared surface, marked by Fwe^{Lose} expression in the loser cells [156]. This finding may explain competition restriction by developmental boundaries [124]. Since tumour parenchyma is stiffer than normal tissue [158], it possibly uses cell-cell intercalation to invade and propagate into the organ, and "fitness fingerprints" may be particularly visible at the tumour borders. The Fwe1 mouse isoform has been identified as a putative homologue of the fly $Flower^{Lose}$ forms, and it has been found to be predominantly expressed at the outer border of skin papillomas; *Fwe*-deficient mice develop a significantly lower number of DMBA/TPA-induced skin papillomas, suggesting that hampering cell competition may partially restrict the expansion of cancer cells [159]. SPARC has also been found upregulated in the normal tissue at the tumour/stroma interface in several types of human tumours [160]. Of note, the higher expression of SPARC was observed in tumours associated with field cancerisation [160].

The concept of "field cancerisation" was introduced in the '50s by Slaughter to explain local recurrence after resection of oral cancers [161], and refers to the existence of pre-malignant cells around a primary tumour which, although not showing overt phenotype, carry molecular alterations that make them susceptible to multifocal growth [162, 163]. As MYC OE in normal cells induces stress-related responses, as described in paragraph 2.3, it has long been speculated that MMCC may pioneer field cancerisation [16, 17]. In this sense, a recent study carried out by quantitative immunohistochemistry (qIHC) and neighbourhood analysis suggests that the progression from oral submucous fibrosis to oral squamous cell carcinoma may be shaped by stage-dependent competitive interactions between cells with different levels of MYC, p53 and the regulator of the hypoxic response HIF-1α [164]. Field cancerisation is not restricted to the oral mucosa since it has in time been found to subtend the formation of many types of cancer [165]. For its part, MYC OE is an

early alteration in mammalian cancers from several organs, such as prostate [166-168], lung [169] and gastric carcinomas [170]. We recently investigated in the *Drosophila* wing disc the functional impact of a pre-cancerous field composed of MYC-OE cells on the behaviour of cells mutant for different neoplastic tumour suppressor genes (nTSGs, [171]) [172] (Figure 3). Starting from the observation that MYC OE did not *per se* promote relevant morphological alterations in our system (Figure 3A), although eliciting a number of stress-related responses similar to those found in human pre-malignant tissues [172], we induced second mutations in the nTSGs *lethal giant larvae* (*lgl*) and *rab5* later in development and we observed an unreported growth phenotype consisting in multiple, small mutant *foci* scattered all across the MYC-OE field [172]. Those mutant *foci* showed loss of apical-basal cell polarity and 3D growth (Figure 3B). Of note, both *lgl* and *rab5* mutant cells are usually outcompeted in a wild-type background [23, 173] and MYC OE in *lgl* mutant cells makes them overgrow, circumventing cell competition [23]. This novel, multifocal phenotype results from complex competitive interactions occurring between MYC-OE lgl^{wt} and MYC-OE lgl^{mut} cells, and highlights how MYC-mediated field cancerisation may favour multifocal carcinogenesis following second mutations affecting cell polarity and vesicle trafficking [172]. Cells bearing mutations in genes owing to the Hippo pathway, classified as hyperplastic TSGs [171], rather use the extra-MYC to grow faster and outcompete the neighbours with higher efficiency, while maintaining a hyperplastic phenotype [77].

MMCC has also been found to play essential roles in the clonal expansion of Hippo pathway mutant cells: we and others indeed demonstrated that MYC is a transcriptional target of this signalling cascade in *Drosophila*, consistently upregulated in cells mutant for different components of the pathway, and the growth of Yki-OE clones in the wing disc is severely restricted either by MYC knockdown or by MYC-OE in the surrounding tissue [77, 78]. In addition, it has been shown that an auto-regulatory feedback loop between Yki and MYC is critical for growth stabilisation [78]. MYC is a target of the Hippo pathway also in mammals [174], and an aberrant auto-regulatory feedback loop between the mammalian homologues YAP and c-MYC has been found to drive liver carcinogenesis [79]. The plenty of literature about the pervasive dysregulation of this pathway in human cancer [175] strongly suggests that MMCC may support Hippo-driven tumorigenesis by remodelling the ongoing venue at the tumour/host interface.

Moreover, MYC is necessary to support the growth of polarity-deficient *lgl* mutant cells in heterotypic contexts; we indeed demonstrated that aberrant *lgl* mutant cells are eliminated by MMCC in those regions of the wing disc carrying high levels of MYC [23] (Figure 2A). MYC OE in *lgl* mutant cells is sufficient as to turn them from losers to super-competitors, which develop into frank cancers while outcompeting surrounding wild-type cells [23]. Our and parallel studies [23, 24, 176, 177] were the first evidence that some potentially dangerous but suboptimal cells, such as those carrying mutations in polarity genes, need to bypass cell competition or other intrinsic tumour suppression mechanisms to survive and succeed in the context.

Experimental evidence on the involvement of cell competition in cancer initiation in an adult somatic tissue was however still lacking. MYC has been implicated in *Apc*-driven tumorigenesis in the fly intestine, where it has been shown to be necessary both for tumour initiation and maintenance [178], as it is in the mammalian model of Wnt-dependent colorectal carcinoma [70, 179]. In the original study by Clarke and colleagues, the authors hypothesised that the $Apc^{-/-}$, $MYC^{-/-}$ double mutant stem cells may be outcompeted and replaced by the surrounding wild-type cells, posing the question if the rescue of the aberrant intestinal phenotype were due to MMCC [70]. A recent study carried out in the *Drosophila* adult midgut investigated the role of cell competition in *Apc*-driven adenomas [180]. The authors demonstrated that cell competition is essential to tumour initiation, and the process is dependent on relative Yki activities in tumour and host tissues [180]. MYC knockdown in the *Apc* mutant clones did rescue wild-type dimensions, but its overexpression

in the host tissue did not restrict tumour growth, so concluding that cell competition is in this case mediated by other factors downstream of Yki activation.

4.3. MYC-mediated cell competition in cancer progression

Several *Drosophila* models of cancer have to date been developed that are answering important questions in tumour biology. In particular, the cooperation between TSGs and oncogenes has been finely characterised in the eye and wing disc epithelia, leading to the identification of the molecular basis of cancer-associated cell death, cell growth and cell migration [181]. Many of these models account on the functional cooperation between polarity nTSGs [171], whose loss of function (LOF) usually commits cells to death by some intrinsic tumour suppression mechanisms [23, 177, 182], and oncogenic Ras, which in a favourable environment assigns super-competitive properties to mutant cells, allowing them to grow into overt cancers in the host tissue [183]. Similar models have been developed in mammalian systems with comparable results [184]. In the last 15 years, researchers have accurately characterised *Drosophila* cancer hallmarks, starting from the pioneering study by Xu and colleagues [185] until the recent identification of two still missing traits: tumour-dependent tracheogenesis (equivalent to mammalian angiogenesis) [186, 187] and tumour/stroma interplay [188]. Of note, these tumour models, in their simplicity, show surprising conservation of the molecular networks found aberrantly activated in human cancer [189]. Briefly, loss of apical-basal cell polarity triggered by nTSGs LOF mutations is known to promote the activation of the Hippo downstream effector Yki [24, 176, 190] which, in turn, regulates an ectopic network of transcription factors (including MYC) supporting tumour maintenance [191]. Active Ras diverts JNK's function from tumour-restricting to tumour-promoting by decreasing the activity of the Warts (Wts) kinase [192], a core component of the Hippo pathway involved in Yki's cytoplasmic retention [193]. In this condition, the Hippo pathway switches active Ras from inducing differentiation to promoting aggressive proliferation by regulating its target genes [194]. In this largely interconnected molecular context, *dm* transcription is hyperactivated by Yki [77, 78], and MYC protein is stabilised by the dpERK downstream of active Ras [195], resulting in aberrant MYC expression [24, 186]. Consistent with a role for MMCC in tumour expansion, clones mutant for the polarity gene *lgl* carrying the active form of Ras, Ras^{V12}, induce extensive apoptotic death in the surrounding wild-type cells [24].

A recent study investigated the role of MMCC in the formation of metastatic tumours induced specifically in the *Drosophila* wing disc epithelium. Herranz and colleagues induced carcinogenesis through the expression of an active form of the Epithelial Growth Factor Receptor (EGFR), whose constitutively active mutations are known to occur in a large fraction of human cancers [196], combined with ectopic expression of the conserved miR-8, the sole fly homologue of the human miR-200 family [197]. The authors observed these tumours were highly aggressive and metastatic in the larva and contained a fraction of giant, polyploid cells upregulating MYC which were found to engulf smaller dying cells [25]. Interestingly, miR-8 was demonstrated to disrupt cytokinesis so favouring genomic instability, recently shown to promote invasive behaviour in *Drosophila* epithelial tissues [198]. Suppression of cell engulfment or apoptosis inhibition blocked the formation of giant cells; furthermore, the same mutant clones induced in a MYC high-expressing background failed to produce giant cells and were eliminated from the tissue, demonstrating that this metastatic cancer model depends on MMCC. This was first functional evidence that MMCC can promote metastatic cancer growth in *Drosophila* epithelia.

Two recent studies demonstrated that human cancer cells are also able to undergo MMCC. Shrivastava and colleagues indeed showed that MCF7 breast cancer cells undergo competitive interactions following co-culture of the native, MYC high-expressing cells with *c-myc* shRNA siblings [26]. Cells with low MYC levels were sometimes observed to be engulfed by neighbours

with higher MYC, and their final number in the plate was very low compared to that of the MYC-upregulating cells. The authors also found that the mechanism was JNK-dependent, so suggesting that the basic principles of MMCC so far described in *Drosophila* are conserved in human cancer cells [26]. We expanded on these findings by carrying out heterotypic co-cultures of human cancer cell lines displaying different native levels of MYC. After assessing for each couple of cell lines that those showing higher MYC levels behaved as winners, we inhibited MYC expression in the prospective winners and found it was sufficient as to turn them into losers, irrespective of the genetic/genomic anomalies carried by the confronting cells [27]. We speculate that, since MYC expression is regulated by many aberrant signalling networks in human cancer cells [199], such as it happens in *Drosophila* tumours [191], its protein level represents a universal "performance flag" on the basis of which cells compare their overall fitness. Moreover, an IHC analysis on human breast, lung and colon cancer samples allowed us to observe stereotypical patterns of MMCC at the tumour/stroma interface, with a mixture of stromal and MYC low-expressing cancer cells undergoing cell death when adjacent to or surrounded by MYC high-expressing tumour cells (Figure 4) [27]. This observation led us to conclude that MMCC is likely to play a role in modelling human cancer, and functional studies are expected that help understand its true functions in cancer evolution.

4.4. Competition-associated cell death and its relevance to cancer

Cell death is an inherent feature of cell competition; apoptosis inhibition indeed blocks its completion, being the loss of the loser cells essential to the proliferation of the winners [200]. In *Drosophila*, apoptotic cells are known to produce mitogenic signals [201], which are also likely to stimulate the expansion of the winner cells during cell competition. In post-mitotic tissues, winner cells rather undergo hypertrophy to restore organ size and function [202]. That being said, cancer is under many aspects comparable to a hyper-demanding developing organ [203], and it is likely that signals emanating from the loser cells, being them stromal or tumorous, be intercepted and exploited by fitter neighbours to enhance their performance. It is now accepted that, although cell death resistance is a typical hallmark of cancer cells, a model considering apoptosis induction as an unambiguous strategy to fight cancer is quite naive: therapies inducing cell death may indeed increase proliferative pressure and clonal selection, hence promoting relapse [204]. While cell death causes tumour mass reduction in the short term, it is known to enhance tumorigenesis in the long term by disturbing the "dormant" phases of the tumour, characterised by balanced cell death and proliferation [205]. Moreover, if cell death is sporadic, fewer division cycles are necessary to the tumour to reach a certain mass, limiting genetic heterogeneity, while a high rate of death would implicate many more division cycles as to reach a comparable mass, which would then display more mutant cells and a consistent higher probability to bypass selective barriers [206]. Our recent study suggests MMCC is diffusely associated with human cancer development, from early to metastatic lesions [27]. The great amount of dying cells we observed nearby and amid the MYC-OE cancer tissue, possibly resulting from continuous production and incomplete clearing, may fuel proliferation of the neighbouring tumour cells by local release of growth-promoting factors, such as it happens in *Drosophila* tumours [173]. Moreover, this proliferative advantage would make the winner cells even more susceptible to further mutations, ultimately fostering genetic heterogeneity. For all these reasons, apoptosis inhibition in highly competitive tumours may prove effective in containing organ attrition and cancer aggressivity.

5. Concluding remarks

Cell competition is emerging as a robust, evolutionarily conserved mechanism imposing the supremacy of fit cells on weaker neighbours. The increasing belief that it may play a role in human cancer is partly due to the fact that this process involves in *Drosophila* well-known homologues of

mammalian oncogenes and tumour suppressor genes. In particular, the identification of MYC-mediated cell competition has revealed how cells overexpressing MYC supersede neighbouring cells expressing endogenous levels of this protein. Although the mechanisms through which MYC provides cells with super-competitive abilities are not clarified yet, it has emerged that prospective winner and loser cells usually show different metabolic profiles. Consistently, protein synthesis and aerobic glycolysis are well-characterised mediators of cell competition in *Drosophila* and mouse, both fostered by MYC overexpression. Another process promoted by high MYC levels is transcriptional hyperactivation, which may favour cell competition by generating a molecular signature positively correlated to cell fitness. Of note, MYC upregulation, enhanced metabolism and hypertrascription are typical traits of transformed cells. In human cancers, super-competitive behaviours are mainly evident at the tumour/stroma interface, where the tumour parenchyma is known to show the highest proliferation rate. This is a likely consequence of the fact that nearby stromal cells, while undergoing apoptotic death, release mitogenic factors into the local milieu, intercepted by competent cells that profitably use them to accelerate metabolism and growth. Since tumour cells face ever-changing environments during their life, and must cooperate or contend with different neighbours to disrupt tissue homeostasis, MYC-mediated cell competition is likely to represent an emerging trait of cancer, but functional studies on this process in overt malignancies are still missing, and many questions remain unanswered about the significance of cell competition in clone selection, cancer growth and aggressiveness.

Acknowledgements

We apologise to our colleagues whose work was not cited or discussed in full due to space limitations. Research in our lab is funded by "Associazione Italiana Ricerca sul Cancro" (AIRC IG17252), by a Fellowship to SP from the PhD Programme in "Cellular and Molecular Biology", University of Bologna, and by a Senior Research Fellowship to DG from the Department of Pharmacy and Biotechnology, University of Bologna. Original illustrations are by Simona Paglia.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Figure legends

Figure 1: MYC-mediated cellular processes.
MYC protein dictates cell behaviour by governing central cellular processes.

Figure 2: MYC-Mediated Cell Competition in Development.
(A). A depiction of the *Drosophila* larval wing disc showing MYC expression pattern (red). When a suboptimal cell happens in a MYC high-expressing region, it is promptly eliminated by MMCC (magnification on the right), while it can survive or even outcompete surrounding cells in a MYC low-expressing territory (magnification on the left). (B). The mouse epiblast at day 6.5 is composed of cells with different levels of MYC (red), with low-expressing cells being eliminated and replaced by adjacent, fitter siblings (magnification). (C). During heart development, myocardial cells showing higher levels of MYC (red) eliminate and replace less fit adjacent cells (magnification on the right). The same has been observed in the epicardial cell lineage (magnification on the left).

Figure 3: MYC in field cancerisation.
(A). MYC upregulation in some cells inside a tissue (red) may favour the formation of a pre-cancerous field by MMCC (B). Additional mutations in some cells of the field (dark red) induce multifocal carcinogenesis associated with loss of apical-basal cell polarity and three-dimensional

growth. Immune cells (purple) and fibroblasts (green) are represented in the underlaying stroma, separated from the epithelium by a basement membrane (grey).

Figure 4: MYC-overexpressing human cancers show massive cell death at the tumour/stroma interface.
(A). An immunofluorescence picture showing a *Drosophila* wing disc carrying *lgl* mutant cells overexpressing MYC (GFP^+ nuclei) that kill wild-type neighbours (Caspase 3, magenta nuclei). The magnification illustrates tissue dynamics at the tumour borders.
(B). A frame from a sample of lung adenocarcinoma showing tumour cells upregulating MYC (red) and stromal cells positive to the activated Caspase 3 staining (brown). Reproduced with permission from [27]. The magnification illustrates the tissue dynamics at the tumour/stroma interface (outlined). A mixture of fibroblasts, immune cells and tumour cells are present in the connective tissue. Dying cells are represented with a misshapen nucleus.

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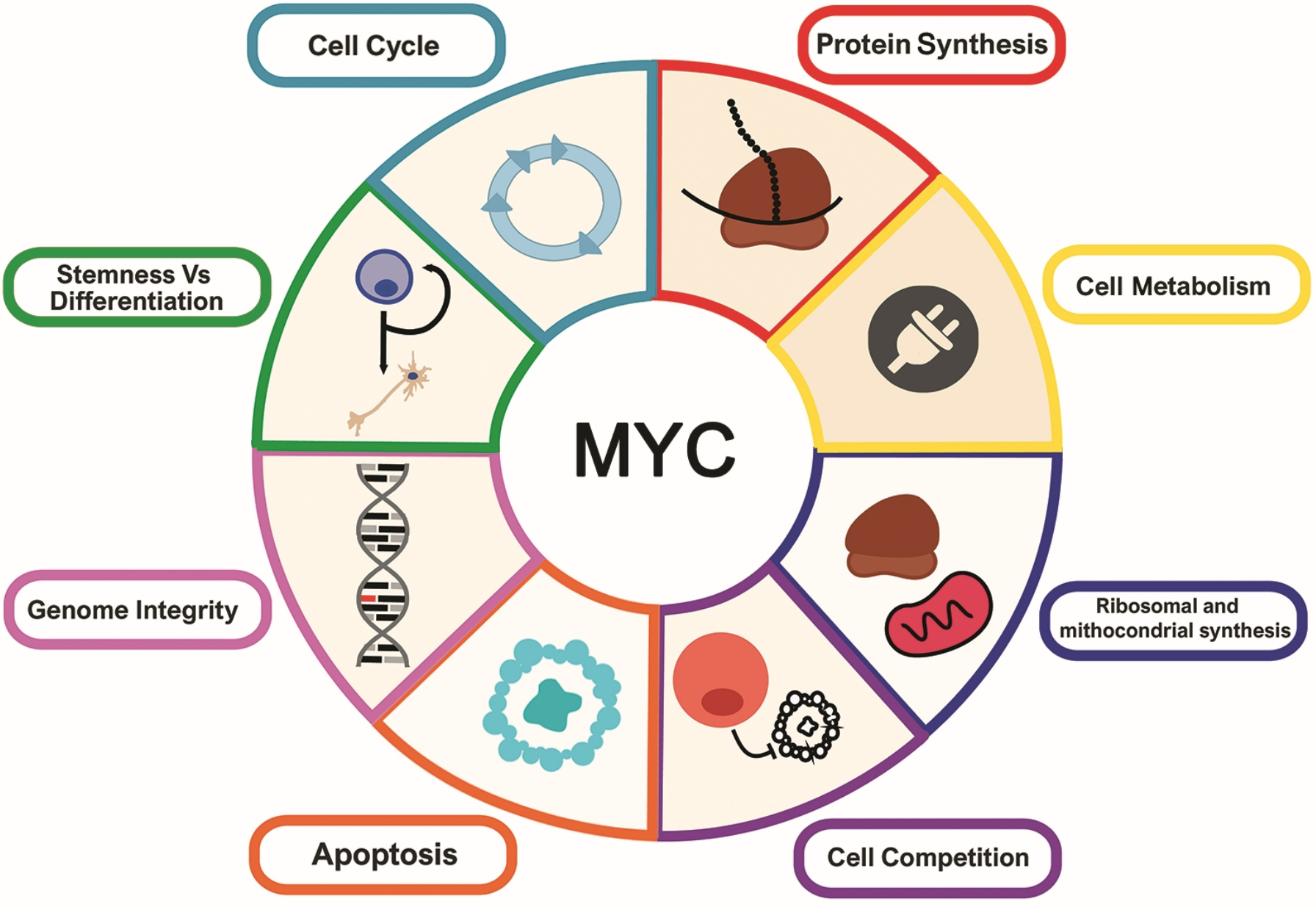
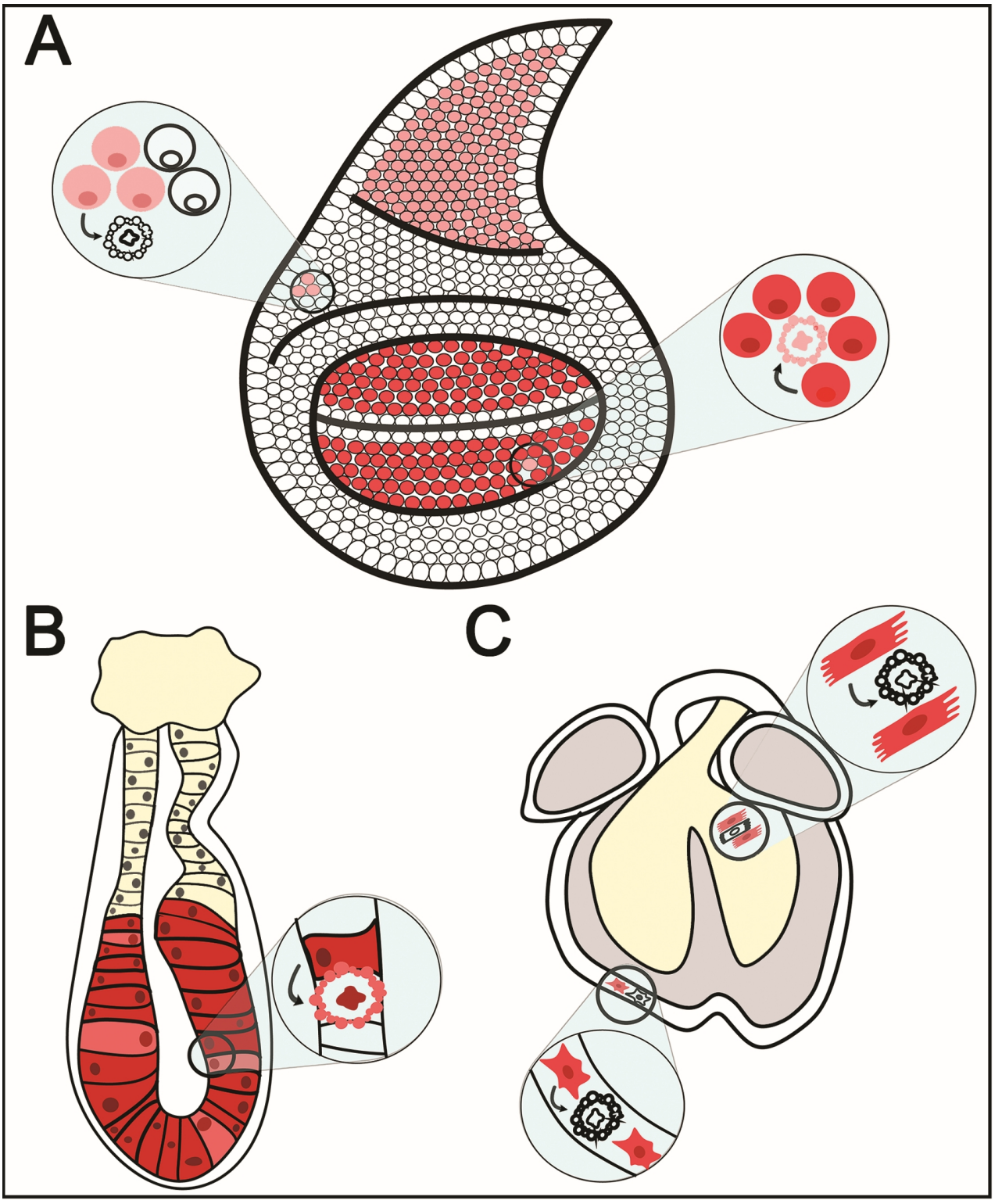

Cell Cycle
Protein Synthesis
Stemness Vs Differentiation
Cell Metabolism
MYC
Genome Integrity
Ribosomal and mithocondrial synthesis
Apoptosis
Cell Competition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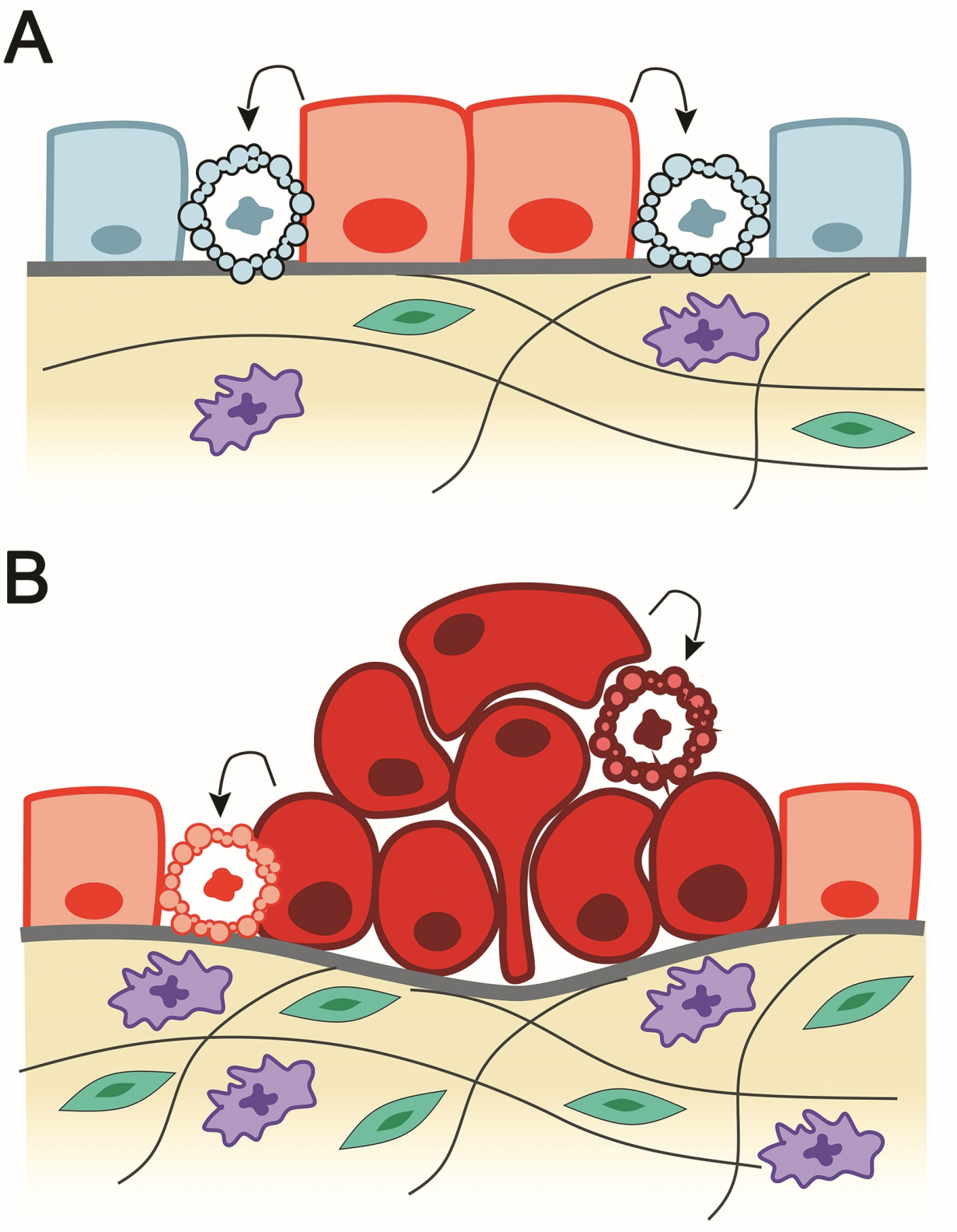
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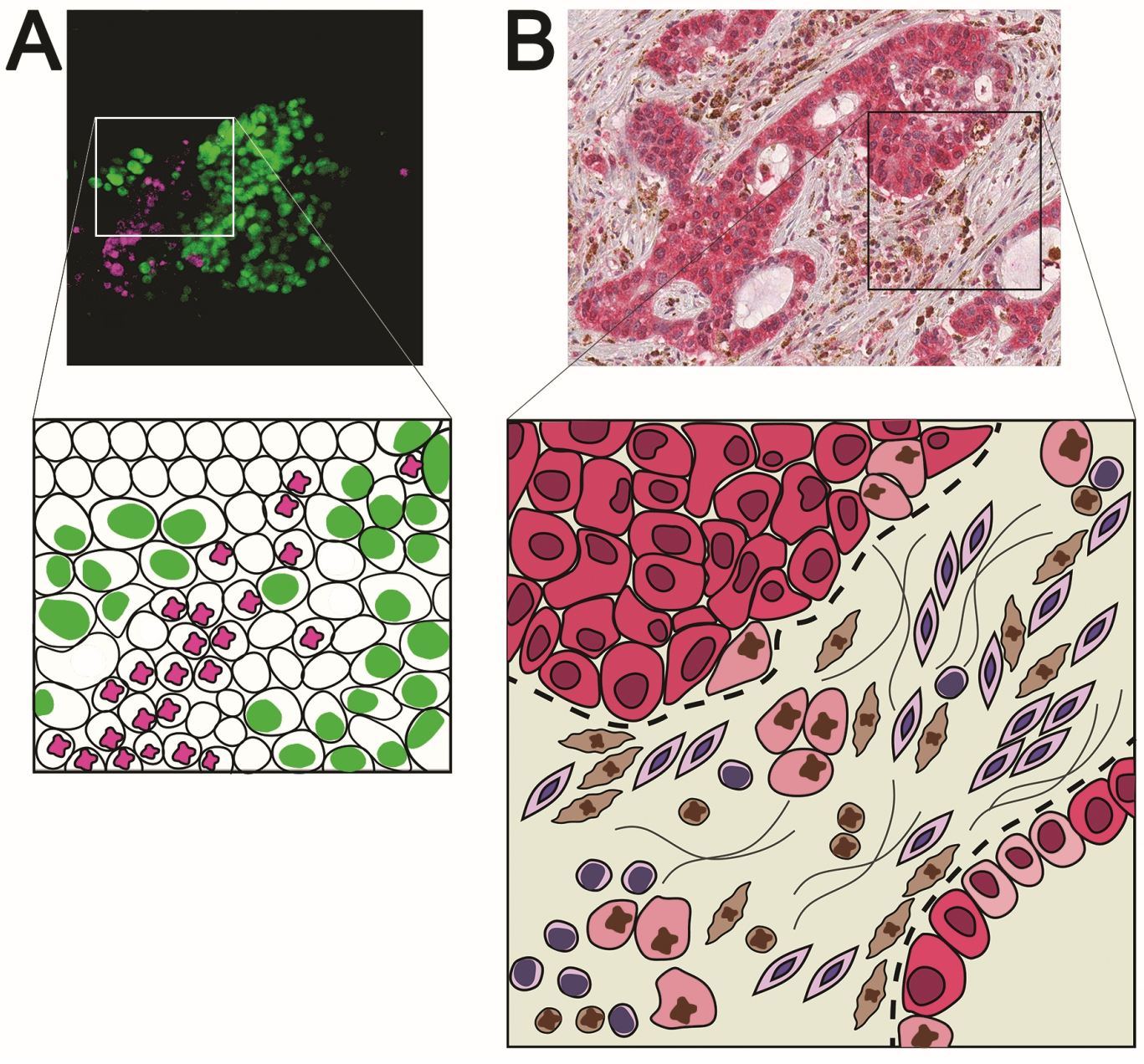
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