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1 **Exploring MYC relevance to cancer biology from the perspective of cell competition**

2
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26
27 **Abstract**

28
29 Cancer has long been regarded and treated as a foreign body appearing by mistake inside a living
30 organism. However, now we know that cancer cells communicate with neighbours, thereby creating
31 modified environments able to support their unusual need for nutrients and space. Understanding
32 the molecular basis of these bi-directional interactions is thus mandatory to approach the complex
33 nature of cancer. Since their discovery, MYC proteins have been showing to regulate a steadily
34 increasing number of processes impacting cell fitness, and are consistently found upregulated in
35 almost all human tumours. Of interest, MYC takes part in cell competition, an evolutionarily
36 conserved fitness comparison strategy aimed at detecting weakened cells, which are then committed
37 to death, removed from the tissue and replaced by fitter neighbours. During physiological
38 development, MYC-mediated cell competition is engaged to eliminate cells with suboptimal MYC
39 levels, so as to guarantee selective growth of the fittest and proper homeostasis, while transformed
40 cells expressing high levels of MYC coopt cell competition to subvert tissue constraints, ultimately
41 disrupting homeostasis. Therefore, the interplay between cells with different MYC levels may result
42 in opposite functional outcomes, depending on the nature of the players. In the present review, we
43 describe the most recent findings on the role of MYC-mediated cell competition in different
44 contexts, with a special emphasis on its impact on cancer initiation and progression. We also
45 discuss the relevance of competition-associated cell death to cancer disease.

46
47 **Keywords:** MYC, Cancer, Cell competition, Cell death

48
49 **Abbreviations:** MMCC: MYC-mediated cell competition; OE: overexpression; nTSGs: neoplastic
50 tumour suppressor genes

51

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

103 proteins are evolutionarily conserved basic helix-loop-helix-leucine zipper (bHLH-LZ)
104 transcription factors [38], whose C-terminal domain is used to dimerise with cognate proteins,
105 forming the so-called MYC network [39]. The major partner of MYC in transcriptional activation is
106 MAX (MYC-Associated protein X) [40], whose structure and function are well conserved in the fly
107 [41], and MYC::MAX complexes bind DNA at short sequences called E-boxes [42]. Highly
108 dynamic interactions among network members shape and refine MYC function in any given cellular
109 condition, from flies to humans [43, 44], and recent work suggests that MYC promotes major
110 changes in chromatin structure, regulating a large fraction of the genome by transcriptional
111 activation or repression [45-48]. This concept is supported by the evidence that MYC network
112 regulates transcription of protein-encoding genes, but also microRNAs-encoding *loci* [49] and long
113 non-coding RNA sequences [50, 51], further to activate transcription of the three RNA polymerases
114 [52-54].

115 116 2.2. Regulation of MYC expression

117
118 MYC's ability to maintain tissue homeostasis by promoting physiological growth and proliferation
119 is mainly associated with development [34, 55-58]. Indeed, while it contributes to the maintenance
120 of cells with regenerative and proliferative potential in adult organs [59-62], its activity decreases in
121 differentiating progenitors to assure proper organogenesis [63, 64]. MYC is indeed one of the
122 original Yamanaka's factors necessary to reprogramme committed cells into pluripotent stem cells
123 [65].

124
125 Given its key roles in cellular physiology, and since even small increases in its levels can drive
126 overgrowth [66], MYC expression is tightly regulated by a number of cellular activities [67].
127 Among the developmental signals converging on MYC to pattern cell and tissue growth, the fly
128 morphogen Decapentaplegic (Dpp) and its mammalian orthologue Transforming Growth Factor
129 β (TGF β) have been found to control, directly or indirectly, MYC transcription [68, 69]. Another
130 morphogenetic protein, Wingless (Wg), and its mammalian counterpart Wnt, are largely known to
131 regulate MYC transcription alone [70, 71] or in combination with Notch [72], which can also
132 regulate MYC promoter activity independent of Wg/Wnt [73-75]. The JAK/STAT signalling was
133 also found to modulate MYC expression in the *Drosophila* intestine [62] and in B-cells, where
134 JAK1 promotes lymphomagenesis by epigenetic activation of the MYC promoter [76]. Moreover,
135 MYC transcription is regulated in *Drosophila* by the Hippo pathway downstream effector Yorkie
136 (Yki) [77, 78] and by the Yki homologues YAP/TAZ proteins in mammals [79]. Of note, all these
137 pathways have been so far implicated in cell competition [80], and their dysregulation contributes to
138 human cancer [81-85].

139
140 With regard to MYC post-transcriptional regulation, several miRNAs have been shown to directly
141 or indirectly target MYC mRNA in the fly [86-88] and in mammals [89, 90]. In addition, MYC
142 protein levels are regulated by ubiquitin-mediated proteasomal degradation [91, 92]. The short half-
143 life of the MYC protein [93] can be extended as a consequence of direct phosphorylation by kinases
144 downstream of the Ras/MAPK and PI3K pathways [94-97], or by inhibition of the Glycogen
145 Synthase Kinase 3 β (GSK3 β), which is known to target MYC for ubiquitination [98, 99]. Point
146 mutations modifying the MYC residues targeted by GSK3 β , found in sporadic cancers [100],
147 possibly contribute to cell transformation by interfering with MYC degradation.

148 149 2.3. MYC relevance to cancer biology

150
151 As mentioned in paragraph 2.1, MYC is considered a global driver of transcription, regulating about
152 15% of all genes from flies to humans, with genes involved in cell cycle, cell metabolism, ribosome
153 biogenesis, protein synthesis and mitochondrial function over-represented in its target network [47]

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

157

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

172

173 MYC upregulation elicits several important cellular responses that depend on MYC protein levels
174 [110]; however, extremely high levels of this protein may overcome cell's capability to resist the
175 stressful condition generated by aberrant transcription; excess MYC in normal cells can indeed
176 result in genetic instability [111, 112] and autonomous cell death [113, 114] (Figure 1), whereas
177 cancer cells exploit the extra-dose of MYC to accumulate mass and proliferate faster [115].
178 Therefore, the outcome of MYC activation seems to depend on whether the cells express a
179 sufficient amount of pro-survival factors as to bypass essential apoptotic checkpoints.

180

181 **3. MYC in physiological cell competition**

182

183 *3.1. Introduction*

184

185 The intimate relationship between cell proliferation and cell death is intrinsic to any developmental
186 programme, where a suitable balance between cell addition and cell elimination ensures tissue
187 homeostasis [116]. The principles of competition and compensation lie at the heart of animal
188 design; however, the process is not as elementary as it seems. The inherent characteristics of a
189 given cell may make it fit enough to inhabit a certain tissue area, while totally inadequate to be part
190 of a distinct region of the same tissue, depending on the fitness requirements of the specific context
191 (Figure 2A). Any multicellular organism is indeed finely monitored, from development to death, by
192 quality checking systems aimed at identifying, eliminating or modifying, any component that
193 interferes with the physiological activity of the residents. Among these systems, cell competition
194 detects viable but suboptimal cells in the context (losers) and removes them from the tissue, which
195 is then usually replenished by overproliferation of the fittest (winners) [117]. Cell competition was
196 first observed in the *Drosophila* wing disc (Figure 2A), a larval epithelial organ giving rise to the
197 adult wing and thorax [118], where cells carrying mutations in genes encoding ribosomal proteins
198 behaved as losers when confronted with wild-type cells [11]. In time, the concept of cell
199 competition has been extended to mammalian systems, and several genetic conditions have
200 demonstrated to make cells acquire a loser/winner status when adjacent to wild-type neighbours
201 [119]. Of note, many of these conditions lower/increase MYC protein levels in mutant cells [21, 23,
202 68, 77, 120], highlighting its prominent role in the phenomenon.

203

204

205 3.2. MYC-mediated cell competition in *Drosophila*

206

207 In early '70s, cell competition was observed in mosaic wing discs containing cells bearing
208 mutations in genes encoding ribosomal proteins, the so-called *Minute* (*M/+*) mutations [121]. While
209 these cells were viable in a homotypic background, though slow-growing compared to wild-type
210 cells [122], when adjacent to wild-type cells they were committed to death, and their loss was
211 compensated by consistent overproliferation of the winners [11]. Cell competition has thus emerged
212 as a mechanism necessary to eliminate viable but suboptimal cells in favour of the fittest, assuring
213 that the developing organ will not undergo morphogenetic alterations due to genetic heterogeneity
214 [123]. The process obeys developmental constraints: cell competition indeed occurs within but not
215 across the borders of a given compartment [124]. MYC entered the still poorly characterised topic
216 of cell competition in 2004, when two parallel studies showed that an equivalent phenomenon took
217 place when cells with different levels of MYC grew juxtaposed in mosaic wing discs [12, 13]. Cells
218 expressing lower levels of MYC behaved as losers and died by apoptosis, while cells with higher
219 levels of MYC behaved as winners and overproliferated at their expense [12, 13]. The modulation
220 of other cell growth inducers was not sufficient to activate cell competition [12, 13], which
221 apparently accounts on additional properties of the MYC protein. In addition, although ribosomal
222 proteins act downstream of MYC in cell competition [12], *Minute*- and MYC-mediated cell
223 competition can use different molecular mechanisms to execute cell competition [125]. Several
224 leading laboratories in the field have used *Minute*, MYC and other paradigms of cell competition to
225 investigate in *Drosophila* mosaic tissues the mechanisms responding to competitive stimuli in loser
226 and winner cells [119]. Here we focus our discussion on the findings derived from studies on MYC-
227 Mediated Cell Competition (MMCC).

228

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

248

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

256 elimination of supernumerary post-mitotic clones in the fly retina [131] and in the regeneration of
257 injured adult fly brains [132], showing that different cell lineages, in physiological or in stressful
258 conditions, have evolved similar strategies to restore organ homeostasis. In addition to Flower,
259 another membrane protein identified as an early marker of MMCC is Sparc, whose upregulation in
260 loser cells in the early phases of cell competition offers them transient protection by setting a higher
261 threshold for caspase activation, so restricting death to the unnecessary cells [133]. The cell-
262 autonomous fitness signals from Flower^{Lose} and Sparc protein levels, together with the levels of
263 Flower^{Lose} isoforms in neighbouring cells, are then integrated into the transcriptional regulation of
264 Azot in the loser cells [134]. Azot has been characterised as a cell-fitness checkpoint protein, active
265 in many different competitive contexts, whose physiological expression in viable but unfit or
266 misspecified cells restricts morphological alterations and tissue degeneration, increasing longevity
267 [134]. Flower^{LoseB} and Azot have also recently been found to be necessary to the neuronal death
268 induced by toxic peptides in a *Drosophila* model of neurodegeneration: neuron culling is also in this
269 case mediated by fitness comparison and, contrariwise to common knowledge, the death of unfit
270 neurons ameliorated motor and cognitive functions, possibly allowing dendritic arborisation of the
271 neighbouring healthy neurons [135].

272
273 Besides inducing the expression of “fitness fingerprints” in the confronting cells, MMCC has been
274 found to stimulate a bi-directional signalling composed of still uncharacterised soluble factors
275 [136]; consistent with this view, an *in silico* screening has led to the identification in the *Drosophila*
276 genome of some miRNAs potentially involved in cell competition whose human homologues are
277 involved in different types of cancer [137].

278
279 With regard to the clearance of the dying cells, they undergo basal extrusion and apoptotic corpses
280 are engulfed and eliminated by circulating hemocytes, the *Drosophila* macrophages [138]. The
281 question about how circulating hemocytes can identify dying cells has been addressed by a
282 successive study, which has demonstrated that loser cells secrete Tyrosyl-tRNA Synthetase which,
283 following to metalloprotease-dependent cleavage, releases the evolutionarily conserved Endothelial
284 Monocyte-Activating Polypeptide (EMAP) fragment, able to guide the hemocytes towards the
285 dying cells [139].

286
287 Finally, different laboratories investigated the possibility that the mechanisms implemented by the
288 innate immune system to detect pathogens may also be used to eliminate potentially dangerous cells
289 in a developing tissue. The innate immune response is governed by the Toll receptors and the
290 immune deficiency signalling pathway [140]. Recent studies have revealed that MYC OE in mosaic
291 wing discs autonomously increases the synthesis of some proteases which process the ligand
292 Spätzle for secretion, allowing its binding to Toll receptors in the adjacent loser cells, whose
293 activation promotes NFkB-mediated apoptosis [125, 141]. This mechanism has however been
294 demonstrated to be infection-dependent, as it does not occur when working in axenic conditions, so
295 the local production of the ligand Spätzle and its proteases may be the result of a systemic response
296 to infection [142]. In a different study, Toll signalling has conversely been found to promote the
297 survival and growth of polarity-deficient cells by activating the Hippo pathway effector Yki in the
298 prospective losers [143], highlighting the essential role of the intrinsic genetic background of the
299 confronting cells in interpreting the signalling activated by the competitive stimulus.

300 301 3.3. MYC-mediated cell competition in mammals

302
303 About thirty years after the observation of cell competition in *Drosophila* [11], a pioneer study
304 demonstrated that murine cells bearing a mutant form of a gene encoding a ribosomal protein were
305 severely outcompeted by wild-type cells in chimeric blastocysts, with about one half of embryos
306 and adults composed exclusively of wild-type cells [144]. Since then, a number of examples of cell

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

313
314 In 2013, two independent studies investigated the role of cell competition in mammalian Embryonic
315 Stem Cells (ESC) [147, 150]. Rodríguez and colleagues showed that, in mosaic embryos, cells
316 defective for the murine homologue of the Dpp receptor Tkv, *BMPRI1A*, were eliminated at the
317 epiblast stage of development [147]. Mutant ESC were consistently out-competed when co-cultured
318 *in vitro* with wild-type ESC; those competitive interactions were found to be apoptosis-dependent
319 and to occur independent of any cell-cell contact [147], as it was previously shown for *Drosophila*
320 S2 cells overexpressing MYC co-cultured with, but physically separated by, native S2 cells [136].
321 These findings indicate that some still uncharacterised soluble factors are involved in the process. In
322 addition, wild-type ESC showed higher levels of MYC respect to the *Bmpr1a* mutant cells when in
323 co-culture, and mouse epiblast at day 6.5 showed chimeric MYC expression (Figure 2B), with a
324 coherent pattern of apoptotic death in cells expressing lower MYC levels [147]. Torres and
325 colleagues investigated in deeper detail the role of MMCC in mouse embryogenesis, demonstrating
326 that endogenous MMCC selects for cells with higher metabolic activity (Figure 2B), and engineered
327 MYC high-expressing ESC were able to outcompete wild-type cells either *in vivo* or in *in vitro* co-
328 culture assays [150]. A similar mechanism has not been found to occur in the extraembryonic
329 tissues, indicating that selection of the fittest cells is especially relevant in long-lived somatic
330 tissues. In a successive study, the authors demonstrated that MYC levels in ESC positively correlate
331 with stemness, and MMCC restricts premature differentiation by eliminating MYC low-expressing
332 cells before gastrulation [22]. On the other hand, MYC downregulation during gastrulation,
333 necessary to coordinate exit from pluripotency and differentiation, may prevent inappropriate
334 competitive interactions among different cell lineages.

335
336 MMCC has also been found to cause cardiomyocyte replacement both in development and adult
337 life, showing it is not a process restricted to stem cell populations [19]. Although previous studies
338 demonstrated that MYC OE leads to cardiac hyperplasia in developing mice [151] and to
339 hypertrophy in adult organs [152], mosaic hearts composed of cells expressing high vs endogenous
340 levels of MYC did not undergo pathological growth [19]. MYC high-expressing cardiomyocytes
341 eliminated and replaced the wild-type neighbours through short-range cell-cell competitive
342 interactions without affecting organ development [19] (Figure 2C). In a successive study, the
343 authors expanded on previous work by investigating the role of MMCC in the epicardial cell
344 lineage, which is known to contribute cells to the developing heart and to the injured adult
345 myocardial tissue [20]. They found that, similar to what happens with myocardial cells, epicardial
346 cells overexpressing MYC are able to colonise the epicardial-derived lineage (Figure 2C) and show
347 increased ability to invade the myocardium [20], confirming the putative relevance of MMCC to the
348 emerging field of regenerative medicine.

349
350 The role of MMCC was also assayed in mouse embryo fibroblasts: Sasaki and colleagues
351 established an *in vitro* system based on co-culture assays of TEAD activity-manipulated fibroblasts,
352 showing that cells with increased TEAD activity overcame the wild-type neighbours [120]. TEAD
353 stands for Transcriptional Enhanced Associate Domain proteins, which bind YAP/TAZ co-
354 activators downstream of the Hippo pathway and activate transcription of target genes [153]. In the
355 same study, TEAD was observed to upregulate MYC RNA, and the authors demonstrated that MYC
356 OE was *per se* sufficient as to outcompete wild-type counterparts [120]. Altogether, these findings

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

359

360 **4. MYC in cancer-associated cell competition**

361

362 *4.1. Introduction*

363

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

372

373 *4.2. MYC-mediated cell competition in cancer initiation*

374

375 Recently, an interesting study found a mechanism by which oncogenic MYC may promote tissue
376 invasion by cell competition. The authors observed that the contact surface shared by winner and
377 loser cells positively correlated with the strength of cell competition, and that cell-cell intercalation,
378 a process occurring throughout animal development by which neighbouring cells exchange places
379 with one other, was necessary to eliminate loser cells [156]. Lower levels of F-actin in the loser
380 cells as compared to the winners favoured the stabilisation of low-tension loser-loser and loser-
381 winner contacts; on the other hand, high-tension winner-winner cell contact stabilisation was
382 restrained, supporting tissue invasion by the winner cells [156]. Moreover, the authors demonstrated
383 that reducing tension at the anterior/posterior (A/P) border of the wing disc, which is known to
384 prevent inappropriate cell mixing [157], was sufficient as to increase winner/loser shared surface,
385 marked by Fwe^{Lose} expression in the loser cells [156]. This finding may explain competition
386 restriction by developmental boundaries [124]. Since tumour parenchyma is stiffer than normal
387 tissue [158], it possibly uses cell-cell intercalation to invade and propagate into the organ, and
388 “fitness fingerprints” may be particularly visible at the tumour borders. The $Fwe1$ mouse isoform
389 has been identified as a putative homologue of the fly $Flower^{Lose}$ forms, and it has been found to be
390 predominantly expressed at the outer border of skin papillomas; Fwe -deficient mice develop a
391 significantly lower number of DMBA/TPA-induced skin papillomas, suggesting that hampering cell
392 competition may partially restrict the expansion of cancer cells [159]. SPARC has also been found
393 upregulated in the normal tissue at the tumour/stroma interface in several types of human tumours
394 [160]. Of note, the higher expression of SPARC was observed in tumours associated with field
395 cancerisation [160].

396

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

408 early alteration in mammalian cancers from several organs, such as prostate [166-168], lung [169]
409 and gastric carcinomas [170]. We recently investigated in the *Drosophila* wing disc the functional
410 impact of a pre-cancerous field composed of MYC-OE cells on the behaviour of cells mutant for
411 different neoplastic tumour suppressor genes (nTSGs, [171]) [172] (Figure 3). Starting from the
412 observation that MYC OE did not *per se* promote relevant morphological alterations in our system
413 (Figure 3A), although eliciting a number of stress-related responses similar to those found in human
414 pre-malignant tissues [172], we induced second mutations in the nTSGs *lethal giant larvae (lgl)* and
415 *rab5* later in development and we observed an unreported growth phenotype consisting in multiple,
416 small mutant *foci* scattered all across the MYC-OE field [172]. Those mutant *foci* showed loss of
417 apical-basal cell polarity and 3D growth (Figure 3B). Of note, both *lgl* and *rab5* mutant cells are
418 usually outcompeted in a wild-type background [23, 173] and MYC OE in *lgl* mutant cells makes
419 them overgrow, circumventing cell competition [23]. This novel, multifocal phenotype results from
420 complex competitive interactions occurring between MYC-OE *lgl*^{wt} and MYC-OE *lgl*^{mut} cells, and
421 highlights how MYC-mediated field cancerisation may favour multifocal carcinogenesis following
422 second mutations affecting cell polarity and vesicle trafficking [172]. Cells bearing mutations in
423 genes owing to the Hippo pathway, classified as hyperplastic TSGs [171], rather use the extra-MYC
424 to grow faster and outcompete the neighbours with higher efficiency, while maintaining a
425 hyperplastic phenotype [77].
426

427 MMCC has also been found to play essential roles in the clonal expansion of Hippo pathway
428 mutant cells: we and others indeed demonstrated that MYC is a transcriptional target of this
429 signalling cascade in *Drosophila*, consistently upregulated in cells mutant for different components
430 of the pathway, and the growth of Yki-OE clones in the wing disc is severely restricted either by
431 MYC knockdown or by MYC-OE in the surrounding tissue [77, 78]. In addition, it has been shown
432 that an auto-regulatory feedback loop between Yki and MYC is critical for growth stabilisation
433 [78]. MYC is a target of the Hippo pathway also in mammals [174], and an aberrant auto-regulatory
434 feedback loop between the mammalian homologues YAP and c-MYC has been found to drive liver
435 carcinogenesis [79]. The plenty of literature about the pervasive dysregulation of this pathway in
436 human cancer [175] strongly suggests that MMCC may support Hippo-driven tumorigenesis by
437 remodelling the ongoing venue at the tumour/host interface.
438

439 Moreover, MYC is necessary to support the growth of polarity-deficient *lgl* mutant cells in
440 heterotypic contexts; we indeed demonstrated that aberrant *lgl* mutant cells are eliminated by
441 MMCC in those regions of the wing disc carrying high levels of MYC [23] (Figure 2A). MYC OE
442 in *lgl* mutant cells is sufficient as to turn them from losers to super-competitors, which develop into
443 frank cancers while outcompeting surrounding wild-type cells [23]. Our and parallel studies [23, 24,
444 176, 177] were the first evidence that some potentially dangerous but suboptimal cells, such as
445 those carrying mutations in polarity genes, need to bypass cell competition or other intrinsic tumour
446 suppression mechanisms to survive and succeed in the context.
447

448 Experimental evidence on the involvement of cell competition in cancer initiation in an adult
449 somatic tissue was however still lacking. MYC has been implicated in *Apc*-driven tumorigenesis in
450 the fly intestine, where it has been shown to be necessary both for tumour initiation and
451 maintenance [178], as it is in the mammalian model of Wnt-dependent colorectal carcinoma [70,
452 179]. In the original study by Clarke and colleagues, the authors hypothesised that the *Apc*^{-/-}, *MYC*^{-/-}
453 double mutant stem cells may be outcompeted and replaced by the surrounding wild-type cells,
454 posing the question if the rescue of the aberrant intestinal phenotype were due to MMCC [70]. A
455 recent study carried out in the *Drosophila* adult midgut investigated the role of cell competition in
456 *Apc*-driven adenomas [180]. The authors demonstrated that cell competition is essential to tumour
457 initiation, and the process is dependent on relative Yki activities in tumour and host tissues [180].
458 MYC knockdown in the *Apc* mutant clones did rescue wild-type dimensions, but its overexpression

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

461

462 4.3. MYC-mediated cell competition in cancer progression

463

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

490

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

505

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

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

527 528 *4.4. Competition-associated cell death and its relevance to cancer*

529
530 Cell death is an inherent feature of cell competition; apoptosis inhibition indeed blocks its
531 completion, being the loss of the loser cells essential to the proliferation of the winners [200]. In
532 *Drosophila*, apoptotic cells are known to produce mitogenic signals [201], which are also likely to
533 stimulate the expansion of the winner cells during cell competition. In post-mitotic tissues, winner
534 cells rather undergo hypertrophy to restore organ size and function [202]. That being said, cancer is
535 under many aspects comparable to a hyper-demanding developing organ [203], and it is likely that
536 signals emanating from the loser cells, being them stromal or tumorous, be intercepted and
537 exploited by fitter neighbours to enhance their performance. It is now accepted that, although cell
538 death resistance is a typical hallmark of cancer cells, a model considering apoptosis induction as an
539 unambiguous strategy to fight cancer is quite naive: therapies inducing cell death may indeed
540 increase proliferative pressure and clonal selection, hence promoting relapse [204]. While cell death
541 causes tumour mass reduction in the short term, it is known to enhance tumorigenesis in the long
542 term by disturbing the “dormant” phases of the tumour, characterised by balanced cell death and
543 proliferation [205]. Moreover, if cell death is sporadic, fewer division cycles are necessary to the
544 tumour to reach a certain mass, limiting genetic heterogeneity, while a high rate of death would
545 implicate many more division cycles as to reach a comparable mass, which would then display
546 more mutant cells and a consistent higher probability to bypass selective barriers [206]. Our recent
547 study suggests MMCC is diffusely associated with human cancer development, from early to
548 metastatic lesions [27]. The great amount of dying cells we observed nearby and amid the MYC-OE
549 cancer tissue, possibly resulting from continuous production and incomplete clearing, may fuel
550 proliferation of the neighbouring tumour cells by local release of growth-promoting factors, such as
551 it happens in *Drosophila* tumours [173]. Moreover, this proliferative advantage would make the
552 winner cells even more susceptible to further mutations, ultimately fostering genetic heterogeneity.
553 For all these reasons, apoptosis inhibition in highly competitive tumours may prove effective in
554 containing organ attrition and cancer aggressivity.

555 556 **5. Concluding remarks**

557
558 Cell competition is emerging as a robust, evolutionarily conserved mechanism imposing the
559 supremacy of fit cells on weaker neighbours. The increasing belief that it may play a role in human
560 cancer is partly due to the fact that this process involves in *Drosophila* well-known homologues of

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

580

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582

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588

589 **Conflict of Interest Statement**

590

591 The authors have no conflicts of interest to declare.

592

593 **Figure legends**

594

595 *Figure 1: MYC-mediated cellular processes.*

596 MYC protein dictates cell behaviour by governing central cellular processes.

597

598 *Figure 2: MYC-Mediated Cell Competition in Development.*

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

607

608 *Figure 3: MYC in field cancerisation.*

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

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

614
615 *Figure 4: MYC-overexpressing human cancers show massive cell death at the tumour/stroma*
616 *interface.*

617 (A). An immunofluorescence picture showing a *Drosophila* wing disc carrying *lgl* mutant cells
618 overexpressing MYC (GFP⁺ nuclei) that kill wild-type neighbours (Caspase 3, magenta nuclei). The
619 magnification illustrates tissue dynamics at the tumour borders.

620 (B). A frame from a sample of lung adenocarcinoma showing tumour cells upregulating MYC (red)
621 and stromal cells positive to the activated Caspase 3 staining (brown). Reproduced with permission
622 from [27]. The magnification illustrates the tissue dynamics at the tumour/stroma interface
623 (outlined). A mixture of fibroblasts, immune cells and tumour cells are present in the connective
624 tissue. Dying cells are represented with a misshapen nucleus.

625

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627

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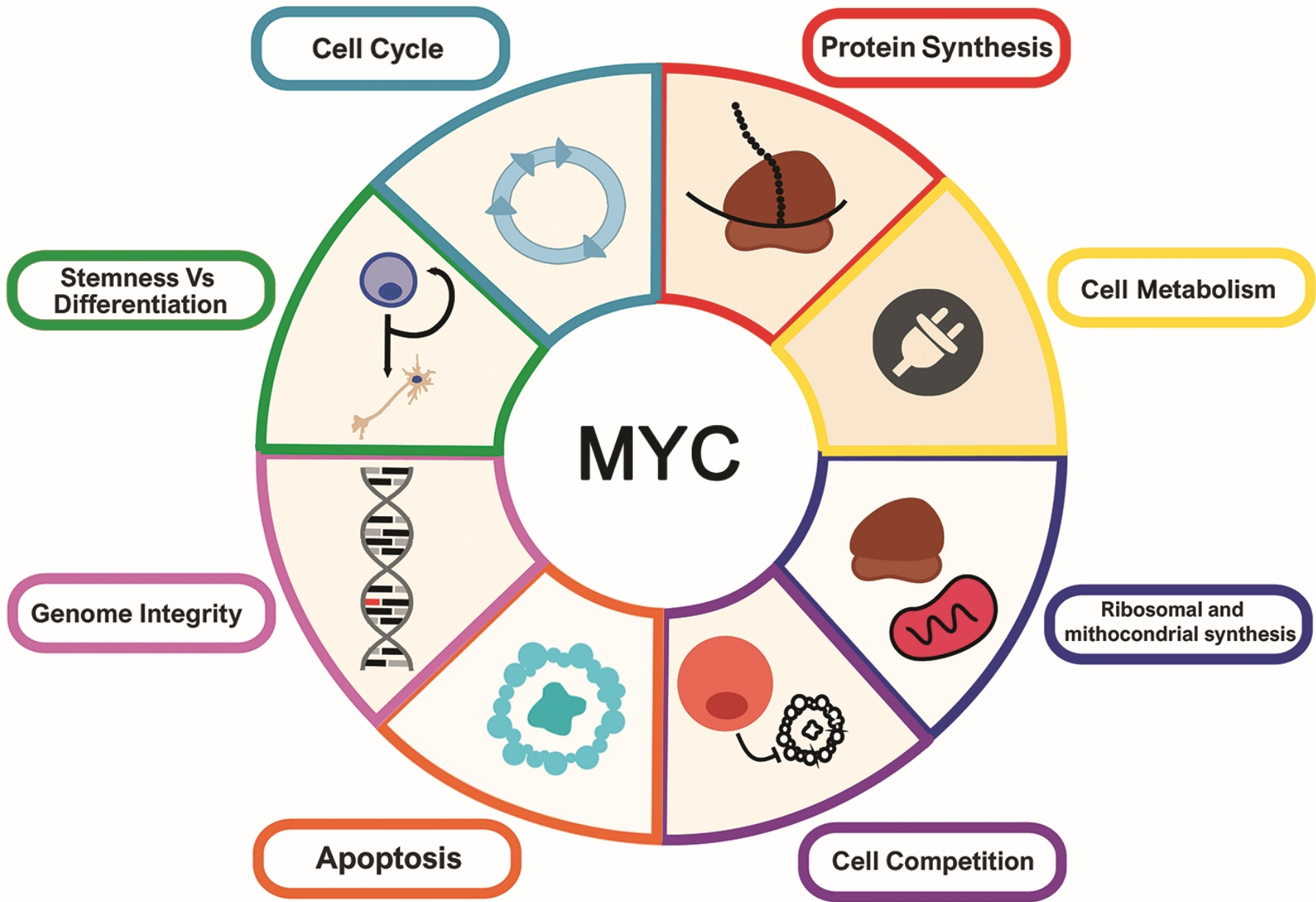
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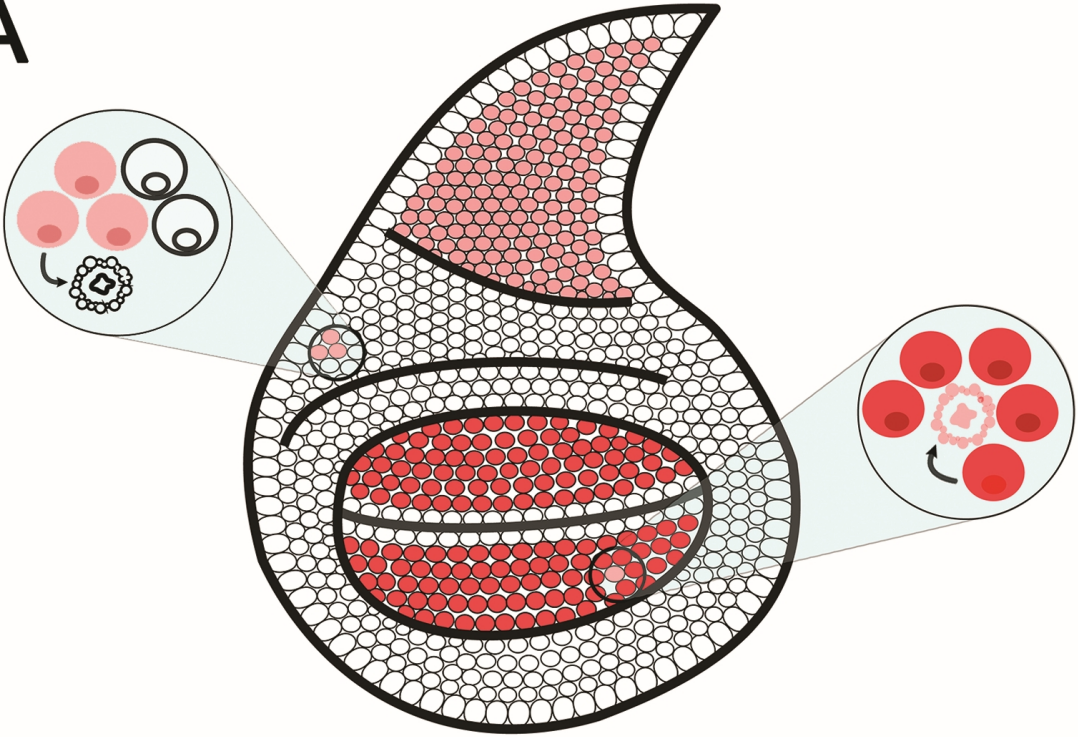
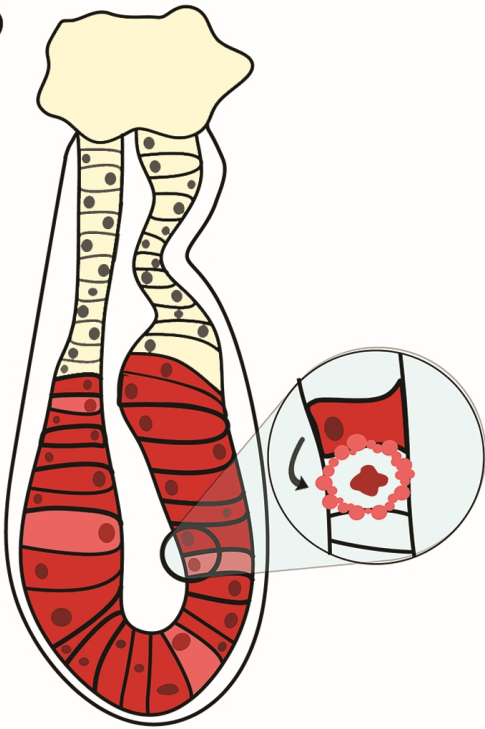
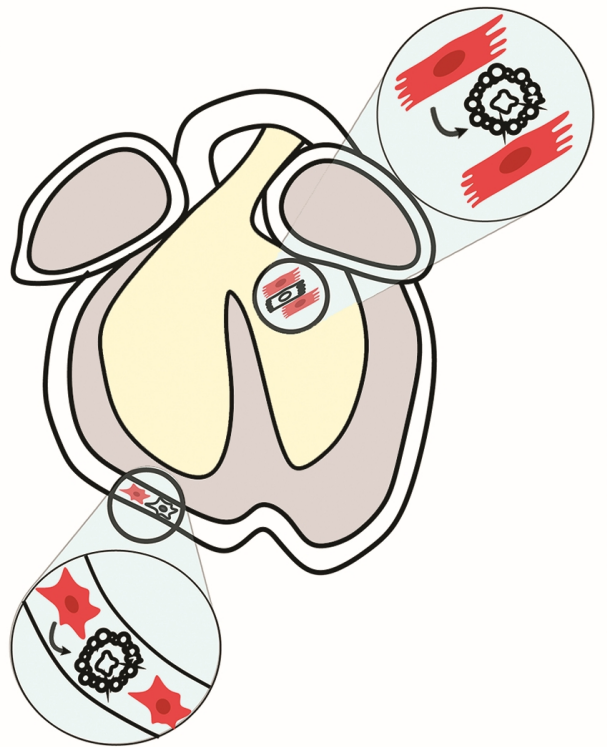
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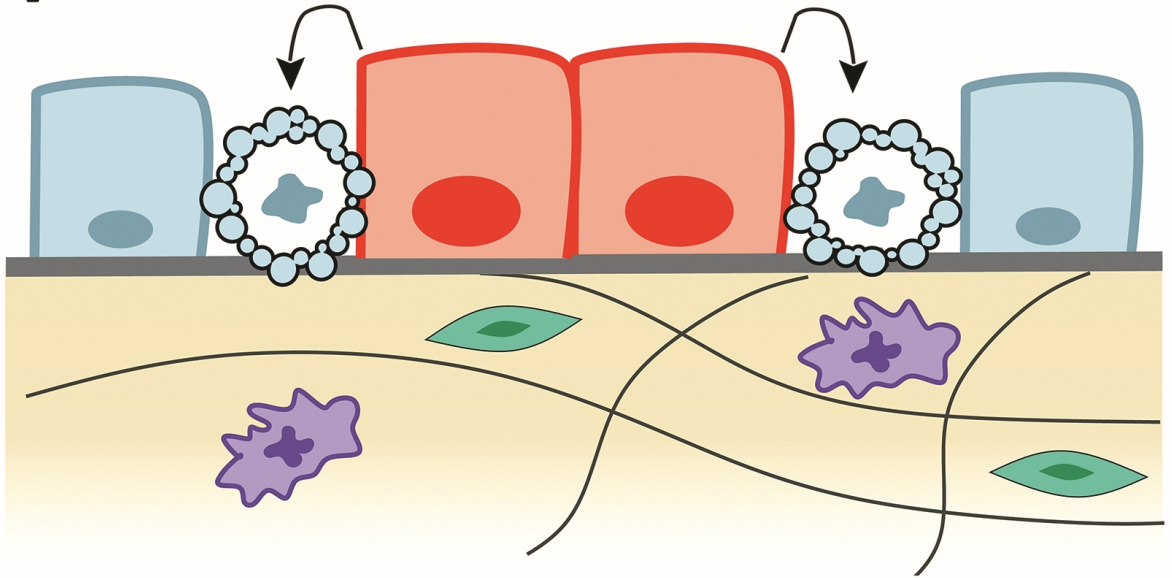
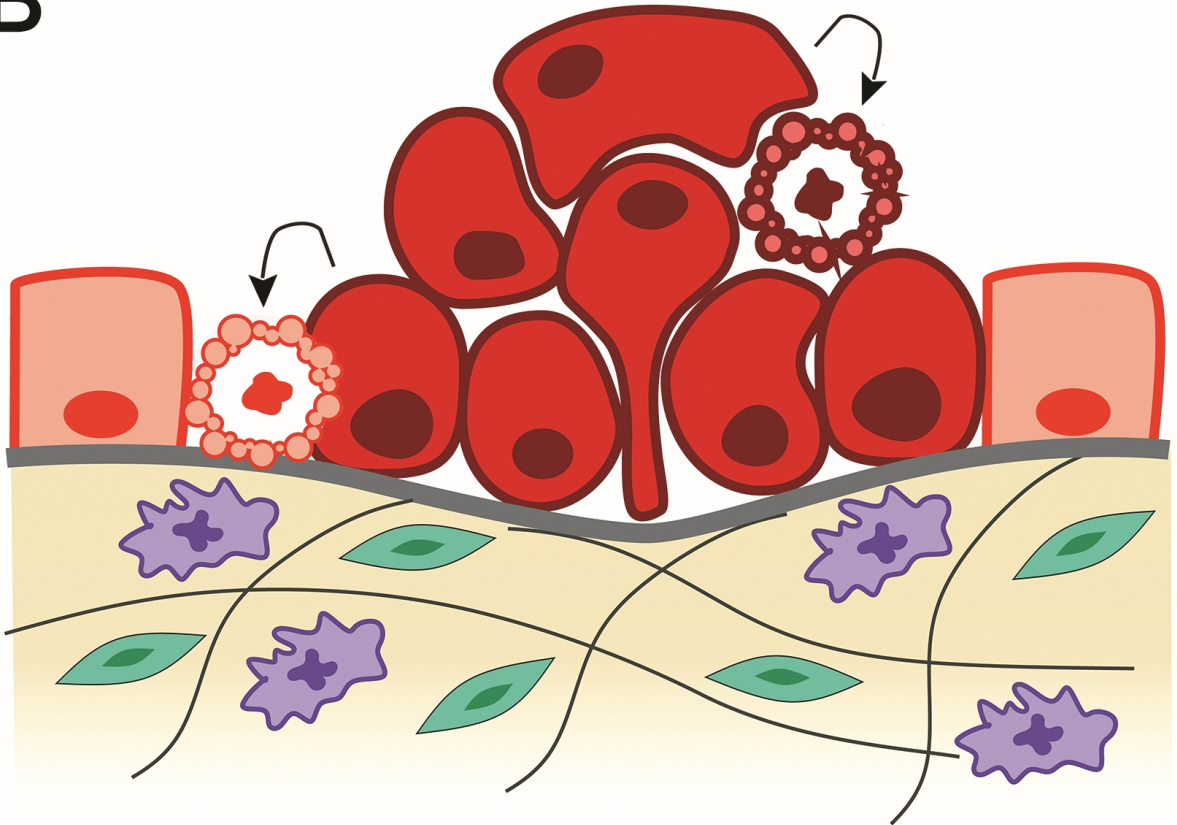
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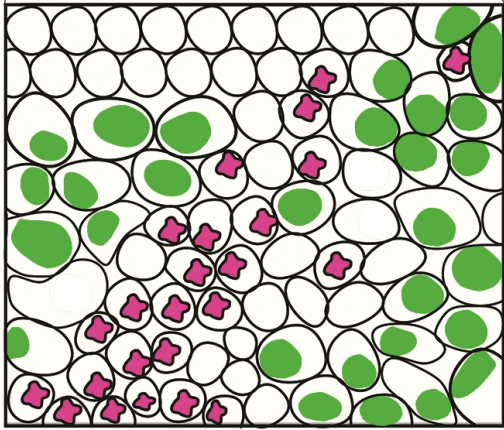
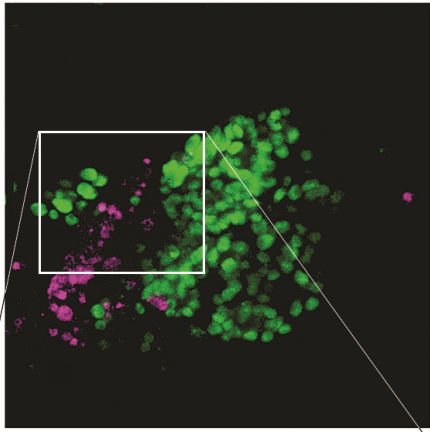
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