Published in final edited form as:
Genes Cancer. 2010 June 1; 1(6): 542–546. doi:10.1177/1947601910377490.

Myc Function in *Drosophila*

Paola Bellosta[1] and **Peter Gallant**[2]

[1]City College of the City University of New York, Department of Biology, New York, NY, USA

[2]Universität Würzburg, Würzburg, Germany

Abstract

Myc proteins control several cellular processes, including proliferation and growth, and they play an important role in human tumorigenesis. Several years ago, single homologs of Myc, its interaction partner Max, and its antagonist Mnt were identified in *Drosophila melanogaster*. Here, we review the function of this so-called Max network in fruit flies, with a particular emphasis on its most obvious biological activity: the control of cellular and organismal growth. We describe the molecular basis for this growth function, as well as the interaction of Myc with other pathways known to control growth, the insulin, TOR, and hippo pathways. In addition, *Drosophila* Myc also controls DNA replication and influences apoptosis, both cell-autonomously and non-autonomously, in a process known as cell competition. In the future, we expect that further functions of Myc will be uncovered and that genetic approaches will increasingly be used to characterize the evolutionarily conserved molecular mechanism of Myc action, thus also benefitting our understanding of Myc biology in vertebrates.

Keywords

growth; cell competition; transcription; ubiquitination; insulin; foxo; TOR; hippo

Introduction

The Myc/Max/Mnt Network

Extensive investigations of Myc proto-oncoproteins in vertebrate systems have revealed a network of interacting and partially redundant factors: the transcriptional activators of the Myc family (c-, N-, L-Myc), several transcriptional repressors (Mxd-1 through 4, Mnt, Mga), and their common dimerization partner Max (reviewed in Meyer and Penn1). The analogous network in *Drosophila* is considerably simpler: it consists of a single transcriptional activator (called Myc; the corresponding gene is named *diminutive*, in short *dm*), a single repressor (called Mnt), and their common partner Max (reviewed in Gallant2). These proteins show similar protein:protein and protein:DNA interaction specificities as their vertebrate counterparts. Thus, Myc:Max heterodimers bind E-box sequences and activate nearby genes, whereas Mnt:Max dimers repress transcription through similar sequence elements. 3,4 Moreover, vertebrate and *Drosophila* Myc proteins can partially substitute for each other: a truncated version of human c-Myc (called c-MycS) rescues a lethal *Drosophila Myc* allele,[5]

Corresponding Author: Peter Gallant, Universität Würzburg, Biozentrum, Physiologische Chemie 2, Am Hubland, 97074 Würzburg, Germany; peter.gallant@biozentrum.uni-wuerzburg.de.

Declaration of Conflicting Interests
The authors declare no conflicts of interest with respect to publication of this article.

and *Drosophila* Myc overcomes the proliferation block in murine embryonic fibroblasts carrying a conditionally knocked-out *c-Myc* gene[6]; *Drosophila* Myc can also cooperate with oncogenic Ras[V12] in transforming rat fibroblasts.[7]

Transcriptional Activity of Myc

Like its vertebrate counterparts, *Drosophila* Myc influences the expression of a large number of genes that are involved in diverse cellular processes.8¯12 A prominent group of Myc-activated targets code for proteins involved in ribosome biogenesis, translation, and metabolism, and many of these genes are repressed by Mnt, consistent with the antagonistic roles for Myc and Mnt in promoting and suppressing cellular growth, respectively (see below). In addition, Myc also stimulates the synthesis of noncoding RNAs that are involved in these processes—on one hand by inducing the expression of the transcription factor TIF-1A (and thereby activating RNA polymerase I), on the other hand by a physical interaction with the transcription factor Brf, which presumably directly increases RNA polymerase III activity. 10،13 Of note, this effect on RNA polymerase III is the only molecularly defined activity of Myc that does not involve Myc:Max heterodimers (i.e., does not require Max).13

The mechanisms by which Myc and Mnt control their target genes are presumably similar to those employed by their vertebrate homologs, but to date, only few transcriptional cofactors have been studied in detail in *Drosophila*. Thus, the DNA helicase Pontin/Tip49 (and, more weakly, the related protein Reptin/Tip48) interacts genetically and physically with Myc and contributes to the repression of certain target genes.[14] In addition, 3 members of the trithorax group of transcription factors bind to Myc and are essential for its biological activities *in vivo*: the histone-methyltransferase subunit Ash2 (ASH2L in vertebrates), the histone-demethylase Lid (related to vertebrate Rbp-2/JARID1A and PLU-1/JARID1B), and the ATPase Brahma (homologous to human hBrm and Brg1),[15] although it is still unclear how they affect Myc's transcriptional output. Finally, the corepressor Groucho (TLE3 in vertebrates) can interact with Myc and prevent it from activating certain target genes.16

The Biological Activity of *Drosophila* Myc: Control of Growth

Downstream Effect on Ribosome Biogenesis

The prominent role for the Myc network resides in the control of growth and animal size. Mutations in *Myc* show profound growth defects: dm^4 (null) mutant embryos hatch as larvae at the same time as wild-type animals but fail to grow and mostly die early in development, [17] while weak hypomorphic alleles (dm^1, dm^{P0}) allow the development of small, but normally proportioned, adult flies carrying disproportionately short and thin bristles. 18،19 All Myc-mutants are composed of small cells containing small nucleoli (with an according reduction of rRNA levels19،13). Conversely, overexpression of Myc increases cell size by accelerating cellular growth.19 Cells overexpressing Myc show a dramatic increase in nucleolar size and of ribosomal contents, 10 and expression of Myc throughout the animal increases the size of the adult fly by nearly 30%.20 On the other hand, Mnt null mutants are viable and have growth phenotypes that are opposite to those of Myc mutants, as cells mutant for Mnt are larger than normal, and Mnt mutant adults are heavier than wild type flies.4 Moreover, loss of Mnt partially rescues Myc mutant larvae, consistent with the opposing effect of Myc and Mnt on growth. 11،13 Taken together, these data, as well as the analysis of the transcriptional target genes (see above), indicate that Myc induces cell-autonomous growth in large part by modulating ribosome biogenesis.

Interaction of Myc with the Insulin Pathway and with TOR

Besides Myc, the target of rapamycin (TOR) and the insulin receptor (Inr) signaling pathway have emerged in recent years as two central players in the control of growth. These pathways

mediate the animal's growth response to changes in nutrient abundance,21 and both of them also influence Myc. On one hand, Myc appears to be an important downstream mediator of TOR activity because many of the genes that are induced in response to TOR activation are also Myc targets, in particular genes involved in ribosome biogenesis and protein synthesis. 12 Indeed, TOR was found to contribute to the stabilization of Myc protein,22 possibly by the inhibition of GSK3β, as has been shown for vertebrate Myc23 (PB, unpublished data).

On the other hand, the activation of the insulin pathway also inhibits GSK3β activity and thereby increases Myc stability (see below). One might thus expect that the Inr pathway also shares some transcriptional targets with Myc. Indeed, such an overlap between Inr and Myc targets can be seen in *Drosophila* S2 cells (PB, unpublished data), although it has not been reported for transcriptome analyses of whole larvae12; however, the effect of the Inr pathway on Myc is known to differ in different tissues (see below), and the complex mixture of tissues in an entire larva is likely to obfuscate some of the interactions between Myc and the Inr pathway. Another downstream effector of this pathway is the transcription factor Foxo, which is active under starvation conditions but inhibited by Inr signaling via protein kinase B (PKB/Akt) when food is plentiful.24 Foxo has been shown to interfere with Myc's transcriptional output in cultured cells, although the molecular basis for this effect is not known.25 In addition, Foxo differentially affects Myc mRNA expression in different tissues; for example, in the fat body, Foxo activates Myc under starvation conditions (see below), whereas it does not contribute to Myc activation in the muscle.22

Myc Activity in the Fat Body

The response to environmental nutrient abundance is (at least in part) mediated by the fat body, an insect organ with some functional homology to vertebrate liver and adipocytes.[26] The fat body produces endocrine signals that are needed for larval growth,27,28 and it thereby contributes to the release of *Drosophila* insulin-like peptide 2 (Dilp2) from the brain, which then activates the Inr cascade throughout the animal.[29] At the same time, the fat body (like any other tissue) also responds to circulating insulin levels, such that the transcription factor Foxo becomes active when the animal is starved and insulin levels are low. In this situation, Foxo was found to be required for maintaining Myc mRNA expression specifically in the fat body. 22 This observation is reminiscent of the finding in vertebrates that Myc mRNA is upregulated in the adipocytes and liver in response to caloric restriction, suggesting that Myc is required for maintaining the metabolic rate of these tissues during starvation.30,31

As a consequence of these different effects of the insulin receptor pathway, Myc activity in the fat body may be kept high when insulin levels are high and the downstream kinase PKB is active (through the inhibition of GSK3β and the concomitant stabilization of Myc protein) but also under starvation conditions when insulin levels are low and PKB is inactive (through the effect of Foxo on Myc expression). This would ensure a minimal metabolic rate in this regulatory organ, the fat body. Preliminary experiments suggest that it is indeed important for the animal to maintain a minimal amount of Myc activity in the fat body because specific knockdown of Myc in the fat body strongly reduces organismal viability (PB, unpublished data). Such animals contain low levels of triacylglycerides and of glucose, possibly because the low level of Myc activity in the fat body impairs its metabolism, which would then non-autonomously affect the growth of the whole larva (PB, unpublished data). Such a non-autonomous effect of Myc on growth was recently also reported in experiments with the molting hormone ecdysone, which was shown to regulate Myc levels in the fat body and thereby control the growth of the entire animal.[32]

Control of Myc Stability

Some of the effects described above affect Myc stability. In mammals, Myc protein has a short half-life of about 30 minutes, which is controlled in part by phosphorylation on specific sites within the conserved Myc box 1 (MB1, amino acids 45–63 in human c-Myc) and Myc box 3 domains (MB3, amino acids 259–266), the latter of which is flanked by putative PEST domains. 33 Upon activation by growth factors, the Raf/Ras/ERK kinase cascade mediates the phosphorylation of Serine 62.34,35 This phosphorylation is required for the scaffold protein Axin to recruit Myc to a multiprotein complex, containing the glycogensynthase kinase 3β (GSK3β) and possibly CK1α,36 and it serves as a priming event for GSK3β, which then phosphorylates Myc on Threonine 58. As a consequence, the ubiquitin-ligase SCF^{Fbw7} (E3-enzyme containing Skp1, a Cullin, and the F-box protein Fbw7) binds c-Myc and promotes its degradation by the proteasome pathway.[37]

The phosphorylation and ubiquitination events that regulate Myc protein turnover seem to be conserved in *Drosophila*. Mutation of the ubiquitin-ligase *archipelago* (*ago*), the *Drosophila* orthologue of mammalian Fbw7, results in Myc protein accumulation,[38] and overexpression of activated Ras augments Myc level *in vivo*, presumably via an effect on its protein stability.[39,40] A sequence analysis of *Drosophila* Myc identified optimal consensus sites for phosphorylation by Shaggy (Sgg), the *Drosophila* orthologue of GSK3β and for CK1α, a member of the casein kinase 1 family.[41] In contrast to its vertebrate homologs, *Drosophila* Myc was shown to contain multiple domains that are responsible for its degradation by these kinases.41 Mutations in these domains result in a partial resistance of Myc to the degradation mediated by Ago.41 Interestingly, one of these domains, situated near the conserved MB3, shows similarity to a sequence in β-catenin that was proposed to mediate binding to Axin, as well as the priming phosphorylation by CK1α and the subsequent degradation by GSK3β.[42] Indeed, Axin was found in a complex with Myc (PB, unpublished data), suggesting that this homologous domain might favor the formation of a complex that presents Myc to GSK3β and CK1 in order to allow its degradation. Consistent with this idea, we have observed that insulin increases Myc stability in *Drosophila* tissue culture, via PKB-dependent inactivation of GSK3β (PB, unpublished data).

A second domain involved in GSK3β-dependent degradation of *Drosophila* Myc also contains consensus sites for another kinase, casein kinase 2 (CK2).[41] Mutation of these sites also stabilized Myc, suggesting that additional signaling pathways contribute to the control of Myc protein stability (PB, unpublished data).

Control of Myc by the Hippo Pathway

As might be expected, Myc activity is also influenced by other growth regulatory pathways. The Hippo tumor suppressor pathway is one of the central controllers of organ size in flies and mammals.43,44 Briefly, inactivation of this pathway allows the downstream component Yorkie (Yki; YAP in vertebrates) to enter the nucleus and, in conjunction with transcription factors such as Scalloped (Sd), activate the expression of genes that promote cellular growth and proliferation and prevent apoptosis.[45,46] c-Myc was found transcriptionally induced in liver of mice expressing YAP,44 raising the possibility that part of YAP's/Yki's functions are regulated by Myc. Similarly in *Drosophila*, Myc was found to be regulated *in vivo* in response to inactivation of the Hpo pathway or ectopic expression of Yki (Laura Johnston, personal communication, 2010; Daniela Grifoni, personal communication, 2010). It will be of interest to understand how Myc contributes to these different activities, particularly because the YAP/Yki axis affects several of the processes that are also influenced by Myc (see below: cellular growth, apoptosis, and cell competition47).

Tissue Regeneration

An important aspect of growth is the capability of some animals to regenerate damaged body parts after an injury.[48,49] This process, called regeneration or regenerative growth, starts with the formation of a blastema, composed of proliferating cells that will give rise to the replacement tissue.[48] Recent studies showed that regenerating *Drosophila* wing imaginal disks upregulate Wingless (Wg), which indirectly induces Myc expression.50 This effect of Wg on Myc may involve a double repression mechanism that has previously been described in a different context, whereby Wg represses Notch (N), which otherwise would repress Myc, resulting in Myc upregulation.51 Consistent with a role for Myc in regeneration, overexpression of Myc after tissue ablation enhanced the regenerative process, whereas stimulation of other growth pathways (e.g., by overexpression of cyclin D and Cdk4) did not, suggesting that Myc may contribute in some specific (as yet uncharacterized) way to tissue regeneration.50

Additional Biological Activities of Myc

Apoptosis and Cell Competition

Another conserved activity of Myc proteins is their ability to induce apoptosis. Strong overexpression of *Drosophila* Myc (or of human c-Myc5) in imaginal disk cells triggers their death, whereas a reduction of Myc levels (by means of a hypomorphic allele) reduces the tendency of imaginal disk cells to undergo apoptosis in response to damaging ionizing radiation.13›52 This process does not require *Drosophila* p53 but involves one or more pro-apoptotic proteins of the *hid*, *grim*, *reaper*, and *sickle* group, whose expression may be directly induced by Myc.[52]

A second type of apoptosis is observed in mosaic imaginal disks, composed of cells with different Myc levels (recently reviewed by Johnston53). In such a situation, cells have a higher probability of undergoing apoptosis when they are situated close to cells with higher Myc levels —such that moderate Myc overexpression in one cell triggers apoptosis non-autonomously in the neighboring cells.20›54 An analogous phenomenon was first described 35 years ago under the name of “cell competition” 55: cells heterozygous for a so-called *Minute* mutation were shown to be outcompeted by neighboring wild-type cells and ultimately lost from the imaginal disk epithelium, even though such *Minute* heterozygous cells are perfectly viable in the absence of wild-type cells.[55,56] Indeed, *Minute*- and Myc-dependent cell competition affect the same process, as most *Minute* genes code for ribosomal proteins and *Minute* mutations reduce the rate of protein synthesis and growth,[57,58] as do mutations in *Myc* (see above). Moreover, heterozygosity for a *Minute* mutation impairs the ability of cells overexpressing Myc to outcompete wild-type neighbors,[54] consistent with the idea that *Minute* and the control of protein synthesis lie downstream of Myc. Therefore, cell competition leads to the elimination of slower growing, “less fit” cells and thereby is thought to increase the overall fitness of a developing organ.[20]

The mechanisms, by which moderate differences in Myc levels (and growth rates) between neighboring cells are translated into differential survival, are only beginning to be understood. Thus, for example, cell competition requires the engulfment of the competed “loser” cells—if engulfment is blocked, these cells are not killed in the first place,[59] but the molecular connection between this pathway and differential Myc activity is currently unknown.

Competition also occurs between female germ line stem cells occupying the same niche.[53] Differences in Myc levels may contribute to this process, as one group recently found that stem cells with comparatively less Myc are evicted from the niche at the expense of their wild-type competitors,[60] although a second report has found no influence of Myc levels.[61]

Cell competition has been best studied in *Drosophila*. However, some forms of cell competition also occur in vertebrates, [62,63] and it has been speculated that Myc-induced competition may contribute to the excessive growth of transformed cells that harbor elevated levels of Myc protein.[64]

Cell Proliferation and Endoreplication

Vertebrate Myc proteins are well known for their effects on cell cycle progression and proliferation rates. In contrast, over-expression of *Drosophila* Myc does not alter the doubling time of normal imaginal disk cells; although such cells have a shorter G1-phase, they concomitantly extend their G2-phase.[19]

A much more dramatic effect of Myc on cell cycle progression is observed in endoreplicating cells.[11,13,17,65] Such cells can reach ploidies of up to 1000 n; they make up most of the larval mass, and they are found in developing egg chambers. In a Myc mutant background, endoreplication is strongly impaired, and the nuclear volume of these cells is reduced; as a consequence, Myc mutant larvae are considerably smaller. Conversely, Myc overexpression in polyploid cells induces overreplication and a massive increase in nuclear volume.[17] We consider it likely that Myc's effects on endoreplication in polyploid cells and on G1-phase length in diploid cells have a common basis, but the molecular mechanisms are currently unknown.

Outlook

Many aspects of Myc function are evolutionarily conserved, to the extent that the fly and vertebrate proteins can substitute for each other. The simplicity of the *Drosophila* Myc/Max/Mnt network, coupled with the experimental tractability of the model system, promises significant progress in our understanding of animal Myc biology. Areas of intensive research include the interaction of Myc with other growth-controlling pathways and the effects of Myc on animal growth. Of particular interest are novel findings showing that Myc also influences growth non-autonomously, in neighboring cells via cell competition and systemically from the fat body. Future investigations will need to address the molecular basis of these phenomena and determine which role they play in vertebrate development and disease.

Acknowledgments

Acknowledgments and Funding

We thank Laura Johnston for critical reading of the manuscript and LJ, Pierre Léopold, and Daniela Grifoni for sharing results prior to publication. Work in the laboratories has been supported by grants of the NIH-DK085047 and by the Foundation CaRisBo (to PB) and by grants of the SNF and the DFG (to PG).

References

1. Meyer N, Penn LZ. Reflecting on 25 years with MYC. Nat Rev Cancer 2008;8:976–990. [PubMed: 19029958]
2. Gallant P. *Drosophila* Myc. Adv Cancer Res 2009;103:111–144. [PubMed: 19854354]
3. Gallant P, Shiio Y, Cheng PF, Parkhurst SM, Eisenman RN. Myc and Max homologs in *Drosophila*. Science 1996;274:1523–1527. [PubMed: 8929412]
4. Loo LW, Secombe J, Little JT, et al. The transcriptional repressor dMnt is a regulator of growth in *Drosophila melanogaster*. Mol Cell Biol 2005;25:7078–7091. [PubMed: 16055719]
5. Benassayag C, Montero L, Colombie N, Gallant P, Cribbs D, Morello D. Human c-Myc isoforms differentially regulate cell growth and apoptosis in *Drosophila melanogaster*. Mol Cell Biol 2005;25:9897–9909. [PubMed: 16260605]

6. Trumpp A, Refaeli Y, Oskarsson T, et al. c-Myc regulates mammalian body size by controlling cell number but not cell size. Nature 2001;414:768–773. [PubMed: 11742404]
7. Schreiber-Agus N, Stein D, Chen K, Goltz JS, Stevens L, DePinho RA. *Drosophila* Myc is oncogenic in mammalian cells and plays a role in the diminutive phenotype. Proc Natl Acad Sci USA 1997;94:1235–1240. [PubMed: 9037036]
8. Orian A, Van Steensel B, Delrow J, et al. Genomic binding by the *Drosophila* Myc, Max, Mad/Mnt transcription factor network. Genes Dev 2003;17:1101–1114. [PubMed: 12695332]
9. Hulf T, Bellosta P, Furrer M, et al. Whole-genome analysis reveals a strong positional bias of conserved dMyc-dependent E-boxes. Mol Cell Biol 2005;25:3401–3410. [PubMed: 15831447]
10. Grewal SS, Li L, Orian A, Eisenman RN, Edgar BA. Myc-dependent regulation of ribosomal RNA synthesis during *Drosophila* development. Nat Cell Biol 2005;7:295–302. [PubMed: 15723055]
11. Pierce SB, Yost C, Anderson SAR, Flynn EM, Delrow J, Eisenman RN. *Drosophila* growth and development in the absence of dMyc and dMnt. Dev Biol 2008;315:303. [PubMed: 18241851]
12. Li L, Edgar B, Grewal S. Nutritional control of gene expression in *Drosophila* larvae via TOR, Myc and a novel cis-regulatory element. BMC Cell Biol 2010;11:7. [PubMed: 20089194]
13. Steiger D, Furrer M, Schwinkendorf D, Gallant P. Max-independent functions of Myc in *Drosophila*. Nat Gen 2008;40:1084–1091.
14. Bellosta P, Hulf T, Diop SB, et al. Myc interacts genetically with Tip48/Reptin and Tip49/Pontin to control growth and proliferation during *Drosophila* development. Proc Natl Acad Sci USA 2005;102:11799–11804. [PubMed: 16087886]
15. Secombe J, Li L, Carlos L, Eisenman RN. The Trithorax group protein Lid is a trimethyl histone H3K4 demethylase required for dMyc-induced cell growth. Genes Dev 2007;21:537–551. [PubMed: 17311883]
16. Orian A, Delrow JJ, Rosales Nieves AE, et al. A Myc Groucho complex integrates EGF and Notch signaling to regulate neural development. Proc Natl Acad Sci USA 2007;104:15771–15776. [PubMed: 17898168]
17. Pierce SB, Yost C, Britton JS, et al. dMyc is required for larval growth and endoreplication in *Drosophila*. Development 2004;131:2317–2327. [PubMed: 15128666]
18. Bridges CB. *Drosophila melanogaster*: legend for symbols, mutants, valuations. Drosophila Information Service 1935;3:5–19.
19. Johnston LA, Prober DA, Edgar BA, Eisenman RN, Gallant P. *Drosophila* myc regulates cellular growth during development. Cell 1999;98:779–790. [PubMed: 10499795]
20. de la Cova C, Abril M, Bellosta P, Gallant P, Johnston LA. *Drosophila* myc regulates organ size by inducing cell competition. Cell 2004;117:107–116. [PubMed: 15066286]
21. Baker KD, Thummel CS. Diabetic larvae and obese flies: emerging studies of metabolism in *Drosophila*. Cell Metab 2007;6:257–266. [PubMed: 17908555]
22. Teleman AA, Hietakangas V, Sayadian AC, Cohen SM. Nutritional control of protein biosynthetic capacity by insulin via Myc in *Drosophila*. Cell Metab 2008;7:21. [PubMed: 18177722]
23. Zhang HH, Lipovsky AI, Dibble CC, Sahin M, Manning BD. S6K1 regulates GSK3 under conditions of mTOR-dependent feedback inhibition of Akt. Mol Cell 2006;24:185–197. [PubMed: 17052453]
24. Puig O, Tjian R. Nutrient availability and growth: regulation of insulin signaling by dFOXO/FOXO1. Cell Cycle 2006;5:503–505. [PubMed: 16552183]
25. Demontis F, Perrimon N. Integration of insulin receptor/Foxo signaling and dMyc activity during muscle growth regulates body size in *Drosophila*. Development 2009;136:983–993. [PubMed: 19211682]
26. Liu Y, Liu H, Liu S, Wang S, Jiang R-J, Li S. Hormonal and nutritional regulation of insect fat body development and function. Arch Insect Biochem Physiol 2009;71:16–30. [PubMed: 19353653]
27. Britton JS, Edgar BA. Environmental control of the cell cycle in *Drosophila*: nutrition activates mitotic and endoreplicative cells by distinct mechanisms. Development 1998;125:2149–2158. [PubMed: 9570778]
28. Colombani J, Raisin S, Pantalacci S, Radimerski T, Montagne J, Leopold P. A nutrient sensor mechanism controls *Drosophila* growth. Cell 2003;114:739–749. [PubMed: 14505573]

29. Géminard C, Rulifson EJ, Lèopold P. Remote control of insulin secretion by fat cells in *Drosophila*. Cell Metab 2009;10:199–207. [PubMed: 19723496]
30. Kim JW, Fletcher DL, Campion DR, Gaskins HR, Dean R. Effect of dietary manipulation on c-myc RNA expression in adipose tissue, muscle and liver of broiler chickens. Biochem Biophys Res Commun 1991;180:1–7. [PubMed: 1930207]
31. Horikawa S, Sakata K, Hatanaka M, Tsukada K. Expression of c-myc oncogene in rat liver by a dietary manipulation. Biochem Biophys Res Commun 1986;140:574–580. [PubMed: 3778468]
32. Delanoue R, Slaidina M, Leopold P. The steroid hormone Ecdysone controls systemic growth by repressing dMyc function in *Drosophila* fat cells. Dev Cell 2010;18:1012–1021. [PubMed: 20627082]
33. Gregory MA, Hann SR. c-Myc proteolysis by the ubiquitin-proteasome pathway: stabilization of c-Myc in Burkitt's lymphoma cells. Mol Cell Biol 2000;20:2423–2435. [PubMed: 10713166]
34. Sears R, Leone G, DeGregori J, Nevins JR. Ras enhances Myc protein stability. Mol Cell 1999;3:169–179. [PubMed: 10078200]
35. Sears R, Nuckolls F, Haura E, Taya Y, Tamai K, Nevins JR. Multiple Ras-dependent phosphorylation pathways regulate Myc protein stability. Genes Dev 2000;14:2501–2514. [PubMed: 11018017]
36. Arnold HK, Zhang X, Daniel CJ, et al. The Axin1 scaffold protein promotes formation of a degradation complex for c-Myc. EMBO J 2009;28:500–512. [PubMed: 19131971]
37. Yeh E, Cunningham M, Arnold H, et al. A signalling pathway controlling c-Myc degradation that impacts oncogenic transformation of human cells. Nat Cell Biol 2004;6:308–318. [PubMed: 15048125]
38. Moberg KH, Mukherjee A, Veraksa A, Artavanis-Tsakonas S, Hariharan IK. The *Drosophila* F box protein archipelago regulates dMyc protein levels in vivo. Curr Biol 2004;14:965–974. [PubMed: 15182669]
39. Prober DA, Edgar BA. Ras1 promotes cellular growth in the *Drosophila* wing. Cell 2000;100:435–446. [PubMed: 10693760]
40. Prober DA, Edgar BA. Interactions between Ras1, dMyc, and dPI3K signaling in the developing *Drosophila* wing. Genes Dev 2002;16:2286–2299. [PubMed: 12208851]
41. Galletti M, Riccardo S, Parisi F, et al. Identification of domains responsible for ubiquitin-dependent degradation of dMyc by glycogen synthase kinase 3{beta} and casein kinase 1 kinases. Mol Cell Biol 2009;29:3424–3434. [PubMed: 19364825]
42. Amit S, Hatzubai A, Birman Y, et al. Axin-mediated CKI phosphorylation of beta-catenin at Ser 45: a molecular switch for the Wnt pathway. Genes Dev 2002;16:1066–1076. [PubMed: 12000790]
43. Pan D. Hippo signaling in organ size control. Genes Dev 2007;21:886–897. [PubMed: 17437995]
44. Dong J, Feldmann G, Huang J, et al. Elucidation of a universal size-control mechanism in *Drosophila* and mammals. Cell 2007;130:1120–1133. [PubMed: 17889654]
45. Yu J, Zheng Y, Dong J, Klusza S, Deng WM, Pan D. Kibra functions as a tumor suppressor protein that regulates Hippo signaling in conjunction with Merlin and Expanded. Dev Cell 2010;18:288–299. [PubMed: 20159598]
46. Saucedo LJ, Edgar BA. Filling out the Hippo pathway. Nat Rev Mol Cell Biol 2007;8:613–627. [PubMed: 17622252]
47. Tyler DM, Li W, Zhuo N, Pellock B, Baker NE. Genes affecting cell competition in *Drosophila*. Genetics 2007;175:643–657. [PubMed: 17110495]
48. Brockes JP, Kumar A. Appendage regeneration in adult vertebrates and implications for regenerative medicine. Science 2005;310:1919–1923. [PubMed: 16373567]
49. Morgan TH. Regeneration and liability to injury. Science 1901;14:235–248. [PubMed: 17806597]
50. Smith-Bolton RK, Worley MI, Kanda H, Hariharan IK. Regenerative growth in *Drosophila* imaginal discs is regulated by Wingless and Myc. Dev Cell 2009;16:797–809. [PubMed: 19531351]
51. Herranz H, Perez L, Martin FA, Milan M. A Wingless and Notch double-repression mechanism regulates G1-S transition in the *Drosophila* wing. EMBO J 2008;27:1633–1645. [PubMed: 18451803]
52. Montero L, Müller N, Gallant P. Induction of apoptosis by *Drosophila* Myc. Genesis 2008;46:104–111. [PubMed: 18257071]

53. Johnston LA. Competitive interactions between cells: death, growth, and geography. Science 2009;324:1679–1682. [PubMed: 19556501]
54. Moreno E, Basler K. dMyc transforms cells into super-competitors. Cell 2004;117:117–129. [PubMed: 15066287]
55. Morata G, Ripoll P. Minutes: mutants of *Drosophila* autonomously affecting cell division rate. Dev Biol 1975;42:211–221. [PubMed: 1116643]
56. Simpson P, Morata G. Differential mitotic rates and patterns of growth in compartments in the *Drosophila* wing. Dev Biol 1981;85:299–308. [PubMed: 7262460]
57. Lambertsson A. The minute genes in *Drosophila* and their molecular functions. Adv Genet 1998;38:69–134. [PubMed: 9677706]
58. Marygold S, Roote J, Reuter G, et al. The ribosomal protein genes and Minute loci of *Drosophila melanogaster*. Genome Biol 2007;8:R216. [PubMed: 17927810]
59. Li W, Baker NE. Engulfment is required for cell competition. Cell 2007;129:1215. [PubMed: 17574031]
60. Rhiner C, Diaz B, Portela M, et al. Persistent competition among stem cells and their daughters in the *Drosophila* ovary germline niche. Development 2009;136:995–1006. [PubMed: 19211674]
61. Jin Z, Kirilly D, Weng C, et al. Differentiation-defective stem cells outcompete normal stem cells for niche occupancy in the *Drosophila* ovary. Cell Stem Cell 2008;2:39–49. [PubMed: 18371420]
62. Oliver ER, Saunders TL, Tarle SA, Glaser T. Ribosomal protein L24 defect in belly spot and tail (Bst), a mouse Minute. Development 2004;131:3907–3920. [PubMed: 15289434]
63. Bondar T, Medzhitov R. p53-Mediated hematopoietic stem and progenitor cell competition. Cell Stem Cell 2010;6:309–322. [PubMed: 20362536]
64. Moreno E. Is cell competition relevant to cancer? Nat Rev Cancer 2008;8:141. [PubMed: 18185517]
65. Maines JZ, Stevens LM, Tong X, Stein D. *Drosophila* dMyc is required for ovary cell growth and endoreplication. Development 2004;131:775–786. [PubMed: 14724122]