Abstract
Myc proteins seem to regulate diverse biological processes, but their role in tumorigenesis remains enigmatic. Here we use *Drosophila* imaginal discs to mimic situations in which cells with unequal levels of Myc protein are apposed and show that this invariably elicits a win/lose situation reminiscent of cell competition; cells with lower levels of dMyc are eliminated by apoptosis whereas cells with higher levels of dMyc overproliferate. We find that this competitive behavior correlates with, and can be corrected by, the activation of the BMP/Dpp survival signaling pathway. Hence the heritable increase in dMyc levels causes cells to behave as "super-competitors" and reveals a novel mode of clonal expansion that causes, but also relies on, the killing of surrounding cells.

RESULTS
Substantial progress has been made over the past decade in elucidating the molecular circuitries that control individual cellular behaviors, such as cell death or cell proliferation. However, the properties of entire cell groups can only in part be predicted from adding up those of individual cells. The ultimate understanding of tissue development and organ function will require a better knowledge of how cellular behaviors are interconnected. Understanding the coordination of cell death and cell proliferation within multicellular communities is a challenging task, especially in systems with high plasticity where changes in one process have an impact on the extent of the other. Such a plastic system is exemplified by the phenomenon known as "cell competition" ([Morata and Ripoll 1975](#)) where clonal cell populations expand with differential success, depending on their genetic constitution regarding ribosomal protein genes. Cells with reduced ribosomal activity are eliminated by apoptosis ([Moreno et al., 2002](#)), but only if situated amongst cells with wild-type activity. Since extra compensatory cell divisions occur to replace apoptotic cells during cell competition, the total number of cells in the developing tissue remains unchanged and no morphological alterations ensue in the resulting organ. This plasticity allows cells within a tissue to freely
interact with each other and may contribute to the optimization of organ function. Cell competition has recently been speculated to be involved in cancer through the acquisition of mutations that transform cells into "super-competitors" \citep{Moreno2002, deCova2002}. A hypothetical super-competitor cell could clonally expand within a tissue, propagating an initial mutation within the cell field and thereby increasing the number of target cells for further oncogenic lesions.

We have studied cell proliferation and apoptosis when two cell populations with different levels of dMyc are confronted with each other in the Drosophila wing. We show that the clonal proliferation behavior of cells exhibiting a set amount of dMyc is strongly influenced by surrounding cells if these express different amounts: cells with lower levels of dMyc are eliminated by apoptosis while cells with higher levels proliferate more. This rule also holds when the lower level of dMyc is set at wild-type and when the difference in levels vis-à-vis surrounding cells is merely two-fold. We further find that cells with higher dMyc levels overproliferate at the expense of cells with lower levels, and thus no morphological alterations arise. Our results provide evidence that dMyc can confer super-competitor properties to cells and suggest that deregulation of its mammalian homologs may contribute to cancer by similar means. Our observations illustrate how emerging properties of cell groups cannot be predicted by analyzing the behavior of isolated units but instead need to be considered in the context of surrounding cells sharing the same trophic environment.

References