

Omomyc, un mutante ad alterata dimerizzazione, permette la dissezione di programmi genetici regolati da Myc

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The Myc bHLHZip domain determines dimerization with Max and binding to the DNA E-box, both of which play a critical role in Myc regulation of growth, proliferation, tumorigenesis and apoptosis. The mutant bHLHZip domain, Omomyc, dimerizes with Myc, sequestering it in complexes unable to bind the E-box and so acting as a potential dominant negative. Consistent with this, Omomyc reverses Myc-induced cytoskeletal disorganization in C2C12 myoblasts. Surprisingly, however, Omomyc strongly potentiates Myc-induced apoptosis in a manner dependent on Myc expression level. Expression analysis of single Myc target genes and of 9000 genes on Affymetrix genomic chips, performed by turning on Myc expression in the presence or absence of Omomyc, indicates that Omomyc inhibits transcriptional activation but enhances repression. These findings suggest that Omomyc can selectively trigger apoptosis in cells over expressing Myc, possibly through the transcriptional repression of specific genes. Surprisingly, cluster analysis of the microarray data shows that large sets of genes are affected within a short time, pointing to Myc as a global regulator of gene expression. This work shows that mutant domains such as Omomyc are useful for dissection of genetic programs involved in Myc function and design of therapeutic strategies.