

P029 Uncoupling of Src-induced morphological and oncogenic transformation by distinct integrin domains

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Increased activity of the proto-oncogene c-Src and elevated levels of integrin $\alpha v \beta 3$ are frequently found in melanomas and multiple carcinomas. The inactive conformation of c-Src can be “primed” through disruption of SH2 and SH3-mediated intramolecular interactions and subsequently “activated” through cross-phosphorylation in the kinase domain. Interactions with overexpressed receptor tyrosine kinases or mutations in the *SRC* gene can induce priming of c-Src in cancer. Recently, we have found that integrin $\alpha v \beta 3$ drives activation of primed c-Src (Src^{YF}) causing enhanced survival, proliferation, and tumor growth. Experiments using various mutants of Src and $\alpha v \beta 3$ indicate that a functional interaction of the $\beta 3$ cytoplasmic tail with the c-Src SH3 domain is required for this cooperation.

Hyperactive Src also triggers a morphological transformation process that includes scattering, cell rounding, and a conversion of cell-matrix adhesions into podosomes. These aspects of Src transformation may contribute to malignant progression rather than tumor growth. In complete contrast to Src^{YF}-mediated tumorigenicity, this typical Src^{YF}-induced morphological alteration is not supported by integrin $\alpha v \beta 3$. Our findings demonstrate that these processes are regulated by separate pathways that are controlled by distinct regions of $\beta 1$ and $\beta 3$ integrins. Thus, Src-induced oncogenic transformation can be uncoupled from morphological transformation implying that different conditions regulate the ability of Src to support cancer development and malignant progression.