

Tumor stroma-derived TGF-beta limits myc-driven lymphomagenesis via Suv39h1-dependent senescence.

Reimann M, Lee S, Loddenkemper C, Dörr JR, Tabor V, Aichele P, Stein H, Dörken B, Jenuwein T, Schmitt CA.

Source

Charité - Universitätsmedizin Berlin/Molekulares Krebsforschungszentrum der Charité - MKFZ, 13353 Berlin, Germany.

Abstract

Activated RAS/BRAF oncogenes induce cellular senescence as a tumor-suppressive barrier in early cancer development, at least in part, via an oncogene-evoked DNA damage response (DDR). In contrast, Myc activation-although producing a DDR as well-is known to primarily elicit an apoptotic countermeasure. Using the Emu-myc transgenic mouse lymphoma model, we show here in vivo that apoptotic lymphoma cells activate macrophages to secrete transforming growth factor beta (TGF-beta) as a critical non-cell-autonomous inducer of cellular senescence. Accordingly, neutralization of TGF-beta action, like genetic inactivation of the senescence-related histone methyltransferase Suv39h1, significantly accelerates Myc-driven tumor development via cancellation of cellular senescence. These findings, recapitulated in human aggressive B cell lymphomas, demonstrate that tumor-prompted stroma-derived signals may limit tumorigenesis by feedback senescence induction.

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