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Regulation of angiogenesis by angiostatin through immune cells and IL 12 production

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Immune cells and cytokines can either promote or repress angiogenesis in physiological and pathological processes. We previously showed that low level IL-12 gene therapy blocked Kaposi's sarcoma (KS) xenograft growth in vivo by angiogenesis inhibition. Recruitment and activation of neutrophils and monocytes, critical regulators of immune response and IL-12 producers, are repressed by angiostatin, an anti-angiogenic molecule that also inhibits KS xenograft growth, and whose mechanism remains poorly understood. We reasoned that angiostatin could induce angiostatic cytokines by immune cells. Angiostatin retained its capacity to repress angiogenesis in IFNγ gene targeted animals. Function blocking antibodies to IL-12 strongly reverted angiostatin inhibition of angiogenesis. Angiostatin lost its anti-angiogenic potential in animals gene targeted for the IL-12 receptor IL12RB2 as well as in animals with the IL-12 p40 subunit deleted. The interference of angiostatin action was specific as fenretinide retained angiostatic activity. Endothelial cells lack an IL-12 receptor and do not respond to IL-12 stimulation in vitro, indicating that a secondary immune cell mediated signal is required in the angiostatic cascade induced by IL-12. Taken together, these data show that angiostatin induces IL-12 production by either/or neutrophils, macrophages, dendritic cells, resulting in IL-12 production that is a key component in angiostatin action. It is clear that the immune system is tightly intertwined with the vascular system and that angiogenesis inhibitors may principally target immune components rather than vascular cells.