RUNX1 PROMOTES TUMORIGENESIS THROUGH A p21 MEDIATED PATHWAY IN SKIN

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Runx1, a transcription factor with a potential to work both as an oncogene and a tumor suppressor in various cell types, has previously been suggested to work as an oncogene in the skin. Runx1 is important for hair follicle stem cell activation and is highly expressed in chemically induced skin tumors (papillomas). Furthermore, Runx1-deple- ted epidermis shows an increased resistance to the formation of tumors along with an up-regulation of the tumor suppressor, p21 (cyclin-dependent kinase inhibitor 1a, cdkn1a). *In vitro*, cell cycle progression of keratinocyte stem cells is regulated by Runx1 through a p21-mediated pathway. Here, we show that *in vivo* during tumor formation, Runx1 also promotes tumorigenesis through a p21-mediated pathway. The decreased tumor acquisition and tumor susceptibility in Runx1-depleted skin is partially rescued by additional p21 depletion. We use single and double knock-out mice ($Runx1^{ko}$, $p21^{ko}$, and $Runx1p21^{double\ ko}$), as well as wild type mice, to study the interactions between Runx1 and p21 during tumorigenesis. The back skin of these mice was treated with a two-step carcinogenic protocol over a period of 20 weeks, during which tumor formation was recorded weekly. Our study reveals that $Runx1p21^{double\ ko}$ mouse skin acquire significantly more tumors compared to $Runx1^{ko}$, implying p21 as a down stream target of Runx1 during *in vivo* tumorigenesis. Additionally, $Runx1p21^{double\ ko}$, along with $p21^{ko}$ and wt mouse skin, start to develop tumors earlier than $Runx1^{ko}$. Understanding the pathway by which Runx1 mediates carcinogenesis may be crucial for tailor-made cancer therapy. This study suggests that the status of p21 and its maintained expression may be crucial for the potential use of Runx1 as a target in cancer prevention and treatment.

DIPOSE DERIVED STEM CELLS PROMOTE BREAST TUMORIGENESIS

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Although mesenchymal stem cells have been shown to contribute to tumor growth, the role of adipose derived stem cells (ASCs), which are abundant in the host tissue within the mammary tumor microenvironment, in tumorigenesis is less well understood. Tumor-derived soluble factors (TDSFs) and increased tissue stiffness (i.e. chemical and mechanical cues inherent to the tumor microenvironment) are known to contribute to tumor cell malignancy; however, the effect of these cues on ASCs is currently unknown. Chemical cues were mimicked *in vitro* using conditioned media collected from MDA-MB231 and MCF-7, a more and less aggressive human breast cancer cell line, respectively. TDSFs increased the self-renewal and pro-angiogenic potential (e.g. secretion of vascular endothelial growth factor) of ASCs, while also promoting differentiation toward tissue stiffening lineages (e.g. myofibroblasts) and preventing differentiation toward softer tissue cells (e.g. adipocytes). The altered behavior of ASCs with TDSFs was more marked in response to the more aggressive tumor cell line. Alginate scaffolds of varying stiffness were used *in vitro* to mimic the moduli of normal to malignant breast tissue. Increased progenitor cell proliferation and pro-angiogenic behavior as well as decreased adipogenic differentiation was noted on matrices similar in stiffness to malignant breast tissue as compared to normal breast tissue. *In vivo* studies of orthotopic MDA-MB231 breast tumors in SCID mice also indicated the tumor enhancing effect of ASCs through increased tumor size and vascularization. Additionally, extracellular matrix (ECM) components potentially involved in stiffening (e.g. collagen and fibronectin) were found in greater quantities in MDA-MB231 tumors produced with ASCs rather than alone, as well as larger numbers of myofibroblasts. Collectively, our data indicates that tumor-derived chemical and mechanical cues alter the behavior of ASCS in a manner which promotes tumorigenesis by increasing microenvironmental angiogenesis and ECM stiffening.

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