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Regulation of Ctsk+ chondroid progenitors by the PTPN11 Gene

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Abstract

Cartilage tumors, accounting for 22% of skeletal system tumors, are characterized by the formation of osteochondromas, enchondromas, or both and cause significant morbidity and mortality. The molecular mechanism underlying the development and progression of these cartilaginous lesions remains incompletely understood. Shp2, encoded by the Ptpn11 gene, is one of two vertebrate Src homology 2 domain-containing protein-tyrosine phosphatases, and is required for most, if not all, receptor tyrosine kinase, cytokine, and integrin signaling pathways. Global deletion of Shp2 in mice results in early embryonic lethality, whereas postnatal Shp2 deficiency in various tissues/cells has diverse effects on their development and function. Several human malignancies, most notably childhood myeloproliferative disorders, are associated with PTPN11 gain-of-function (GOF) mutations. Several lines of evidence indicate that Shp2 plays an important role in skeletal development and homoeostasis; however, little is known about its role in vivo. Recently PTPN11 heterozygous loss-of-function (LOF) mutations are reported to cause human metachondromatosis (MC), a benign cartilage tumor syndrome with malignant potentials. By using cell lineage tracing and tissue-specific gene knockout approaches, we report here the identification of a novel population of cathepsin K-expressing (Ctsk+) chondroid progenitors (CCP) and that Shp2 deletion in CCP, in contrast to its GOF mutants in other tissues/cells, causes cartilaginous tumorigenesis recapitulating the features of MC, strongly suggesting that Shp2 has a tissue specific-tumor suppressor function; CCP is a novel population of cartilage stem cells and Shp2 negatively regulates their proliferation and chondrocytic differentiation. These findings open an exciting possibility to promote the innate rejuvenation capability of articular cartilage by mobilizing cartilage stem cells.

Biography:

Wentian Yang is a faculty member at the Department of Orthopaedics of the Brown University Alpert Medical School and the COBRE Center for Stem Cell Biology. He obtained his Ph.D. and M.D. degrees in China and completed his postdoctoral training at Harvard Medical School. Dr. Yang has published more than 20 papers in peer reviewed journals.