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Cancer Stem Cells in Bone

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Long bones, meant to bear weight and resist torsion, are initially formed from chondrocytes, which create a flexible cartilage scaffold. Blood vessels then invade this cartilage mould to bring in blood-forming cells that ultimately form bone marrow, within which reside bone-resorbing osteoclasts. From within the vessel wall arise mesenchymal progenitors that give rise to osteoblasts, cells that mineralize cartilaginous matrix to form a rigid structure, bone¹. However, chondrocytes persist and proliferate at the tips of long bones in the so-called “growth plate” to allow for linear bone growth up to puberty. Thereafter, bone is remodelled continuously with packets of old bone being replaced by new bone, a reparative process that maintains skeletal integrity throughout adult life².

Uncontrolled chondrocyte proliferation, mainly at the tips of long bones, causes benign cartilage tumour syndromes, such as metachondromatosis. This inheritable disease results mainly from heterozygous loss-of-function mutations of *PTPN11*, a gene encoding the ubiquitously expressed protein-tyrosine phosphatase SHP2³. Metachondromatosis is phenotypically and genetically distinct from related cartilage tumours, such as hereditary multiple exostoses and the enchondromatosis disorders Ollier disease and Maffucci syndromes. However, the cell population that becomes tumourigenic, in particular due to the loss of SHP2, has *hitherto* remained a mystery.

Yang *et al* attempted to delete Shp2 in osteoclasts using *lysosome M-Cre (LysM-Cre)* and *cathepsin K-Cre (Ctsk-Cre)* mice. Contrary to expectations from SHP1 deletion⁴, SHP2 excision in *LysM-Cre:Ptpn11^{fl/fl}* mice showed mildly reduced, rather enhanced, bone resorption. Serendipitously, however, in *Ctsk-Cre:Ptpn11^{fl/fl}* mice, where the authors had meant to delete *Ptpn11* even more selectively in osteoclasts by using a *Ctsk-Cre* driver, a conspicuous cartilage phenotype with bone exostoses typical of human metachondromatosis was noted. This intriguing observation suggests that *Ctsk*-mediated *Ptpn11* excision occurred in a yet uncharacterized cell type, which the authors identified, by lineage tracing, as a perichondrial cell pool that surrounds the growth plate. Cells within the perichondrial ring have been reported to be a source of chondrocytes, but their identity and function has remained unclear. By documenting their migration towards articular cartilage, the authors have to an extent indicated that these perichondrial progenitors may have a broader role in cartilage physiology and pathophysiology.

Of equal significance is the identification of a new destination for Ctsk, a cysteine protease that was thought to be primarily located in the osteoclast and to function in bone matrix degradation⁵. That Ctsk was found to be highly expressed in the perichondrial progenitor pool and may therefore have a role in cartilage degradation means that drugs, such as

cathepsin K inhibitors currently being developed for the therapy of osteoporosis, could conceivably affect cartilage homeostasis. The results also mandate that we re-visit the extensive and often zealous use of the *Ctsk* promoter as a driver of *Cre* recombinase selectively in the osteoclast⁶.

Interestingly, the *Ctsk*+ perichondrial cells express mesenchymal stem cell markers, are multipotent and capable of forming osteoblasts, adipocytes or chondrocytes, and expand during disease progression (Fig. 1). While they appear to constitute a pool of novel Shp2-regulated mesenchymal lineage cells in bone, it is not clear whether they fulfil the criteria for *bonafide* mesenchymal stem cells or simply represent more committed skeletal precursors *akin* to the recently described Mx1+ progenitors that function in bone remodeling^{7,8}. Of note is that both *Ctsk* and *Ptpn11* are highly expressed in nestin+ mesenchymal stem cells; the latter may, in fact, be the true precursors⁹. In contrast, *Ctsk* protein has been identified in self-renewing spheres derived from nestin+ mesenchymal stem cells isolated from human bone marrow¹⁰.

Whether or not perichondrial cells are proven to be true mesenchymal stem cells, Yang *et al* establish the presence of a “cancer stem cell” in bone for the first time. This is particularly noteworthy as skeletal neoplasms are relatively uncommon, and cancer stem cell *niches* in bone have rarely, if ever, been described. The discovery, however, raises the question whether Shp2 deletion in the perichondrial cell is the sole driver of tumorigenesis, or whether a “second hit” in any other chondrogenic derivative is required. This is important as the authors used a constitutively active *Ctsk-Cre* line to delete *Ptpn11* not only in progenitor cells, but also in derivatives that could potentially impact disease pathogenesis and progression.

In addition to metachondromatosis, germ-line mutations in *PTPN11* also cause Noonan, Noonan-like and LEOPARD syndromes, all of which are associated with a high risk of cancer¹¹. Somatic *PTPN11* mutations, in contrast, predispose to leukaemias and solid cancers. The question therefore arises how *PTPN11*, a known oncogene can, as in the case of metachondromatosis, suppress cell proliferation. As with other instances of genotype-phenotype discordance¹², specific point mutations in *PTPN11* can change the conformation of the SHP2 enzyme in ways that will either activate or inhibit oncogenic pathways¹¹. Mutations in LEOPARD syndrome, for example, cause an open, but catalytically dead SHP2 conformation, which acts as a dominant-negative construct to inhibit Erk activation^{11,13}. While this loss-of-function conformation would be expected to reduce oncogenesis, LEOPARD syndrome is associated with a high cancer incidence¹¹.

Similar to loss-of-function mutations in LEOPARD syndrome, frameshift, missense and splice site *PTPN11* mutations in metachondromatosis should result in catalytically dead SHP2 and reduced Erk activation. Yang *et al* found that Erk activation was indeed inhibited in *Ctsk-Cre:Ptpn11^{fl/fl}* mice. However, the mice developed cartilage tumours. The authors note that the tumorigenesis was due to the reduced secretion of Fgf18¹⁴, which, in turn, elevated the production of Ihh and Pthrp, both of which are potent chondrocyte stimulators. As proof-of-concept, an Ihh receptor inhibitor effectively prevented tumour formation. Whether a defective Fgf18/Pthrp/Ihh axis drives tumour formation in patients with

metachondromatosis as it does in mutant mice, and whether the disease is therefore amenable to Ihh receptor inhibitor therapy, remains to be determined.

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Figure 1. Model of Shp2 Regulation of Chondrogenesis

During normal development, *Fgf18*, produced by perichondrial cells, inhibits *Ihh* production and chondrocyte proliferation. When *Ptpn11* is deficient in progenitors expressing the *Ctsk* gene, increased *Fgf18* unblocks *Ihh* production and enables chondrocyte proliferation, initiating metachondromatosis.