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STEM CELLS

Back to the origins—identifying the skeletal stem cell

Two independent studies published in the same issue of *Cell* identify stem cells in mice that give rise to skeletal tissues—bone, cartilage and bone marrow stroma—but not to adipose, haematopoietic or muscle tissue.

In the first study, a team led by Timothy Wang and Siddhartha Mukherjee used a transgenic mouse model to trace the lineage of cells expressing the BMP antagonist gremlin 1 *in vivo*. This approach led to the identification of a novel population of stem cells, which the researchers called osteochondroreticular stem cells, that self-renew and generate osteoblasts, chondrocytes and reticular marrow stromal cells, but not adipocytes. "This is an important distinction from previously identified mesenchymal stem cells, which are defined, in part, by their capacity to differentiate into bone, cartilage and fat tissue," says Daniel Worthley, first author in the article. "It seems likely that there is not 'one' mesenchymal stem cell, but probably a number of different types of stem cells responsible for mesenchymal tissues, in the same way that there are numerous epithelial stem cells," add Wang and Mukherjee. Interestingly, gremlin 1 expression also characterizes a type of stem cell that gives rise to fibroblast-like cells in the intestine.

In the second study, Charles Chan, Irving Weissman, Michael Longaker and colleagues set out to search for the parental cell type of all skeletal progenitor cells. Investigation of clonal relationships and lineage development in mice *in vivo* led to the isolation of a population of postnatal mouse skeletal stem cells (SSCs) and to the characterization of its downstream progenitors, which give rise to bone, cartilage and stromal cells. Transcriptome analysis of these cell populations clarified the pathways involved in self-renewal of mouse SSCs and those needed for specification of the different progenitor lineages. The researchers also showed how administration of specific soluble morphogenetic factors can lead to reprogramming of non-skeletal mesenchymal tissue into cartilage.

Both sets of research groups are interested in exploring the applications of their findings to therapy of diseases of skeletal tissues. "We are trying to develop new cellular approaches to treat skeletal disorders such as osteoarthritis and osteoporosis using the different types of skeletal stem cells," comments Worthley. "We are now focused on identifying and characterizing the human SSCs to speed clinical translation of methods for regulating skeletogenesis that were identified in mice," says Chan.

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Original articles Worthley, D. L. *et al.* Gremlin 1 identifies a skeletal stem cell with bone, cartilage, and reticular stromal potential. *Cell* **160**, 269–284 (2015) | Chan, C. K. *et al.* Identification and specification of the mouse skeletal stem cell. *Cell* **160**, 285–298 (2015)