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Mechanism of BMP2 action in the adult: Progenitors in the peripheral nerve

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Injection of BMP2-producing cells into the quadriceps of a normal mouse causes bone formation irrespective of the cell type used1, since the cell simply supplies the BMP2 and all new tissue is derived from the host. Bone with a fully functional marrow cavity is formed within muscle in two weeks. This bone is also innervated and vascularized. Surprisingly, we have found that many or most of the progenitors for formation of this new bone are not within the bone marrow of the existing skeleton, but rather originate from local peripheral nerves. One of the first cells induced by BMP2 originates from the epineurium of local peripheral nerves. However, it must leave the nerve by induction of a process of neuroinflammation, mediated by mast cells as well as the pain mediators' substance P and CGRP2. This cell, once differentiated, has many of the properties of brown fat3. However, we have recently shown that the induction of this cell does not depend on some of the known mediators of brown fat biogenesis such as PPARG. Upon BMP2 induction this new cell can be isolated from either nerve or muscle by FACS for the β3 adrenergic receptor 3 (ADRB3). Using these FACS-isolated cells we have shown that the new cell also expresses UCP1and that the UCP1 expression is very transient. These levels rise 70-fold two days after BMP2 induction, yet by five days after BMP2 induction these levels are at baseline. UCP1 is solely responsible for lowering the oxygen tension in the microenvironment 3 and in so doing starts the process of chondrogenesis. UCP1 accomplishes this by a combination of oxygen burning and heating, since the solubility of oxygen decreases with increasing temperature. However this new cell also produces VEGF-D 4, and its secretion sets in motion neovascularization and also osteogenesis since osteoblast progenitors, also most likely arising from the nerve 2, are endothelial in origin. Additionally this new cell expresses the astrocytespecific molecule glial fibrillary acidic protein (Gfap) as well as the neural guidance molecule reelin. This cell is therefore most likely an astrocyte or astrocyte-like cell, albeit transient, that is induced in the peripheral nervous system for tissue repair. Astrocytes in the brain have many of the properties we see in this new transient glial cell in the peripheral nervous system. They are intimately involved in formation and maintenance of the cerebral vasculature and also are an important cell in the energy metabolism of the brain in that they supply ApoE to the neuron. The detailed analysis of the mechanism of action of BMP2 in the adult mice has shown the existence of an extremely rapid and tightly coupled system for tissue repair and maintenance that exists within the peripheral nervous system. We have found preliminary evidence that this system when induced in the wrong tissue, at the wrong time, or suffers genetic mutations, plays an important role in major human diseases including atherosclerosis 5, breast cancer (Salisbury, Olmsted-Davis, Davis, and Li, unpublished), and neurofibromatosis

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