# Divergent effects of vascular endothelial growth factor, VEGF and the N-terminal fragment of the parathormone-related protein, PTHrP on human adipose derived from mesenchymal stem cells

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The possibility of obtaining stem cells from adult tissues is highly attractive as they can potentially generate a variety of differentiated cells and be used in tissue regeneration. The study of stem cells obtained from adult organisms began some 50 years ago, when hematopoietic stem cells were described, which give rise to all blood cells[1]. Later, researchers described mesenchymal lineage stem cells and differentiated them into adipocyte, osteoblastic and chondrocytic cells. Mesenchymal stem cells were originally discovered in bone marrow, but were later found in other adult tissues, including peripheral adipose tissue. As Bravo et al.[2] report in their study, mesenchymal cells are characterized by the expression of surface markers, including CD90, and the use of others, such as CD45 and CD34.

The advantages of adipose tissue as a source of stem cells are its abundance in adults and the fact that it can be obtained by minimally invasive procedures such as liposuction. Once adipose tissue is obtained and treated enzymatically to remove extracellular proteins, stem cells can be separated from mature adipocytes by centrifugation, taking advantage of the low density of the adipocytes floating in the isolation medium. The cells at the bottom of the centrifuge tube, called the vascular stromal fraction, contain the so-called ASC (adipocyte stem cell or adipocyte stem cells). In the appropriate medium, ASCs can be differentiated into adipocytes, osteoblasts/osteocytes and chondrocytes or even into glial and neuronal cells[1].

The beneficial effect of parathyroid hormone (PTH) on the bone is widely recognized[3,4]. When the hormone is administered intermittently, it can activate the parathormone 1 receptor (PTH1R), triggering an increase in the number of osteoblasts, which leads to increased bone formation and bone mass. Its administration in humans is the only anabolic treatment approved by the Food and Drug Administration (FDA). Parathyroid hormone-related protein (PTHrP) is an analog of PTH capable of activating PTH1R through its N-terminal region[5]. Similar to PTH, clinical studies have shown that fragments containing the N-terminal region of PTHrP increase bone mass in postmenopausal women with osteoporosis.

Vascular endothelial growth factor (VEGF) is a cytokine produced by cells that are part of, or directly associated with, blood vessels[6]. VEGF is also produced by osteoblasts and participates in the development of endochondral, intramembranous bone and bone repair.

The research group that carried out this study[2] previously demonstrated the role of receptors for PTH and VEGF in the response of osteocytes to mechanical impulses[7,8]. These studies established the involvement of PTH1R and VEGF receptor 2 in the anti-apoptotic effect of mechanical stimulation exerted by fluid flow. In the present study by Bravo et al.[2] ASCs are shown to respond differently to VEGF and PTHrP (1-36). Treatment with pro-differentiating media leads to the production of alkaline phosphatase and mineral accumulation, along with the expression of osteoprotegerin and Runx2 in the ASCs. In contrast to the similar effect that receptors for PTH and VEGF exert on the viability of osteocytes subjected to mechanical stimulation, PTHrP (1-36) and VEGF do not have the same effect on the proliferation of ASCs. In particular, VEGF stimulates the proliferation of undifferentiated cells, whereas PTHrP (1-36) has no effect on growth medium. On the other hand, PTHrP (1-36), but not VEGF, stimulates the proliferation of ASCs maintained in medium supplemented with ascorbic acid and β-glycerophosphate to induce differentiation of cells into the osteoblastic lineage. The authors suggest that VEGF would be more effective in increasing the number of cells that remain undifferentiated in the vicinity of blood vessels, particularly in the presence of endothelial cells. On the other hand, PTHrP stimulates the proliferation of cells involved in the osteo-

blastic lineage in the proximity of more mature cells. These studies suggest the possibility of treatments combining the 2 agents to increase the amount of cells in cultures of ASCs that can be used to promote bone regeneration, for example, in individuals with fractures that cannot spontaneously weld.

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