

HUMAN CHONDROCYTE ADHESION MOLECULES - ROLES IN REGULATION OF CELL FUNCTION AND CARTILAGE REMODELLING

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INTRODUCTION: Cell-matrix interactions are known to be critical in the regulation of a variety of activities including cell proliferation, differentiation and death. In cartilage, where chondrocytes are isolated from neighbouring cells, a specialised pericellular matrix appears to be very important in the regulation of a range of metabolic activities and responses to environmental stimuli such as mechanical loads. These cell-matrix interactions are mediated by a variety of specialised cell surface molecules that can transmit signals from the extracellular space to the cell interior and through activation of intracellular signal cascades regulate gene expression.

The major cell adhesion molecules expressed by chondrocytes are members of the integrin family, CD44 and human melanoma proteoglycan (HMPG/NG2). The function of these molecules, as they relate to chondrocytes are only just beginning to be defined. Integrins such as $\alpha 10\beta 1$, $\alpha 1\beta 1$ and possibly $\alpha 2\beta 1$ appear to be important in chondrocyte adhesion to pericellular type II and type VI collagens whereas $\alpha 5\beta 1$ is involved in adhesion to fibronectin. Evidence is now accumulating for additional, important, roles for these molecules in recognition of mechanical stimuli and regulation of remodeling activities including matrix metalloproteinase production and modulation of apoptotic pathways. $\alpha 5\beta 1$ integrin, in particular, appears to be an important chondrocyte mechanoreceptor stimulation of which results in activation of an interleukin 4 dependent anabolic response. Expression of chondrocyte integrins varies during development and in diseases such as osteoarthritis where novel matrix molecules are expressed and active matrix remodelling is taking place. CD44 is a transmembrane molecule which may be expressed as a number of different isoforms as a result of

alternative splicing. It has been shown to be the major receptor for hyaluronan and is important for the retention of the gel like proteoglycan rich pericellular matrix around chondrocytes. CD44 may also act as a receptor for collagen and is known to transmit extracellular signals and regulate function of a variety of cell types. Roles in cartilage remodeling are beginning to be defined. HMPG/NG2 is a chondroitin sulphate-rich cell surface proteoglycan which although having collagen and fibronectin binding activities appears to function in cartilage indirectly by regulating integrin interactions with extracellular matrix molecules such as type VI collagen.

The nature of chondrocyte-matrix interactions will depend on the range of integrins and other adhesion molecules expressed by the cells and also the content of the pericellular matrix to which these cells are adherent. The result is a mutual reciprocity influencing cell differentiation and function. Understanding of these interactions, which are modified by a diverse range of factors including cytokines, mechanical stimuli, growth factors and matrix molecules themselves, is important for tissue engineering strategies aimed at production of different forms of cartilage for use in the treatment of human diseases.

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