

P015 Pharmacological regulation of adult stem cells: Chondrogenesis can be induced using a synthetic inhibitor of the retinoic acid receptor

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There is a growing interest in using adult stem cells for the repair of cartilage lesions. This requires well-defined and efficient protocols for directing the differentiation of stem cells into the chondrogenic lineage. Because the process of chondrogenesis is so closely intertwined with osteogenesis, many of the cytokines and growth factors that promote chondrogenic differentiation are also implicated in osteogenic differentiation. We have investigated the possibility of using pharmacological manipulation of adult human stem cells in place of growth factors as a means of regulating differentiation. In order to exemplify this approach we have determined which, if any, of the nuclear receptor superfamily might be involved in chondrogenesis using RT-PCR and FACS analysis. In this way we identified retinoic acid receptor β (RAR β) as a potential pharmacological target. A low molecular weight synthetic inhibitor of the RAR α and β receptors was able to induce chondrogenic differentiation in 2D and 3D cultures of mesenchymal stem cells derived from osteoarthritis patients, in the absence of serum and growth factors. Furthermore, the pathway is independent of SOX9 upregulation as shown using SOX9 siRNA knockdown analysis and does not lead to hypertrophy. These results demonstrate the feasibility of a pharmacological approach to the regulation of stem cell function both *in vitro* and *in vivo*.