

Increasing adipocyte size as well as numbers are important in the pathogenesis of obesity and type 2 diabetes in humans. Adipocytes are generated from mesenchymal precursor cells during the so called adipogenesis. This process consists of two related steps, the *determination* of multipotent mesenchymal stem cells into preadipocytes and the *differentiation* of preadipocytes into mature fat cells. While the differentiation is highly investigated, the determination in humans is poorly understood. The aim of the present study was to investigate, if wnt-5a is important in the determination process in humans. Therefore, human multipotent mesenchymal stem cells were isolated from umbilical cord blood and preadipocytes from fat biopsies of human subjects. These two primary cell populations exhibited similar morphology and expression of the mesenchymal surface markers (CD29, CD44, CD73). However, while mesenchymal stem cells were able to differentiate into adipocytes and osteocytes, preadipocytes were only able to undergo adipogenesis. Expression of wnt-5a was significantly higher in mesenchymal stem cells compared to preadipocytes, suggesting that wnt-5a is important to maintain osteogenic potential. Indeed, treatment of mesenchymal stem cells with neutralizing anti-wnt-5a antibodies inhibited osteogenesis and promoted adipogenesis. In agreement to these *loss of function* experiments, *gain of function* experiments using recombinant wnt-5a showed inverse effects on osteogenesis and adipogenesis. On a molecular level, wnt-5a was found to promote JNK non-canonical signalling pathway. Activation of this pathway resulted in increased osteopontin promoter activity and expression. These data suggest, that wnt-5a is necessary to maintain osteogenic potential of human mesenchymal stem cells and that down-regulation of wnt-5a expression is an important molecular process in the determination of these cells into preadipocytes. Furthermore, using immunohistochemistry, wnt-5a was also found to be expressed in adipose tissue macrophages. On a cellular level, macrophages were found to inhibit adipogenesis of mesenchymal precursor cells via wnt-5a. In summary, these data suggest, that the proosteogenic capacity of wnt-5a is crucial in maintaining multipotency of human mesenchymal stem cells, while the antiadipogenic effects of wnt-5a are important in the interaction of macrophages and adipose tissue in humans.