Induction of chondrogenic differentiation after Notch1 activation is regulated by Sox9

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The Notch pathway is an evolutionary highly conserved intercellular cell communication mechanism, involved in various cell lineage determination processes during embryonic development. Here we show the influence of Notch1 signalling on chondrogenic differentiation via Sox9 as a regulatory protein. We have previously demonstrated, that stages of early chondrogenesis can be recapitulated during ES cell differentiation in vitro. Condensed mesenchymal cells developed into mature chondrocytes. After prolonged cultivation cells showed the phenotype of hypertrophic chondrocytes and at later stages signs of ossification. For studying the influence of Notch signalling on chondrogenic differentiation in vitro, we used murine ES cells carrying a tamoxifen inducible form of the Notch intracellular domain (NICD) of the Notch1 receptor. The cells were differentiated in vitro as embryoid bodies (EBs). Activation of Notch1 at an early stage of EB differentiation results in an initial upregulation of Sox9 expression and induction of chondrogenic differentiation at later stages of EB cultivation. Using siRNA targeting Sox9 we were able to knock down and adjust this early induced Sox9 expression peak to non-induced levels accompanied by reversion of late chondrogenic differentiation induction. Our data indicates that Notch1 signalling plays an important role during early stages of chondrogenic lineage determination by regulation of Sox9 expression.