

P035 Regulation of Murine Embryonic Stem Cell Lineage Specification by PI3K-Dependent Signals

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Embryonic stem (ES) cells show great potential for the future of regenerative medicine but for this to be realised, an extensive understanding of the mechanisms governing cell fate is required. The two key features of murine ES (mES) cells, pluripotency and self-renewal, are dependent on bone morphogenetic protein (BMP4) and leukaemia inhibitory factor (LIF)-induced signalling and on the expression of the transcription factors Oct4 and Nanog. Phosphoinositide 3-kinase (PI3K) activity is important for proliferation and the maintenance of mES cell self-renewal in culture. The molecular mechanisms governing the relationship between PI3K, self-renewal and cell fate remain to be clarified. Despite the requirement for PI3K activity to maintain self-renewal, PI3K inhibition was demonstrated to have no regulation over lineage specification of differentiating mES cells. A chemically defined media was used to assess intracellular signalling responses to insulin and BMP4 stimulation. BMP4-induced mitogen-activated protein kinase (MAPK) signalling was shown to be regulated by PI3K. Following on from this, the effect of enhancing MAPK pathway activation was investigated. Self-renewal was maintained despite MAPK pathway activation, a known promoter of differentiation. These findings suggest the existence of PI3K-dependent regulatory and/or compensatory signalling mechanisms that may oppose differentiation promoting signals.