

P020 The involvement of phosphoinositide 3-kinases in regulating self-renewal of embryonic stem cells.

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Leukaemia inhibitory factor (LIF) is important for maintaining self-renewal of murine embryonic stem (ES) cells. Previous studies have shown that LIF-induced activation of Signal transducer and activator of transcription 3 (STAT3) is essential in mediating this response, while LIF-induced activation of extracellular regulated kinases (ERKs) promotes commitment. We demonstrate a role for PI3Ks in regulation of murine ES cell self-renewal. Treatment with LY294002, or inhibition of class I_A PI3K via regulated expression of dominant negative $\Delta p85$, dramatically reduced the ability of LIF to maintain self-renewal, with cells adopting a differentiated morphology. LY294002 had no effect on expression of STAT3 or Oct-4 or upon LIF-induced phosphorylation of STAT3 at Y705. However, LIF-induced phosphorylation of ERKs in both short and long-term incubations was augmented, while phosphorylation of GSK3 α and β were reduced. Inhibition of MEK, with either U0126 or PD98059, reversed the effects of PI3K inhibition on self-renewal. These findings demonstrate that phosphoinositide signalling, via PI3Ks, plays an important role in regulation of self-renewal of ES cells and increases our understanding of the signalling components involved in regulating stem cell fate.