AUTOCRINE FACTOR(S) SUPPORT EARLY EMBRYO SURVIVAL BY MAINTAINING P53 LATENCY VIA ACTIVATION OF THE 1-O-PHOSPHATIDYLINOSITOL-3-KINASE/ AKT SIGNALING PATHWAY.

V. Chandrakanthan[1], A. Cahana[1], C. O'Neill[1]

The mammalian preimplantation embryo develops and survives in vitro in defined media in the absence of exogenous trophic factors or hormones. It is the only normal mammalian cell type to do so. Recent evidence shows that this is dependent upon the action of one or more autocrine trophic loops that are activated soon after fertilization. The autocrine loops appear to operate survival signaling relays involving the activation of 1-o-phosphatidylinositol-3-kinase (PI3K).

We show that a downstream effector of PI3K, Akt, is present in the early embryo and its activity is necessary for normal embryo development and survival. Inhibition of PI3K (LY294002) or Akt (Akt-inhibitor or deguelin) induced dose-dependent embryopathy in zygotes cultured in vitro. This embryo was significantly reversed by simultaneous treatment of embryos with a defined autocrine embryotrophin (1-o-alkyl-2-acetyl-sn-gylceryl-3-phosphocholine, paf). Paf acted in both an Akt-dependent calcium-independent and a calcium-dependent Akt-independent manner to promote embryo survival. An important target for Akt is the phosphoprotein mdm2 that acts to induce p53 latency. Both p53 and mdm2 were expressed in the preimplantation embryo. P53 is a transcription factor that commonly acts to reduce cell proliferation or induce apoptosis. The inhibition of PI3K (LY294002), Akt (Akt-inhibitor) or autocrine signaling (pafr-/- embryos) in the preimplantation phase broke p53 latency and resulted in increased expression and nuclear accumulation of p53. The absence of p53 expression (p53-/- embryos) significantly reversed the embryopathy induced by the inhibition of the PI3K pathway.

The results show that one mechanism of action for autocrine survival factors is the maintenance of p53 latency via the stimulation of the PI3K-dependent survival pathway (260 words).

[1]Human Reproduction Unit, Department of Physiology, University of Sydney, Royal North Shore Hospital, St Leonards, NSW, 2065, Australia