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METABOLIC DETERMINANTS OF IMPLANTATION SUCCESS AND PROGRAMMING LONG TERM VIABILITY IN EMBRYOS

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It has long been recognised that energy substrate supply and metabolism are key determinants of early embryo development during *in vitro* culture. Recently it has been revealed that exposure to suboptimal metabolic environments during early embryo development can 'programme' subsequent development, leading to perturbed fetal development. For example, amino acid uptake profiles during early cleavage have been found to predict subsequent embryo development and potentially implantation success. However, the by-product of amino acid metabolism, ammonium, has also been found to significantly alter development, possibly through perturbed methylation of imprinted genes. Our own work has focussed on the role of oxygen availability and subsequent embryo development. Somatic cells respond to changing oxygen concentration by altering intracellular REDOX state (the balance between oxidative and reductive power within a cell), which in turn can alter transcription via REDOX-sensitive transcription factor activity. Furthermore, oxygen is known to have direct effects on transcriptional activity via the hypoxia-inducible factors (HIFs), transcription factors whose stability and DNA-binding activity are directly regulated by pO_2, in particular under hypoxic conditions. Using a mouse model, we have demonstrated that reducing pO_2 from 50 mmHg to 15 mmHg during the compaction and blastulation periods alone significantly alters expression patterns of oxygen-sensitive genes (such as glucose transporters), without significantly altering developmental progression to the blastocyst stage. Following transfer, embryos cultured under 15 mmHg O_2, despite similar implantation rates, produced fewer viable and lighter fetuses than *in vivo*-derived control embryos or those cultured in either atmospheric or 50 mmHg pO_2. This demonstrates that mouse embryos are sensitive to changes in their metabolic state during the post compaction period and that operating through causal pathways, the environment during this period of development can significantly affect subsequent developmental potential. Ironically, bovine embryo development appears to benefit under a low O_2 concentration. Furthermore, HIF protein stability appears to differ between the two species, which may be the underlying cause for the differences in gene expression and developmental competence.

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