Nutrient sensing by the early mouse embryo

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(Introduced by David Adams)

Early mammalian embryos display environmental sensitivities which may affect future growth and developmental potential both pre- and post-natally (Fleming, 2004). The causal mechanisms involved in this early environmental sensitivity however are unknown. It occurs prior to implantation, when the newly formed zygote cleaves and differentiates to form a blastocyst and acquires the metabolic competence to utilise glucose as an energy substrate on day 4 in development. We have identified that nutrients such as glucose can act beyond their role as energy substrates and modulate gene expression very early in development suggesting a critical role in metabolic programming. Significantly, we have found that a perturbed glucose environment results in cellular stress responses that are apparent within two hours of culture and prior to the first cell division. This leads to significant changes in the expression of key membrane transporter proteins associated with metabolic differentiation and blastocyst formation. So whilst glucose is not essential to the cleaving embryo as an energy substrate its presence is nonetheless critical for the maintenance of cellular homeostasis with perturbations leading to decreased levels of cellular proliferation and survival. Our work demonstrates that propagation of this nutrient signal potentially involves several different signaling mechanisms. These include glucose metabolism through hexosamine biosynthesis and downstream O-linked glycosylation of key intracellular proteins and transcription factors thus altering their activity. Moreover intracellular calcium release and oxidative stress response pathways are also implicated in embryonic glucose sensing. It is currently unclear how these signals integrate to facilitate development and modulate cellular physiology in response to nutrient availability. We believe that this work is the first to demonstrate a nutrient effect on levels of transcriptional regulators in early development. Elucidation of the mechanisms by which the nutrient environment influences embryonic development is of fundamental importance to our understanding of the origins of adult disease.

Fleming TP, Kwong WY, Porter R, Ursell E, Fesenko I, Wilkins A, Miller DJ, Watkins AJ & Eckert JJ (2004) *Biology of Reproduction*, **71**: 1046-54.