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Foreword

A developmental tale – metabolism takes centre stage

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The study of metabolism has undergone a major renaissance in recent years, and it is now 're'-accepted that metabolism pervades every aspect of homeostasis and physiology, from the subcellular level to the whole body (DeBerardinis and Thompson 2012). Great leaps are being made in our understanding that metabolism does much more than provide energy and biosynthetic precursors, and is not just a diagram of pathways resembling a 'map of the London Underground' relegated to undergraduate Biochemistry text books. Indeed, recent high profile discoveries (Radford *et al.* 2014; Kaelin and McKnight 2013) support the notion that metabolism is the driver of cellular development and differentiation, rather than the passenger. It now seems likely that metabolism has a major influence on genome remodelling, with the possibility of regulating change in gene expression and ultimately phenotype.

Nowhere is this more important than in the developing embryo. In the days immediately after fertilisation the preimplantation embryo undergoes significant reprogramming during the transition from two highly specialised cells (oocytes and sperm) through totipotent blastomeres in the cleavage stage embryo and into the differentiating blastocyst. Much is known already about the metabolic processes that power preimplantation events, thanks to pioneering work from the likes of Brinster, Whittingham, Biggers, Bavister, Whitten and Menezo, as well as a great many contributors to this special issue. However, the next great frontier is to understand how metabolic regulation in the early embryo during a period of great plasticity influences the phenotype of the resulting fetus and subsequent offspring. This is important in the context of the Developmental Origins of Health and Adult Disease concept, first proposed by the late David Barker. Barker spoke of the importance of the 'first 1000 days' in determining health throughout the life course of an offspring, and was mindful to point out that day 1 of this 1000 was the day of conception.

In late summer 2014, Edinburgh, Scotland hosted a meeting in which the unifying theme was 'oocyte and embryo metabolism'. We were fortunate to bring together many of the leaders in this field who treated the audience to a range of talks in which exciting new data describing how metabolism in the days surrounding conception can influence the life of the offspring – and some of this has subsequently been published in its own right. For example, Rebecca Robker and colleagues have recently published their findings on maternal obesity-induced oocyte endoplasmic reticulum stress (Wu *et al.* 2015). Additionally, we heard a compelling idea from David Gardner behind the up-regulation of lactate production synonymous with formation of the blastocyst (Gardner 2015).

Henry Leese began the proceedings with a personal, historical perspective of the history of the study of embryo metabolism, summarised stylishly in the opening article in this issue. Stephen Downs revelled in AMPKinase in the oocyte, before Jeremy Thompson reminded us that 'the oocyte is a *lazy* girl; the cumulus cells are the hard workers' with respect to oocyte glucose metabolism. Rebecca Robker presented her elegant data on endoplasmic reticulum stress in the oocyte of obese mothers, and how this stress persists into the offspring. In a first, we were treated to a Skype presentation by Christina Ferreira, who excitedly described the enormous power of modern mass spectrometry in the study of oocyte and embryo metabolism. Rebecca Krisher followed this up by summarising the great strengths and, importantly, limitations of applying metabolomic approaches to embryo biochemistry. John Carroll took us 'back to the cell', with an important reminder that all things metabolic link into the mitochondria, before David Gardner summarised the current state of knowledge of blastocyst metabolism. Randy Prather presented fantastic new insights into the links between metabolic activity and gene function, really setting the scene for Kevin Sinclair to discuss in depth the 1 carbon cycle as the important lynchpin between metabolism and gene expression. Of course, understanding embryo metabolism has clinical real-world applications, and it was Nick Macklon who spoke on the role of maternal nutrition; specifically about the [lack of] evidence in support of single nutritional supplements in altering embryo heath. Continuing this theme, Tom Fleming and Jo Leroy respectively presented data on the impact of protein and lipid in the maternal diet. In a particularly powerful demonstration, Abigail Fowden shared data on the susceptibility of the fetus to early life interventions. Regine Steegers Theunissen outlined methods to utilise our understanding of the links between maternal lifestyle, embryo metabolism and health of the offspring in a clinical setting. The meeting concluded with Kelle Moley sharing her expertise and knowledge of the extent to which metabolic-induced damage in the oocyte might be repaired; offering both hope that the metabolic destiny of an offspring is not set at conception, and caution that some perturbations were not reversible.

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Combined, the assembled speakers were able to describe, with great authority, the history, elegance, and importance of oocyte and embryo metabolism to both preimplantation development as well as offspring health. In addition, significant new questions for investigation were proposed. Support is growing for the notion that oocyte and embryo metabolism play an important role in the origins of non-communicable diseases that are so prevalent in modern society.

Within the pages that follow this special issue, you will find a collection of thoughts and data from our meeting in Edinburgh. By combining these manuscripts, which are an enjoyable and fascinating mixture of review and new data, this special issue forms an authoritative and timely collection of the very latest understanding of oocyte and embryo metabolism, as well as future directions to investigate intriguing new hypotheses.

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