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Modelling the developmental origins of health and disease in the early embryo

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Abstract

The concept that certain adult diseases, such as hypertension, type 2 diabetes and dyslipidaemia can originate from events occurring in utero arose from epidemiological studies in humans but has since been supported by numerous animal-based studies. Referred to as the ''developmental origins of health and disease'' or ''DOHaD'' hypothesis, nutritional studies to date have largely focused on two experimental paradigms involving either calorie or protein restriction for varying intervals during pregnancy, where the favoured animal models have been the sheep and rat. In recent times, attention has been directed towards the earliest stages of gestation, where there is emerging evidence to indicate that the pre-implantation embryo may be particularly sensitive to environmentally induced perturbations leading to impaired health in adulthood. In this article, we make the case for hESCs as a model of the human pre-implantation embryo. Working with comparatively large populations of embryonic cells from the species of clinical interest, the scope exists to investigate the effects of specific genetic manipulations or combinations of metabolites against contrasting genetic backgrounds, where the consequences can be evaluated in downstream tissue specific progenitor and/or terminally differentiated cells. In order to fully realize these potentials, however, both derivation and culture conditions need to be harmonized and refined so as to preclude the requirement for feeder cells and serum.

Keywords: Fetal programming; Epigenetics; Human embryonic stem cells

1. Introduction

The concept that late onset diseases can originate from events occurring in utero arose from the initial retrospective cohort studies of Barker et al. [1,2], who assessed relationships between size at birth, hypertension and ischemic heart disease in adult humans. Further studies were to establish inverse relationships between birth weight and the incidence of other diseases such as stroke, type 2 diabetes and dyslipidaemia and these observations ultimately led to the ''developmental origins of adult health and disease'' or ''DOHaD'' hypothesis [3]. In the decade or so that followed, numerous animal-based studies have sought to determine the effects of altered fetal nutrition on indices of long-term health (reviewed by ref. [4]). These studies have largely focused on two experimental paradigms involving either calorie or protein restriction for varying intervals during pregnancy and up to weaning, where the favoured animal models have been the sheep and rat. Whilst confirming the principle that nutrient restriction during in utero development can compromise physiological processes that determine long-term health, these studies have suffered from the following limitations. With notable exceptions to be identified later, they have:

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(i) provided little information on the effects of specific dietary nutrients, (ii) failed to establish a mechanistic base for these effects and (iii) generated little information that could reliably be extrapolated to early human development (reviewed by ref. [5]). There is also, currently, insufficient information on which to formulate a consensus regarding the effects of nutrient restriction during specific periods of in utero development, although there is emerging evidence that the earliest stages of pregnancy may be most sensitive to environmentally induced perturbations [6]. To that end, research efforts in the collaborating laboratories of Drs. K.D. Sinclair and L.E. Young at Nottingham are focussed on how specific dietary nutrients can alter epigenetic processes during gametogenesis and pre-implantation development where, in addition to in vivo studies with rodents and large animal species, investigations have been initiated with human embryonic stem cells (hESC), which we believe can serve as a useful model for the human embryo [7,8].

In the present article, we provide a brief overview of some of the unresolved issues and recent concepts to emerge from studies addressing the DOHaD hypothesis, leading to an evaluation of models for developmental programming in the early embryo. A brief overview of hESC biology and culture is provided and, partially drawing from the authors' own experiences, the potential of these cells to serve as a model for the human embryo assessed in relation to the use of contrasting animal models.

2. Developmental origins of adult health and disease

Epidemiological evidence has led to the formation of a number of hypotheses that attempt to explain DOHaD (reviewed by ref. [5]). Whilst some hypotheses adhere closely to the empirical evidence (e.g. effects of catch-up growth during infancy [9]), others attempt to explain this phenomenon in a broader evolutionary context in which DOHaD is viewed as an unfortunate consequence of a series of ill-defined mechanistic responses on the part of the developing organism as it attempts to adapt to changing ecological conditions [10–12]. Although an element of controversy surrounds these hypotheses, they have served to usefully focus the research efforts of a rather diverse group of biological scientists which include human epidemiologists, physiologists, reproductive biologists and, latterly, molecular geneticists. From the current debate emerge a number of poorly addressed issues that are central to the theme of the present review.

2.1. Critical periods of development

The aforementioned hypotheses draw support from the long-term follow-up studies of human populations subjected to famine during the Second World War, for example, in The Netherlands during the winter of 1944–45 [13]. One study of that cohort assessed the effects of maternal undernutrition during early, mid and late gestation in 50 year-old subjects who were born as term singletons [14]. These authors found that the timing of nutritional insult determined the nature of adult disease, which they hypothesized reflected critical periods of development for specific organs. The incidence of impaired glucose tolerance, for example, was greatest in subjects exposed to famine during late gestation. In contrast, the incidence of coronary heart disease, dyslipidaemia and obesity were greatest after exposure to famine during early gestation.

Where studies with animals have limited nutrient restriction to specific periods of gestation (Fig. 1) their findings broadly support the observations from the Dutch famine cohort. For example, calorie restriction during late but not early gestation in sheep led to increased obesity and insulin resistance as young adults [15]. In contrast, protein restriction in rats and calorie (i.e. global nutrient) restriction in sheep during early pregnancy have both been observed to increase systolic or mean arterial blood pressure [16–19] although other studies suggest that nutrient restriction during any stage of pregnancy can program adult hypertension [20].

Nutrient restriction during early pregnancy is interesting clinically for a number of reasons, but not least because up to 80% of women encounter symptoms of nausea and vomiting ('morning sickness') leading to modest weight loss between 4 and 12 weeks of gestation [21], a phenomenon largely overlooked by many working in the DOHaD field. Paradoxically, mild forms of morning sickness leading to modest weight loss are associated with positive pregnancy outcomes (e.g. reduced risks of miscarriage, perinatal death, low birth weight and congenital heart defects) [22], leading some investigators to question if the absence of 'morning sickness' is teratogenic [23]. Indeed, moderate nutrient restriction from 4 to 12 weeks of gestation in mature sheep can increase placental development in ewes of good but not poor body condition [24] and there is evidence of similar responses associated with increased fetal growth in humans [25]. The fact that women also develop cravings and aversions suggests that, during this very sensitive period of embryonic development, intake is modified in an attempt to avoid the consumption of foodstuffs that contain potential