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Developmental origins of metabolic disorders: The need for biomarker candidates and therapeutic targets from adequate preclinical models

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ABSTRACT

The investigation on obesity and associated disorders have changed from an scenario in which genome drove the phenotype to a dynamic setup in which prenatal and early-postnatal conditions are determinant. However, research in human beings is difficult due to confounding factors (lifestyle and socioeconomic heterogeneity) plus ethical issues. Hence, there is currently an intensive effort for developing adequate preclinical models, aiming for an adequate combination of basic studies in rodent models and specific preclinical studies in large animals. The results of these research strategies may increase the identification and development of contrasted biomarkers and therapeutic targets.

1. Introduction

Currently, nutrition-related disorders (obesity, metabolic syndrome and diabetes) are in the focus of intense research and debate. First, the appearance of obesity and associated conditions like diabetes is linked to other non-communicable disorders; e.g. cardiovascular disease. In fact, 50% of deaths caused by diabetes are related to cardiovascular disease (primarily heart disease and stroke; [1]). Second, obesity and associated disorders were traditionally reported in adult individuals of wealthy populations from high-income countries. However, in recent years, the global changes in lifestyle and dietary patterns have modified the distribution of the diseases and therefore obesity and diabetes affect both children and adults of different socioeconomic classes in both developed and developing countries [2]. Hence, obesity was declared a global pandemic by the World Health Organization (WHO) in 2005, when the affected population reached 400 million of adults and at least 2.6 million of people were dying each year as a result of being overweight or obese. Furthermore, WHO predicted that around 2.3 billion adults would be overweight and 700 million would be obese by 2015 (http://www.who.int/features/factfiles/obesity/en/index.html). This prediction was not too much inaccurate since in the last year, 2014, around 1.9 billion of adults were reported to be overweight and 600 million to be obese (http://www.who.int/mediacentre/factsheets/fs311/en/). These data mean that 39% of adults are overweight and 13% are obese; of them, 9% are affected by diabetes. Diabetes caused 1.5 million deaths in 2012; more than 80% of them occurring in low- and middle-income countries (http://www.who.int/mediacentre/factsheets/fs312/en/).

Moreover, the problem is aggravated by the causal relationship among nutrition-related diseases and other non-communicable diseases (i.e. renal, immune, inflammatory and reproductive disorders, and cancer [3–7]). Hence, the epidemics is becoming a major worldwide public health problem since it does not only affects directly life-quality and wellbeing of individuals but also constitutes a strong economic challenge to health-care systems and governmental administrations. Thus, there is an urgent need to tackle the situation, by both increasing research in the area and developing adequate strategies for prevention and treatment.

The studies performed in the last decades have changed substantially the vision of the causal factors of obesity and associated disorders. We have moved from a gene-centric static perspective, in which genome drove the phenotype with secondary

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influence of lifestyle and nutrition, to a much more holistic and dynamic approach in which environmental, parental, prenatal and early-postnatal conditions are strongly determinants of postnatal development and homeostasis and therefore health status and disease risks. In this scenario, the development of proteomics and other "-omics" during the last years is giving a complimentary tool that may help to accurately elucidate the condition and identify therapeutic targets [8–13].

2. The Developmental Origins of Health and Disease (DOHaD)

The DOHaD concept points out that prenatal and early-postnatal conditions (mainly nutrition and lifestyle) determine growth, life-time fitness/obesity and the risks for non-communicable diseases via epigenetic changes induced during development (reviewed in Ref. [14]). In all the mammalian species, foetal development is dependent on adequate transfer of oxygen and nutrients from the mother to the foetus via the placenta. Inadequate maternal conditions (e.g. deficiency or excess in food intake or hypoxia) and/or metabolic disturbances (e.g. obesity, metabolic syndrome or diabetes) and insufficient placental function may affect the supply of oxygen and nutrients to the foetuses. Hence, such conditions may affect foetal development and may compromise homeostasis, metabolism and health of the offspring throughout life, and even may affect subsequent generations (transgenerational programming [15]).

In case of maternal food-intake excess, obesity and metabolic disorders, the excess in the supply of nutrients induces an excessive development of the foetuses. At birth, in situations of maternal overnutrition, neonates are frequently large-for-gestational age (LGA) and obese, having high amounts of body fat; moreover, they can manifest macrosomia with severe enlargement of heart, liver and spleen [16].

In case of maternal food intake deficiencies or hypoxia and in case of placental insufficiency, the shortage in the supply of oxygen and nutrients to the foetuses causes deficiencies in their development. The neonates are small-for-gestational-age (SGA), with reduced body-weight at birth as a consequence of a process known as intrauterine growth restriction (IUGR). In humans, the incidence of IUGR infants ranges between 7 and 15% depending on sociodemographic issues [17]. Classically, IUGR has been associated with maternal malnutrition but, currently, 60% of IUGR offspring are identified as mainly caused by placental insufficiency [18,19].

Maternal obesity and metabolic disorders may also cause IUGR [20–22], mainly due to vascular alterations affecting the placental development and function and causing foetal hypoxia [23]. Women with alterations in glucose and lipid metabolism may also develop hypertensive disorders in pregnancy (HDP). HPD includes a spectrum of disorders varying, according to severity, from chronic pre-existing hypertension and gestational hypertension to preeclampsia and eclampsia. Occurrence of HDP usually induces IUGR and SGA [24].

SGA offspring, depending on the severity of IUGR, may be predisposed to high neonatal morbidity and mortality rates, with early death or life-long alterations in their development, health and welfare [25]. In offspring with extreme IUGR, deficiencies of development are unavoidable and viability of the neonate is strongly compromised, causing death. In less-critical IUGR, the central nervous system functionality is assured but the functionality of the other organs can be severely affected. Hence, health and welfare of these IUGR offspring is compromised by gastrointestinal (alterations in development and function of the intestine, which predispose to feeding intolerance and digestive disorders), metabolic (inadequate liver development, which is essential for the metabolism of glucose, amino-acids, proteins, lipids and vitamins), respiratory (abnormalities in the airways and lungs, causing impaired respiratory function), renal (compromising homeostasis and causing hypertension) and immune disfunctions (immune depression and high susceptibility to infection) [26–30].

At adulthood, both LGA and SGA phenotypes are affected by different health complications, such as obesity, metabolic, and cardiovascular pathologies [25,31–34].

The profound implications of these disorders in perinatal survival and lifelong performance and health have boosted research efforts. The perspective on future research is based on three pillars: the complete understanding of the underlying biology of the disease, the availability of contrasted biomarkers for diagnosis, and the assessment of preventive and curative treatments. These three keystones would allow the improvement of both individualised healthcare and wide population strategies focussed on diagnostic and treatment.

3. The usefulness of animal models for the screening of adequate biomarker candidates and therapeutic targets

Biomarkers are essential tools for delineating adequacy or inadequacy of biological processes (for allowing early and accurate diagnosis) and the spectrum of biological effects of intervention strategies (for developing optimal dosage and treatment strategies). However, the a priori discovery of biomarker candidates in patient populations is difficult due to the inherent high variability of data caused by a plethora of confounding factors (including genetic, lifestyle and socioeconomic heterogeneity, as well as co-morbidities and their treatments, to name but a few). In addition, research in human beings is obviously limited by ethical issues.

Hence, preclinical studies in animal models are an important source of biomarker candidates for the systematic analysis of pregnancy disturbances and for the efficacy and safety evaluations of new treatments. The translation from basic research into practice is a long, often inefficient and costly process. The choice of appropriate animal models with adequate features is critical for the success of translational research.

Models in experimental studies on obesity and metabolic disorders have been traditionally based on laboratory rodents, especially rats and mice [35–38]. The rodents need little space, are relatively inexpensive to maintain, easy to manage, have a short life cycle, have a sequenced genome and are easily modified by genetic engineering. However, rodents are the election model for studies on a concrete mechanism but there are also certain severe limitations. The main constraints are the marked differences with humans in cell and tissue biology, metabolic and endocrine routes, and developmental patterns and physiology of organs and systems [39,40]. Moreover, placentation of rodents is a very specific evolutive strategy of these species and show large differences when compared to humans [41]. Hence, findings in rodents are very different from those in human patients in many diseases and developmental areas. Different large animal species overcome these limitations and offer numerous profitable characteristics for the discovery and testing of biomarkers.

In brief, housing and management of large animals are well-developed, behavioural patterns are diurnal and body size allows application of imaging techniques and serial sampling of large amounts of blood and tissues. Moreover, pathways regulating appetite, energy balance and adipogenesis in large animals are more similar to humans than in rodents. Finally, in the last years, the genomic analysis is well-advanced and it is possible to obtain targeted gene mutations for specific models.

The most prominent large animal model for translational studies in nutritional and metabolic disorders is the pig [42,43]. At the same time, the mammalian species with the highest rate of IUGR is the swine with an average incidence of 15–20% [44,45].