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Review

Transgenerational inheritance of metabolic disease

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ABSTRACT

Metabolic disease encompasses several disorders including obesity, type 2 diabetes, and dyslipidemia. Recently, the incidence of metabolic disease has drastically increased, driven primarily by a worldwide obesity epidemic. Transgenerational inheritance remains controversial, but has been proposed to contribute to human metabolic disease risk based on a growing number of proof-of-principle studies in model organisms ranging from *Caenorhabditis elegans* to *Mus musculus* to *Sus scrofa*. Collectively, these studies demonstrate that heritable risk is epigenetically transmitted from parent to offspring over multiple generations in the absence of a continued exposure to the triggering stimuli. A diverse assortment of initial triggers can induce transgenerational inheritance including high-fat or high-sugar diets, low-protein diets, various toxins, and ancestral genetic variants. Although the mechanistic basis underlying the transgenerational inheritance of disease risk remains largely unknown, putative molecules mediating transmission include small RNAs, histone modifications, and DNA methylation. Due to the considerable impact of metabolic disease on human health, it is critical to better understand the role of transgenerational inheritance of metabolic disease risk to open new avenues for therapeutic intervention and improve upon the current methods for clinical diagnoses and treatment.

Contents

1. Introduction

Metabolic disease includes obesity, type 2 diabetes (T2D), insulin resistance, atherosclerosis, hyperlipidemia, and hepatic steatosis. This class of disorders is driven by abnormalities in the conversion of food to energy, often as the result of prolonged under- or overnutrition. This shared etiology often results in the clustering of multiple metabolic risk factors in an individual, which is referred to as metabolic syndrome [1]. The prevalence of metabolic disease has increased dramatically over the past few decades, largely driven by a worldwide obesity epidemic [2,3]. Collectively, comorbidities of obesity now cause 3 million premature deaths annually worldwide and make obesity the sixth leading risk factor for loss of health

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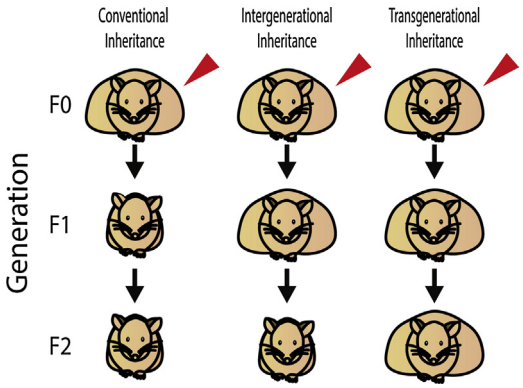

Fig. 1. Characteristics of epigenetic and conventional inheritance patterns. The red arrow indicates a triggering event (genetic or environmental) in the F0 generation. Obesity is shown as a representative phenotype. Although the F0 mice are represented as obese, the triggering event need not induce a phenotype in the F0 generation and may instead be restricted to future offspring. Phenotypic transmission to offspring is indicated by an obese mouse in the F1–F2 generations, whereas a lean mouse in the F1–F2 generations indicates failure to transmit the phenotype. Intergenerational inheritance describes phenotypic transmission to the F1 generation. Transgenerational inheritance describes phenotypic transmission to the F2 generation.

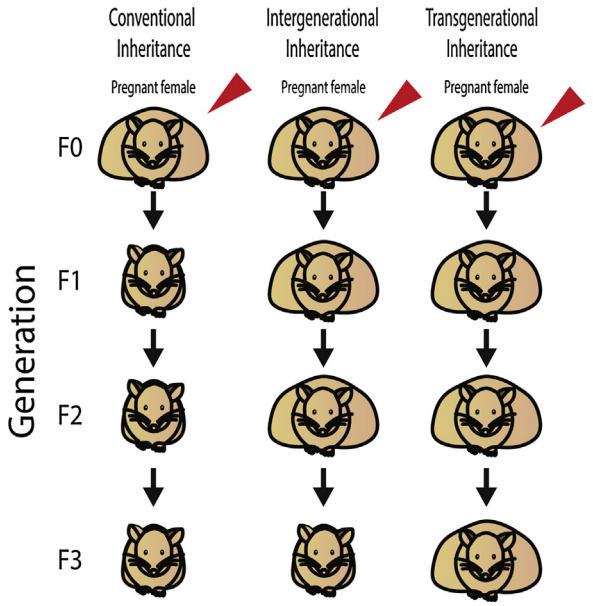

Fig. 2. Characteristics of epigenetic and conventional inheritance patterns in pregnant females. The red arrow indicates a triggering event (genetic or environmental) in the F0 generation. Obesity is shown as a representative phenotype. Although the F0 mice are represented as obese, the triggering event need not induce a phenotype in the F0 generation and may instead be restricted to future offspring. Phenotypic transmission to offspring is indicated by an obese mouse in the F1–F3 generations, whereas a lean mouse in the F1–F3 generations indicates failure to transmit the phenotype. Intergenerational inheritance describes phenotypic transmission to the F1 or F2 generation. Transgenerational inheritance describes phenotypic transmission to the F3 generation, due to the presence of germ cells *in utero* of the F0 female that will eventually develop in the F2 generation.

and life [4,5]. Given the considerable impact on human health, it is critical to better understand the factors driving the recent increase in metabolic disease.

Metabolic disease can result from mutations in single genes such as leptin (obesity), peroxisome proliferator-activated receptor gamma (T2D), and apolipoprotein C-II (hypertriglyceridemia) [6–8]. However, monogenic disease causing mutations are relatively rare, and metabolic disease is more often the result of a complex and poorly understood relationship between multiple genetic risk factors and the environment. Estimates of the heritable contribution to adiposity-related traits are typically between 45 and 75%, with the remaining phenotypic variability the result of environmental factors or gene–environment interactions [9]. Heritability estimates of other metabolic traits including levels of glucose, insulin, triglycerides, cholesterol, and blood pressure are similar [10,11]. Unfortunately, pinpointing the exact genetic risk factors for most complex multifactorial traits and diseases has proven challenging [12,13]. Genome wide association studies for many complex traits and diseases, including height and body mass index (BMI), have estimated that all common single nucleotide polymorphisms (SNPs) collectively account for approximately half of trait heritability in an additive fashion [11,14–17]. The nature of the remaining half of the heritable risk remains unknown, but various hypotheses have been proposed that implicate epistasis, rare variants, allelic heterogeneity, locus heterogeneity, small effect sizes, copy number variants, and epigenetics [12,13,18]. It is likely that each of these mechanisms contributes to human variation and disease, with this review focusing on the subset of epigenetic effects that demonstrate transgenerational inheritance.

Transgenerational epigenetic inheritance refers to the transmission of phenotypes over generations that are not due to inherited changes in the primary DNA sequence [19,20]. Transgenerational effects are passed across generations in the absence of exposure to the original trigger to either the developing fetus or the germ cells that will eventually become the fetus [21]. Thus, when inherited through the paternal lineage, transgenerational inheritance is established by phenotypes transmitted for 2 generations, to the grandchildren (F2 generation) (Fig. 1). When inherited through the maternal lineage, transgenerational inheritance is similarly established by phenotypes transmitted 2 generations to the grandchildren, unless the F0 female is pregnant during exposure to the triggering event. In this case, the presence of both the fetus *in utero* and the developing germ cells within the fetus require phenotypic transmission for 3 generations to the great-grandchildren (F3 generation) to establish transgenerational inheritance (Fig. 2). This review is restricted to studies meeting this strict definition of transgenerational inheritance, with other excellent reviews provide a more comprehensive review of epigenetic inheritance, describing both transgenerational and intergenerational inheritance [22].

A trait can be transgenerationally inherited resulting from both environmental exposures such as diet or toxins or by ancestral genetic variants [23,24]. The phenotype can be passed from one generation to the next via cultural inheritance, microbiota, or through the germline [20]. Cultural inheritance refers to the often shared learning and choices of relatives, including smoking and alcohol consumption [25]. Another example is the prion-mediated inheritance of kuru, a lethal neurological disorder found among the Fore people of Papua New Guinea. Kuru was at first mistaken to be a Mendelian inherited genetic disorder, but was later shown to be mediated by a prion protein transmitted through the practice of cannibalism of deceased relatives [26]. Microbiota are also shared vertically within a family, as an individual's early microbiome in particular is in part acquired via maternal transmission during delivery, with long term effects on metabolism [27,28]. Finally, transgenerational inheritance can be transmitted through the germline, including through both male and female germ cells, which carry dozens of epigenetic marks on the genomic DNA and the histones upon which the genomic DNA is wrapped [19,20]. Importantly, although many epigenetic marks were largely considered absent in human sperm, many nucleosomes remain associated with chromatin in sperm and DNA methylation not only remains present at specific loci, but is hypermethylated at many loci relative to later embryonic stages [29,30]. Of note, it is unlikely that all epigenetic marks have been discovered, as highlighted by the recent identifications of many novel histone marks including lysine crotonylation and glutamine methylation [31]. In addition to the

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