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Preconception cold-induced epigenetic inheritance

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Abstract

Preconception cold-induced alterations of sperm DNA methylation result in offspring with altered brown adipose tissue and improved adaptation to overnutrition and hypothermia.

Environmental exposures have been shown to promote epigenetic alterations in the germline (that is, the sperm or the egg) that may be inherited, which allows traits to be transmitted between generations¹. This nongenetic form of inheritance allows the environment to alter the phenotypes and pathologies of subsequent generations. A wide variety of environmental factors, such as toxicants, nutrition and stress, have been shown to influence epigenetic inheritance¹. Temperature is one of the main climate-associated environmental factors to which nearly all organisms are required to respond in order to survive, and temperature-induced epigenetic inheritance in flies, mosquitos, fish and plants has been observed^{2–6}. Sun et al.⁷ now show that a similar phenomenon occurs in mammals. In a study involving over 8,000 people, the authors show that participants had differences in brown fat characteristics and metabolic phenotypes depending on whether they were conceived in a cold versus a warm season or environment. This phenotype appears to be primarily paternally transmitted. The identification of cold-induced epigenetic inheritance in mammals, including humans, helps to explain some of the physiological parameters that have evolved and the impacts on human health observed in the present.

Sun et al.⁷ carry out a retrospective study of over 8,000 humans who were conceived in cold or warm temperatures and find associated metabolic changes in brown adipose tissue that correlate to preconception cold exposure of the parents and, in particular, of the father (Fig. 1). In contrast to white fat, brown fat is metabolically hyperactive and beneficial, and is associated with reduced weight gain. The authors also carried out a corresponding mouse study that confirmed that preconception cold exposure of fathers results in metabolic alterations that are transmitted paternally to the offspring. They found that offspring of cold-exposed fathers had metabolic and morphological changes in their brown adipose tissue when compared with offspring from fathers not exposed to cold. The changes were independent of the environmental exposure of the mothers. The authors also found that gene expression changes in the brown fat of the offspring of cold-exposed males indicated more metabolically active brown fat that resulted in improved systemic metabolism, which protected them from diet-induced obesity and insulin resistance. To further confirm the

Competing interests

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paternal influence on the offspring phenotype via epigenetic alterations, the authors analyzed the sperm of the fathers. They found that preconception exposure of these male mice to cold induced alterations in DNA methylation in their sperm that could be correlated with alterations in gene expression that resulted in metabolic changes in offspring⁷ (Fig. 1).

The direct exposure of an organism to an environmental factor can, through a variety of signaling processes, alter the epigenomes and transcriptomes of somatic cells and germ cells at various stages of development. The simultaneous direct exposure of different generations to an environmental condition is referred to as a multigenerational exposure (Fig. 1); when an environmental exposure results in germline transmission of the changes induced by this event, this is termed intergenerational inheritance, as is exemplified in a recent study¹. That is, the preconception exposure of a male or female directly exposes that generation and the germline that will generate the next generation. The immediate impact of a preconception exposure on the subsequent generation can be to influence the health and adaptation physiology of the offspring to respond to the environment.

In this study, the paternal cold exposure that impacts the offspring metabolism via induction of hyperactive brown fat tissue in the offspring can better accommodate overnutrition and hypothermia, which is a classic example of a rapid adaptive process⁷. As the authors discuss, this can potentially be related to the current global obesity epidemic in the human population. The cold-induced change in brown adipose tissue could be leveraged to reduce metabolic disease and obesity⁸. In addition, the cold-induced metabolic phenotype reduces the impacts of hypothermia in the offspring. This cold-induced phenotype and the mechanism involved in its induction may provide insight into potential future therapeutics for obesity. For example, therapeutics to hyperactivate brown fat adipose could be considered.

One of the more classic examples of parental environmental exposure that impacts offspring metabolism is the thrifty phenotype⁹, in which caloric restriction of the fetus results in the affected offspring adapting to an environment with fewer calories. In contrast, the preconception exposure of males to high-fat diets has been shown to promote metabolic syndrome in offspring¹⁰. The Sun et al.⁷ study identifies a cold-induced metabolic thrifty phenotype that is similar in impact to the nutrition-adaptive thrifty phenotype, both of which are mediated by epigenetic changes.

The ability of environmental epigenetics to promote an adaptive phenotype to cold has impacts on evolution¹¹. However, the impacts would be far greater if the phenomenon was transgenerational. Future studies are now needed to determine whether the cold-induced thrifty metabolic phenotype is transmitted to subsequent generations. If exposure not only impacts the health of offspring, but also of all subsequent generations, the impact is significant Fig.1.

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Fig. 1. Preconception exposure to cold alters offspring traits.

Wolfrum and colleagues⁷ show that exposure of males to cold (the F_0 generation) results in changes in the epigenetic marks of their sperm that result in metabolic changes in brown fat in the next generation (F_1). Such changes are a result of the multigenerational exposure to cold. Environmentally induced epigenetic transgenerational inheritance of this metabolic phenotype to the F_2 generation would be far more impactful on health and evolution owing to its permanent programming in future generations.