Paternal Epigenetic Transgenerational Inheritance of metabolic disease susceptibility in mice

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Résumé

Obesity is now a serious public health problem. Although this pathology is closely associated with poor lifestyle habits, several epidemiological and experimental data converge on the same idea: our genes "remember" our parents' lifestyle habits. Thus, a diet-induced phenotype, such as obesity, can induce epigenetic modifications in the paternal and/or maternal germline, modifications that could be transmitted to offspring via a process called epigenetic inheritance. Unlike genetic modifications, epigenetic modifications induced by the environment are unstable and persist for only 2 or 3 generations. The question was to determine the evolutionary potential of these transient changes. To do this, we maintained male mice on a Western diet for five successive generations and analyzed the phenotypes/traits likely to be altered by this diet, such as body mass, fat mass, glucose and insulin response, and the liver, an organ particularly sensitive to an imbalanced diet. Overall, our analyses show that maintaining paternal Western diet feeding for five consecutive generations in mice induces an enhancement in fat mass and related metabolic diseases over generations. Strikingly, chow-diet-fed progenies from these multigenerational Western-diet-fed males develop a 'healthy' overweight phenotype characterized by normal glucose metabolism and without fatty liver that persists for four subsequent generations. This suggests an accumulation of epigenetic modifications over generations. Sperm RNA-microinjection experiments into oocytes reveal that sperm RNA is sufficient for the establishment, but not for the long-term maintenance, of the epigenetic inheritance of metabolic pathologies. Thus, epigenetic inheritance might play a role in the rapid evolution of a phenotype during permanent environmental changes. Whether spermatic epigenetic changes such as DNA methylation and chromatin structure alterations could be associated with long term inheritance is an open question. Thus, epigenetic inheritance could explain certain differences in individuals' susceptibility to developing severe metabolic diseases. The underlying mechanism of this process is intriguing and deserves to be explored both fundamentally and biomedically.

Mots-Clés: epigenetic inheritance, sperm RNA, obesity, mouse

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