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Commentary

You are what your parents ate: A Darwinian perspective on the inheritance of food effects

Zhengrong Wang [a], Qinglian Wang [b, **], Yongsheng Liu [b, c, *]

[a] School of Food Science, Henan Institute of Science and Technology, Xinxiang, 453003, China
[b] Henan Collaborative Innovation Center of Modern Biological Breeding, Henan Institute of Science and Technology, Xinxiang, 453003, China
[c] Department of Biochemistry, University of Alberta, Edmonton, AB, T6G 2H7, Canada

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ABSTRACT

Darwin's theory of evolution by natural selection is based on a sound understanding of the causes of variability and the mechanism of inheritance. Of all the causes which induce variability, Darwin believed that food was probably the most powerful. He not only held that the amount and nature of food could affect the characters of the future offspring through the reproductive system, but also accounted for the inheritance of such environmentally induced variations by his Pangenesis hypothesis. He proposed that cells could "throw off" numerous, minute molecules called gemmules, which were capable of diffusion from cell to cell, circulation throughout the body, modification by changed conditions of life (food, climate, etc.), aggregation in the reproductive organs, and transmission from parent to offspring. Now there is accumulating evidence that parental diets influence the health and disease of subsequent generations through epigenetic changes in germ cells. Two major underlying mechanisms are DNA methylation and RNA-mediated inheritance. A comparison of Darwin's imaginary gemmules with circulating cell-free DNA and mobile RNAs reveals intriguing similarities. It will be a fascinating episode in the history of science if Darwin's Pangenesis should eventually be rediscovered.

1. Introduction

All of us know that food is of great importance in our lives, we cannot live without it. It is also well known that food or nutrition can influence our health status and risk of disease. However, less well known is that food can influence the health and disease of subsequent generations, thus plays an important role in genetics and evolution. In recent years, there is increasing evidence that altered parental diet affects the metabolic phenotypes of offspring through epigenetic changes in germ cells (Chen et al., 2016; Grandjean et al., 2015; Huypens et al., 2016; Rechavi et al., 2014). These intriguing findings are once again reminiscent of Charles Darwin's belief in the thesis that the amount and nature of food could affect the characters of the future offspring through the reproductive system, and his Pangenesis hypothesis underlying the inherited food effects.

Today our scientific researchers seldom read Darwin in the original, and there is a tendency to neglect the facts collected by the great master and the theory developed by him. So far as we know, no public notice has yet been given to a series of statements by Darwin regarding the inherited food effects. It is worthwhile revisiting Darwin's works not only for historical reasons but also because in many respects they are surprisingly modern. The general plan of this viewpoint article will be, first, to briefly present Darwin's views on the inheritance of food effects and his neglected theory of heredity, and then to briefly review the recent experimental evidence for inherited food effects and the main underlying mechanisms, and finally to make a comparison of Darwin's hypothetical gemmules with circulating cell-free DNA and mobile RNAs.

2. Darwin's view on the inheritance of food effects and its role in evolution

It is well known that evolution is a process of variation and heredity. Darwin's theory of evolution by natural selection is based on a sound understanding of the causes of variability and the mechanism of inheritance. As Darwin (1859) noted, "… unless

* Corresponding author. Henan Collaborative Innovation Center of Modern Biological Breeding, Henan Institute of Science and Technology, Xinxiang, 453003, China.
** Corresponding author.
E-mail addresses: wangql985@163.com (Q. Wang), ysliu63@yahoo.ca (Y. Liu).

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profitable variations do occur, natural selection can do nothing". Throughout his career, Darwin consistently linked the cause of variation with changes in the environment. He favoured the view that "variations of all kinds and degrees are directly or indirectly caused by the conditions of life to which each being, and more especially its ancestors, have been exposed" (Darwin, 1868). Again and again he pointed to changed conditions of life as being responsible for variability.

Of all the causes which induce variability, Darwin believed that excess of food was probably the most powerful. He inferred that changed food might disturb the due and proper action of the reproductive organs, and consequently affected the characters of the future offspring. He observed that "the wild duck, when domesticated, loses its true character, from the effects of abundant or changed food." He also noticed that, in pig, "rich and abundant food, given during youth, tends by some direct action to make the head broader and shorter, and that poor food works a contrary results." He thus concluded that "abundant and rich food supplied during many generations would give an inherited tendency to increased size of body" (Darwin, 1868).

Darwin described the relationship between food supplies and fertility, stating that domestic animals which have regular, plentiful food without working to get it are more fertile than the corresponding wild animals. He held that an individual's fertility was affected by variations in the amount of food (Darwin, 1868). In addition, Darwin noticed that "hemp-seed caused bullfinches and certain other birds to become black", and that "caterpillars fed on different food sometimes either themselves acquire a different colour or produce moths differing in colour." Thus he concluded that "the nature of the food sometimes definitely induces certain peculiarities, or stands in some close relation with them" (Darwin, 1868).

3. Darwin's Pangenesis underlying the inherited food effects

In attempts to explain the inheritance of environmentally induced characters and many other hereditary phenomena, Darwin (1868) developed his Pangenesis – a unifying theory of heredity and variation. By extending the cell theory, he proposed that in addition to cellular division, cells could also "throw off" numerous, minute molecules called gemmules, which were regarded as being capable of diffusion from cell to cell, circulation throughout the body, modification by changed conditions of life, aggregation in the reproductive organs, and transmission from parent to offspring. These gemmules could be modified by the action of changed conditions of life (food, climate, etc.). This caused the affected part of the body to shed modified gemmules, which are transmitted with their newly acquired traits to the offspring (Darwin, 1868; Liu, 2007).

Darwin's Pangenesis is of great importance owing to its inspiring influence on many subsequent theories of heredity, particularly those of Francis Galton, August Weismann and Hugo de Vries. It should be noted that the term "gene", which has passed into everyday language, evolved from Darwin's hypothetical "gemmule". Unfortunately, Darwin's Pangenesis never gained any very wide acceptance. The main reasons have been that there was little good evidence for the inheritance of environmentally induced changes that Pangenesis supposedly explains, and that there was no direct evidence for the existence of his imaginary gemmules (Liu, 2008).

4. Accumulating evidence for the inheritance of food effects

Darwin's description mainly relied on naturalistic observation rather than experimental manipulation. In the early1900s, the food effects were experimentally demonstrated in the laboratory. For example, Paton (1903) found that the birth weight of guinea-pigs whose diets had been severely restricted during pregnancy was significantly reduced as compared with those fed freely, thus concluding that the size of the offspring depended very directly upon the diet and nutrition of the mother. In bees, for a given diet, offspring body size is strongly influenced by the amount of food supplied to their larvae, and it generally increases with an increase in the amount of food ingested (Johnson, 1990). In rats, the larger amount of vitamin B-12 given during pregnancy significantly increased birthweight and subsequent weight of the progeny (Newberne & Young, 1973). All of these experimental results are consistent with Darwin's statement that the amount of food affects the size of the offspring. In addition, Darwin's view of the relationship between food supplies and fertility in animal also apply to human beings (Frisch, 1978).

Darwin stated that the nature of food could induce the colour changes in the offspring. This has been fully confirmed by current studies. The compelling evidence is Agouti Yellow mice. Changes to the dam's diet during pregnancy can alter the proportion of yellow mice within a litter. When the dam's diet is supplemented with methyl donors (including betaine, methionine, choline, vitamin B_{12} and folic acid), there is a shift in the colour of their offspring away from yellow to brown to almost black (Waterland & Jirtle, 2003; Wolff, Kodell, Moore, & Cooney, 1998). Similar effects have been observed following the feed of the dams with genistein, which is found in soy milk (Dolinoy, Weidman, Waterland, & Jirtle, 2006). This suggests that the diet of a pregnant female could affect not only her offspring's coat colour, but also that of subsequent generations.

A well-known example of the inherited food effects is the Dutch Famine. During the Second World War, Germany imposed a food embargo on the Netherlands, causing a severe starvation between November 1944 and May 1945. Mothers who were pregnant during that time gave birth to children who had reduced birth weight and developed a host of clinical disorders during adulthood ranging from obesity to glucose intolerance, hypertension, schizophrenia, diabetes and coronary heart disease (Bohacek & Mansuy, 2013; Kyle & Pichard, 2006; Susser & Stein, 1994). Interestingly, the grandchildren of mothers exposed to the famine also exhibited similar effects (Stein & Lumey, 2000), indicating that starvation during pregnancy might have induced heritable changes. By investigating the Chinese born during the Great Chinese Famine from 1958 to 1961, St Clair et al. (2005) also reported an association between prenatal exposure to severe maternal nutritional deficiency and risk for schizophrenia in adulthood, providing invaluable confirmation of the earlier Dutch work. The schizophrenia findings from the Dutch and Chinese famine studies are in remarkable agreement. In addition, there are also studies showing heritable effects after famines in Russia (Stanner et al., 1997) and other countries.

Now there is accumulating evidence from animal studies that during pregnancy, alterations in diet affect the offspring across several generations. Lillycrop, Phillips, Jackson, Hanson, and Burdge (2005) demonstrated that pregnant rats fed low-protein diets produced two sequential generations of offspring that became diabetic as adults. Ng et al. (2010) reported that a male's diet could affect his daughter's health. When the male rats were fed with a high-fat diet, their daughters developed a diabetes-like condition of impaired glucose tolerance and insulin secretion. More recently, Huypens et al. (2016) demonstrated that a parental high-fat diet renders offspring more susceptible to developing obesity and diabetes in a sex- and parent of origin-specific mode. Genetically identical mice were fed one of three diets (high fat, low fat or standard laboratory chow) for six weeks, and those fed the high-fat diet became obese and had impaired tolerance to glucose. To