Inheritance

Inheritance through the cell cycle

The **cell cycle** poses a serious challenge to preservation of this fine-tuned chromatin state. Histones and all the other chromatin-binding proteins have to be removed to allow genome replication, and then the chromatin architecture has to be restored to the original state. Furthermore, during mitosis, chromosomes condense into a very tight conformation, and decondense very quickly after the cell has divided. The daughter cells must somehow determine the status of each genomic area and re-establish the chromatin conformation according to that. Although the exact details of how this happens are unclear, it is evident that cells are very successful in maintaining the correct chromatin environment through generations, which is important for **continuity of cell fate** (e.g. so that the daughter of a blood cell does not suddenly become a skin cell). The replication machinery itself recruits chromatin-modifying proteins, that help to locally disrupt and then restore chromatin structure, while DNA methylation and histone marks allow recognition of different types of chromatin after division.

Epigenetic mechanisms play an important role in cell **differentiation**. As cells become more specialised, their genome architecture becomes more and more rigid and defined. The amount of repressive marks and DNA methylation increases, blocking expression of genes irrelevant to the chosen cell fate and preventing the cell from de-differentiating. Whether these fundamental changes are the cause or the consequence of differentiation is an open question, the answer to which (as it usually does) probably lies somewhere in between the two extremes.

Intergenerational: genomic imprinting

Reproductive cells, eggs and sperm, are differentiated and express a very specific set of genes. After fertilisation, to be able to give rise to a new organism, cells have to undergo "**de-differentiation**", i.e. erase their epigenetic marks. It might seem like only the genetic, but not epigenetic information is passed from parents to a child… but actually, not quite. About 1% of genes (often developmentally important) escape this reprogramming, and thus they stay "**imprinted**" in a parent-specific manner. In other words, a certain gene might be repressed on the maternally-derived chromosome, but expressed from the paternally-derived chromosome, or vice versa. Sometimes mutations in the same region give rise to different phenotypes, depending on whether they affect the maternal or the paternal chromosome – e.g. this is the case for Prader-Willi and Angelman syndromes.

Additional resources:

Learn.Genetics

http://learn.genetics.utah.edu/content/epigenetics/imprinting/

Nature Education

https://www.nature.com/scitable/topicpage/genomic-imprinting-and-patterns-of-disease-inheritance-899

Department of Biology

https://www.youtube.com/watch?v=3hBoNGozlCo

Task

For a cell to be able to develop into an embryo, it has to have the diploid genome, which is normally obtained as a result of fusion of egg and sperm, which each are haploid. Can an embryo develop from a fusion of two eggs?

Environmental effects

A different way of modifying the epigenome is via the **environmental effect**. A groundbreaking study in this area has been conducted in rats (Figure 1) by Weaver et al (2004). Rat mothers can display two types of behaviour, which are genetically encoded: the “good” mothers lick and nurture their pups, while the “bad” mothers neglect them. The offspring of the two show different stress response (with the “bad” mothers’ offspring having higher levels of anxiety). The same is observed when the pups are swapped between the mothers, showing that this effect is not genetically encoded. This phenomenon has been attributed to changes in the **methylation** status of the stress-related genes, supported by the fact that altering the general DNA methylation levels using drugs changes the phenotype displayed by the offspring.

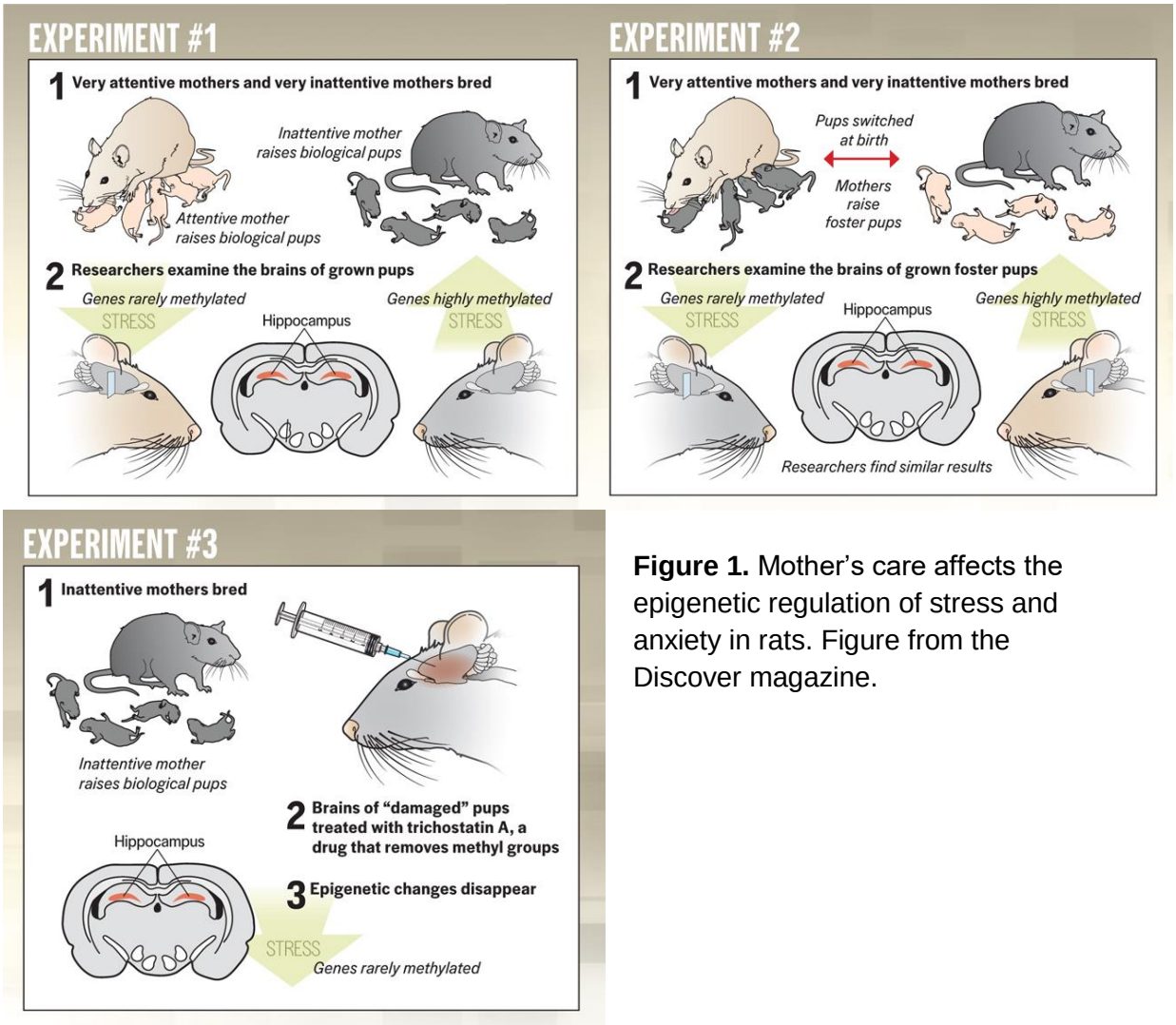

Figure 1. Mother's care affects the epigenetic regulation of stress and anxiety in rats. Figure from the Discover magazine.

Additional resources

Learn.Genetics on rat licking

http://learn.genetics.utah.edu/content/epigenetics/rats/

Task

Why does the above evidence suggest, but not prove that methylation of stress-related genes is indeed responsible for the variation in behaviour between the pups? Can you spot the limitations of the experiment?

Nature or nurture?

Whether these principles are universal and our experience is being “written down” in our epigenome, and furthermore whether this can be passed to our children, is a very intriguing question. In the 18th-19th century, it was hypothesised by a French biologist Jean-Baptiste Lamarck that an organism can pass on the characteristics it has acquired during its lifetime to the offspring. With the development of Darwinian view on evolution, this idea was generally abandoned. Could **Lamarckian inheritance** actually exist, at least to some extent, through epigenetics? Is it possible to inherit not only the “nature” of one’s parents, but also the “nurture” - their experience and adaptations?

To date, many studies indirectly suggest that this might be the case, but the evidence presented is often questionable. It is understandable – achieving large enough sample sizes of animals is hard (and even tougher for humans), especially if the effects observed are very subtle. We still lack technology that would allow us to specifically alter epigenetic marks, e.g. change DNA methylation at a specific site rather than globally, thus making most of the observation suggestive and supportive rather than conclusive. In addition, the present hype around epigenetics creates a favourable environment for publication of “bad science”. Nevertheless, epigenetics is a very exciting (although very controversial at the moment) field that is likely to provide some ground-breaking, fundamental discoveries in the years to come.

Additional resources

Epigenetics, Lamarckism and the hype

https://www.acsh.org/news/2016/06/10/epigenetics-lamarcks-revenge