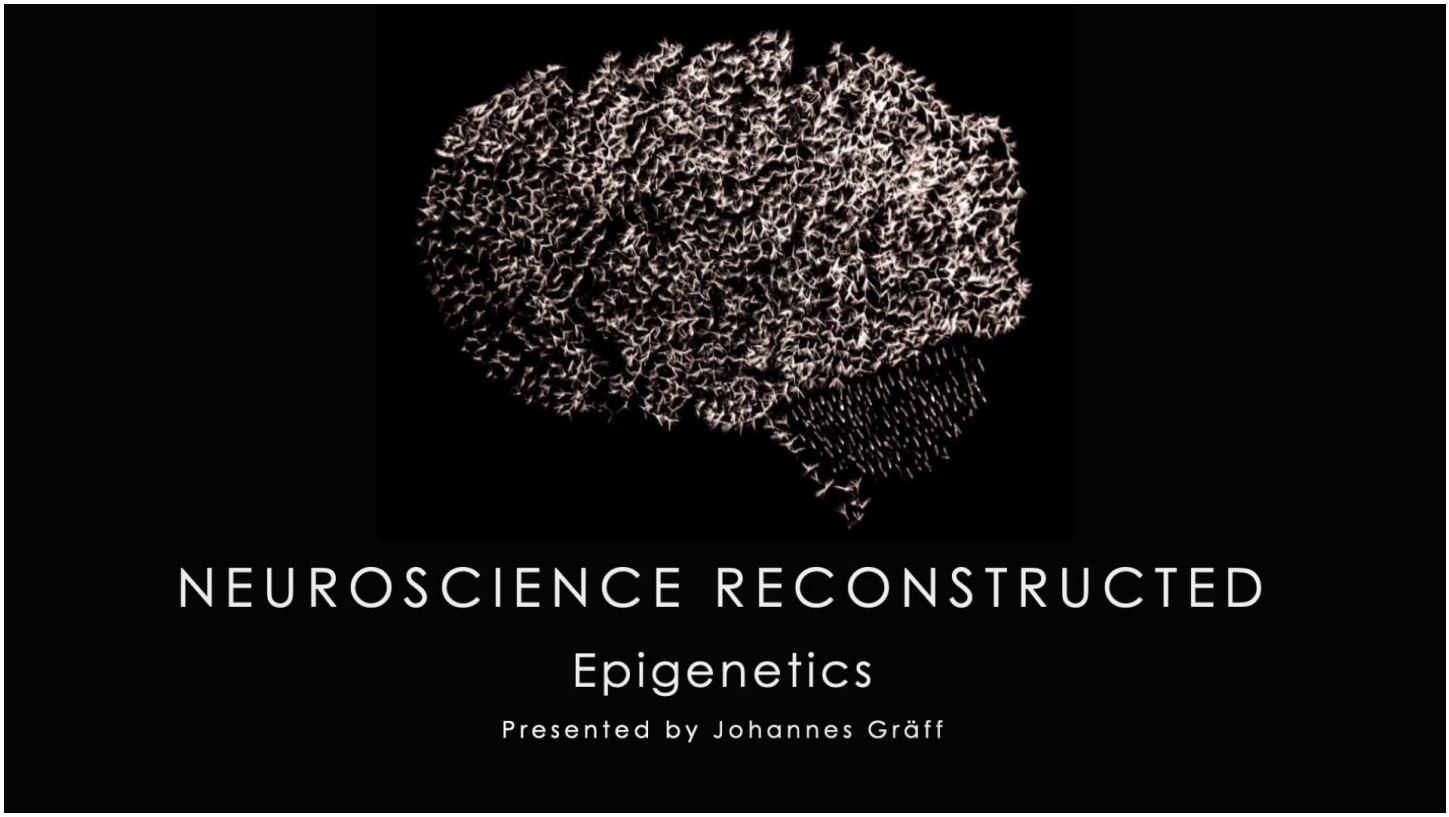
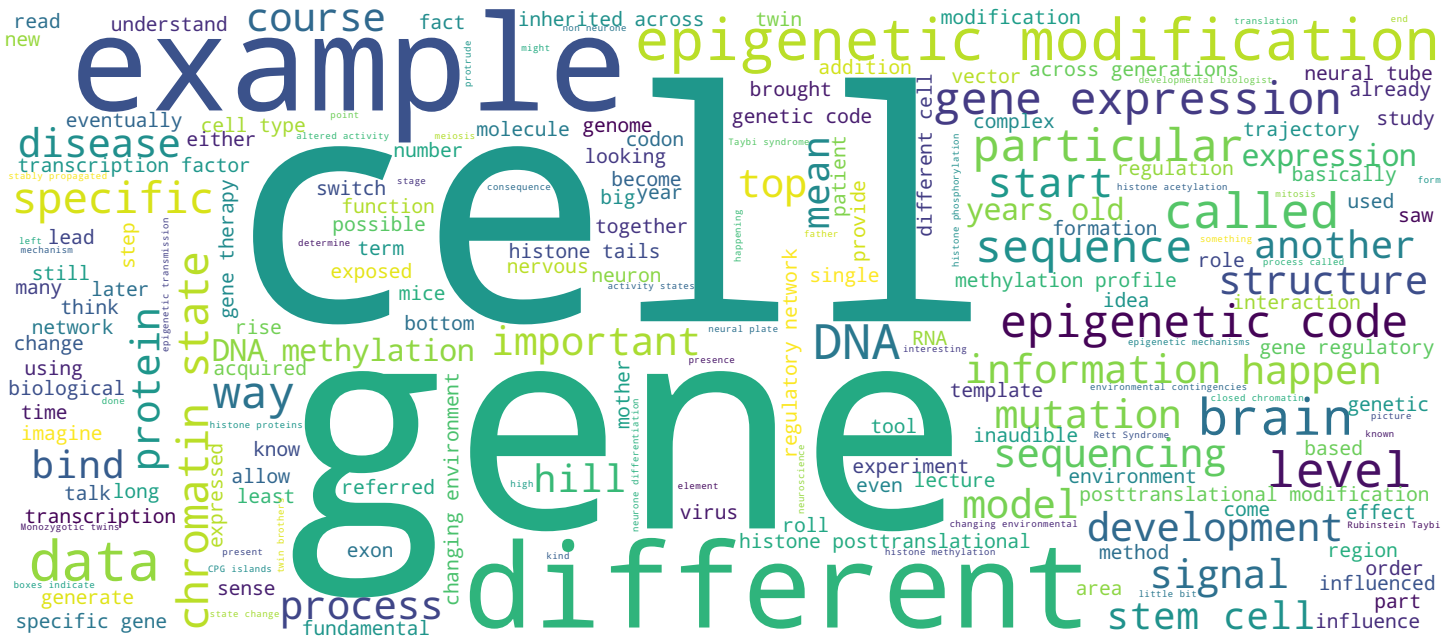

NEUROSCIENCE RECONSTRUCTED
Epigenetics
Presented by Johannes Gräff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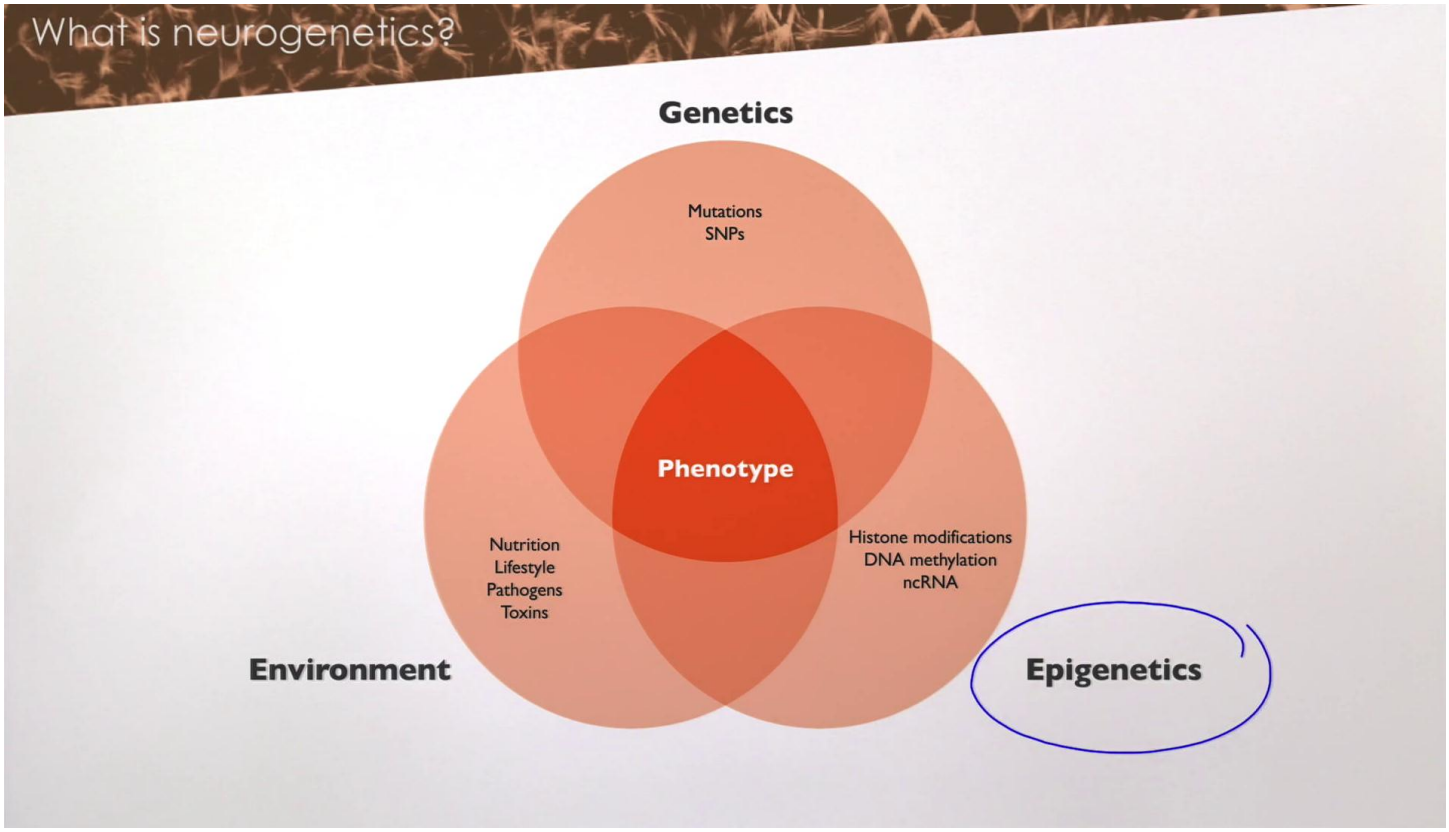
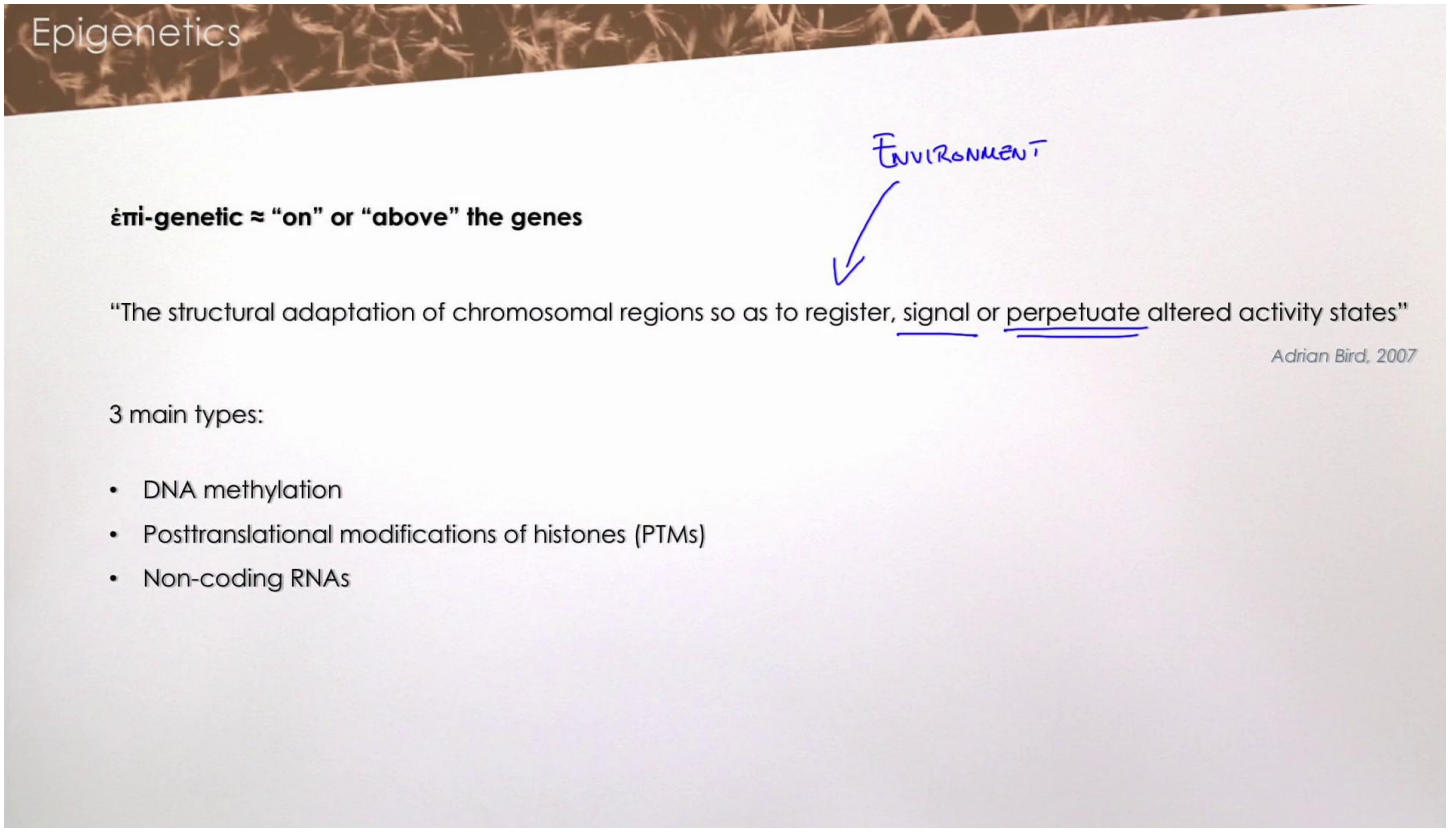


Now that we've covered genetics, we can now spend the rest of the lecture on epigenetics.

Notes

Summary

0m 05s

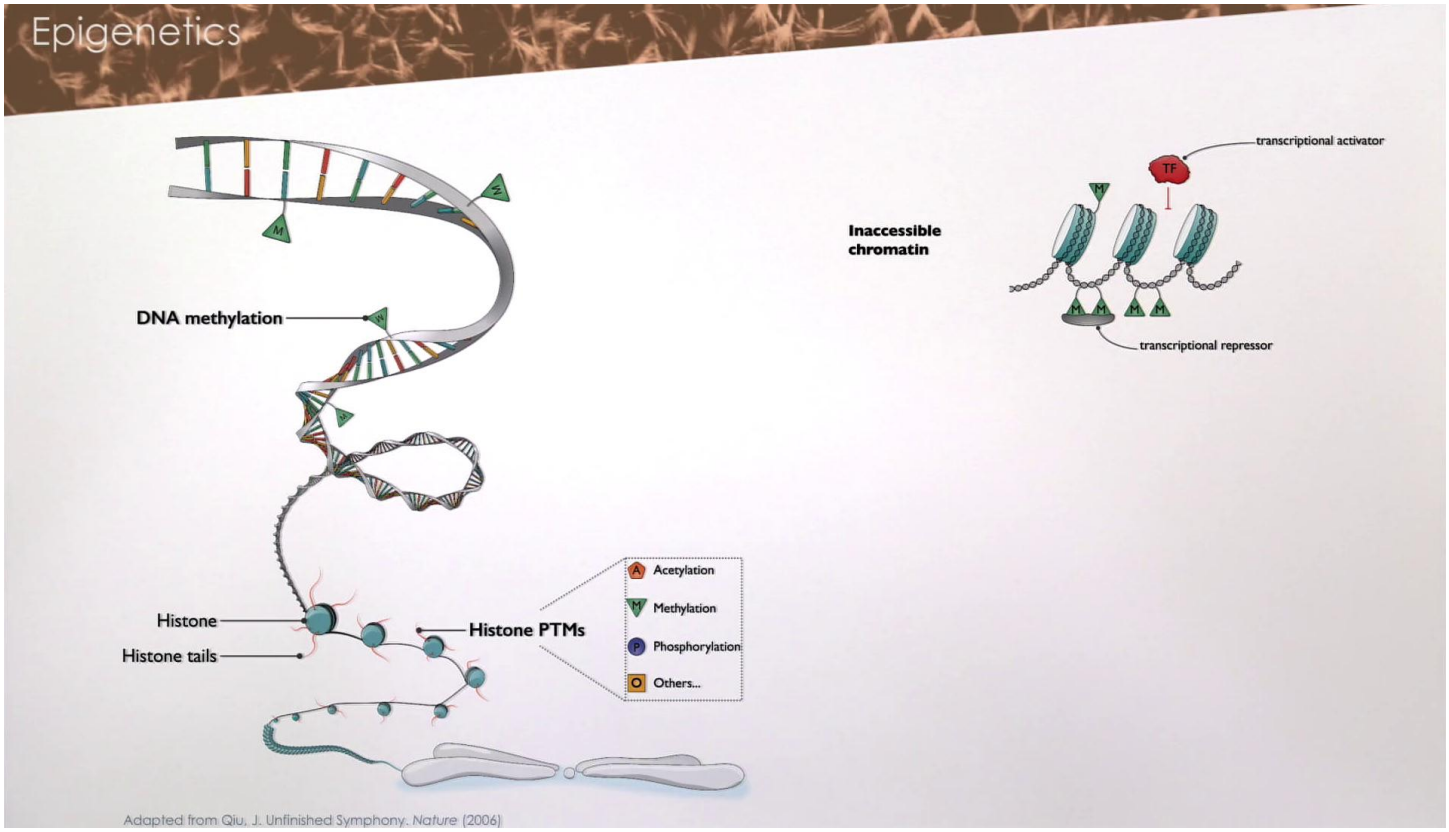


Epigenetics with the Greek prefix epi in front of genetics means what is happening on or above the genes. The most parsimonious definition of epigenetics nowadays is that epigenetics refers to the structural adaptation of chromosomal regions, so as to register signal or perpetuate altered activity states. With this definition, we already have the influence of the environment here. Which means that epigenetic mechanisms have the capacity to register changing environmental contingencies to then signal them inside the cell and thereby also across different cells, to the organism, and finally, as we will see, these epigenetic states can be extremely stable so that they are perpetuated through both mitosis and meiosis and thereby contribute to the perseverance of altered activity states. We have three main types of epigenetic modifications. First, we have the covalent addition of methyl groups to the DNA, a process referred to as DNA methylation. Second, we have modifications of histone proteins that happen after the histones have been translated and hence are referred to as posttranslational modifications of histones or PTMs. Third, we also have the interference of non-coding RNAs, which are RNA species that do not code for specific genes, but nevertheless can bind to either the DNA or the RNA and thereby influence the expression of certain genes.

Notes

Summary

0m 12s

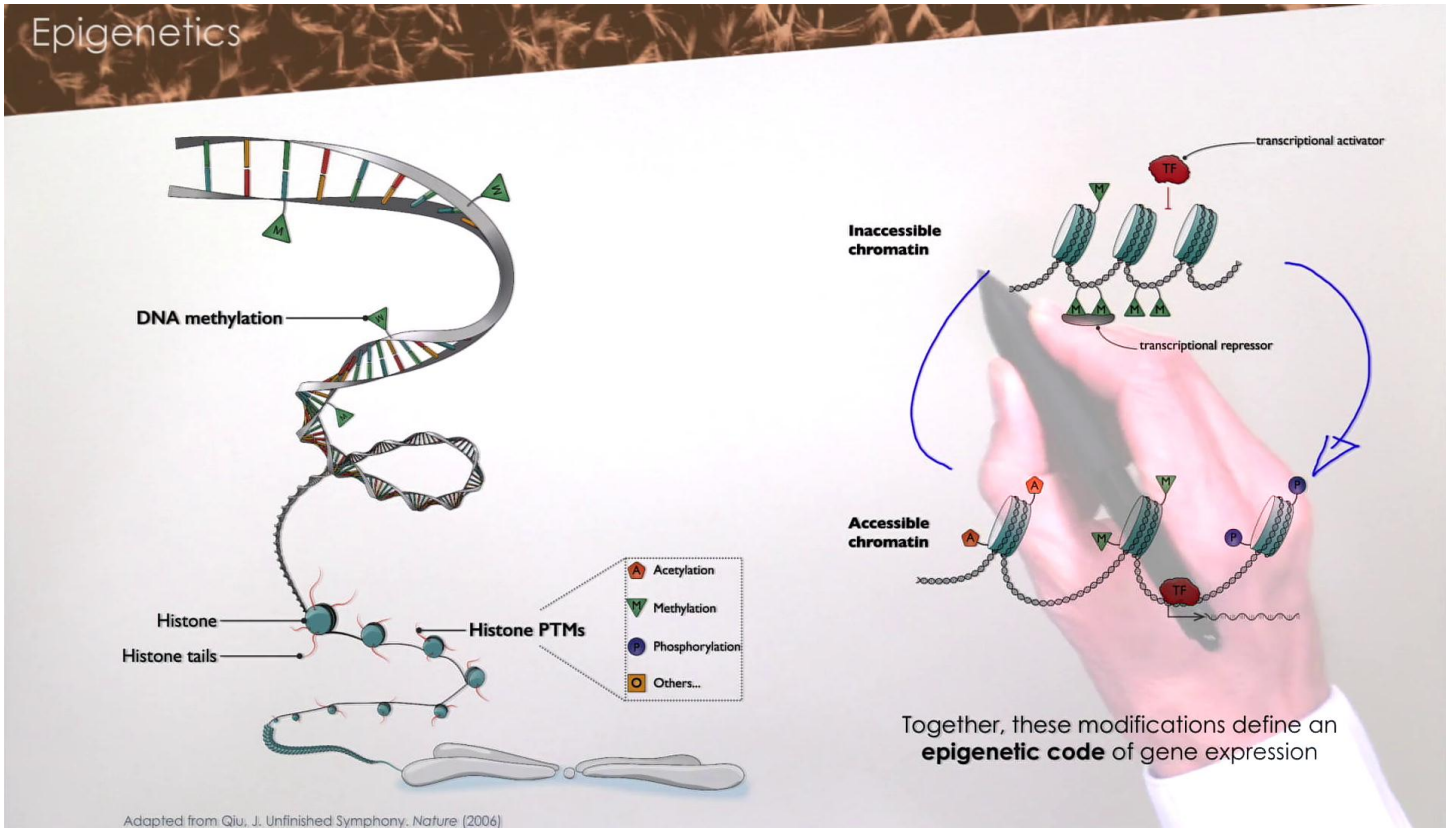


Here is how epigenetic modifications look like. On the top, we have DNA methylation that binds to cytosine residues in the genetic sequence, and often they bind to so-called CG or CPG islands, which are repeats of the CG dinucleotides. Down here we have the histone posttranslational modification, and down here we have the histone posttranslational modifications that preferentially occur on the n-terminal histone tails, that protrude out of the nucleosome structure. Now, what is the effect of these epigenetic modifications? Down here we have the histone posttranslational modifications that predominantly occur on the n-terminal tails of the histone proteins that protrude out of the nucleosome. These histone modifications can come in different flavours. The most predominant ones in the nervous system are histone acetylation, histone methylation, histone phosphorylation and various others that are still being discovered as we speak. What is the consequence of these epigenetic modifications? The primary consequence of epigenetic modifications is to regulate chromatin accessibility. By doing so, epigenetic modifications also regulate the level of gene expression.

Notes

Summary

2m 07s

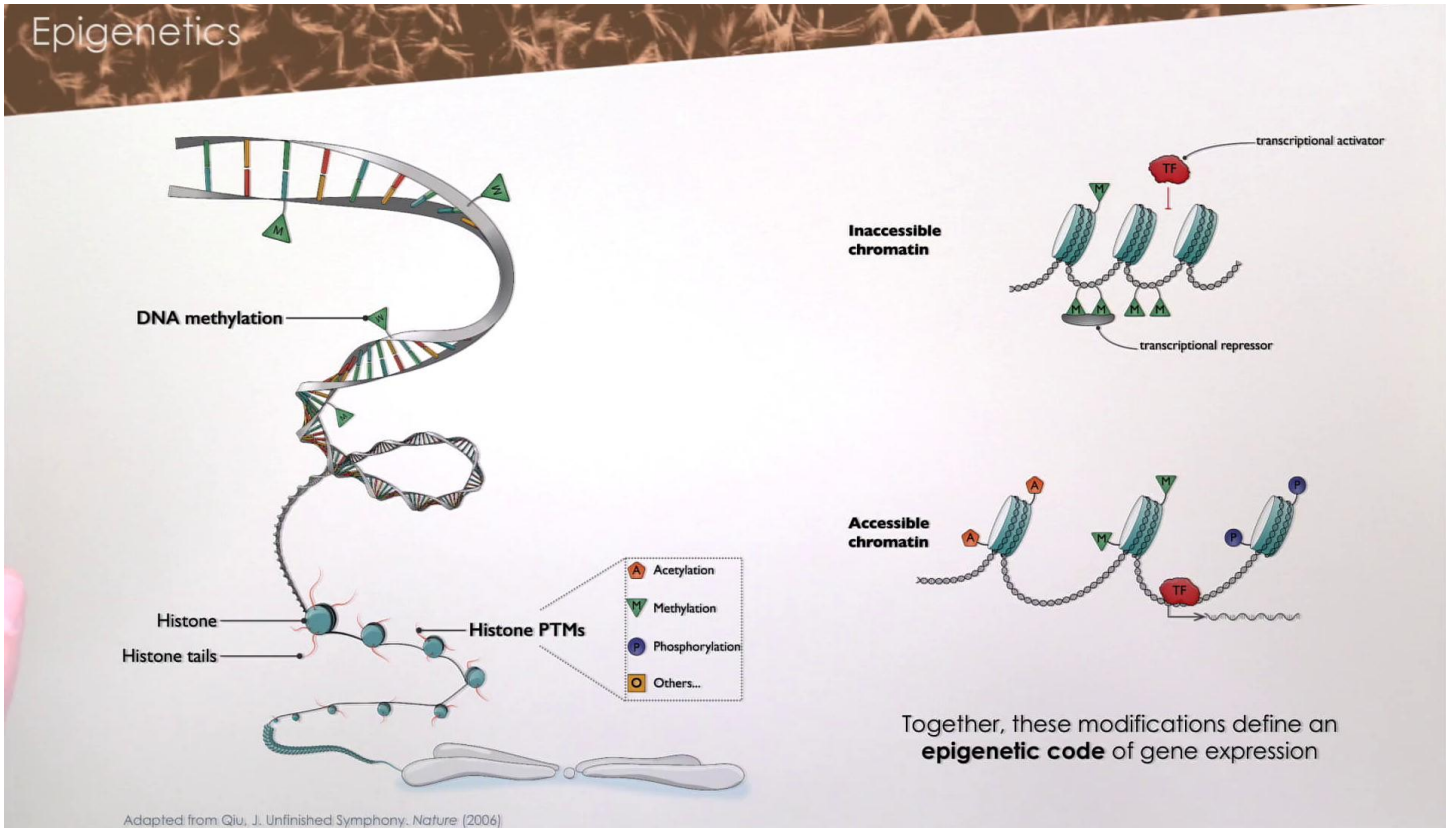


On the top here we are in a situation often condensed off a closed chromatin state that is transcriptionally, not active. In this case, which is often brought about by the DNA methylation to the promoter regions of specific genes, we have that methylated CPG islands that are going to be bound by so-called transcriptional repressors and together with the closed chromatin state, this prevents the transcriptional activators, the transcription machinery from binding. In contrast, we have down here the accessible chromatin state, which is predominantly characterised by an absence of DNA promoter methylation, but by the presence of histone acetylation and histone phosphorylation and site specific histone methylation changes. This grants an opening of the chromatin structure by creating repulsive forces between the histone tails and the DNA, or by reducing the attractive forces between the histone tails and the DNA, thereby opening up the chromatin and granting access to the transcriptional machinery so that gene expression can bind. So what epigenetic modifications do is that they allow to switch from a inactive, chromatin state and inaccessible chromatin state to a transcriptionally active chromatin state that is accessible and vice versa.

Notes

Summary

3m 39s

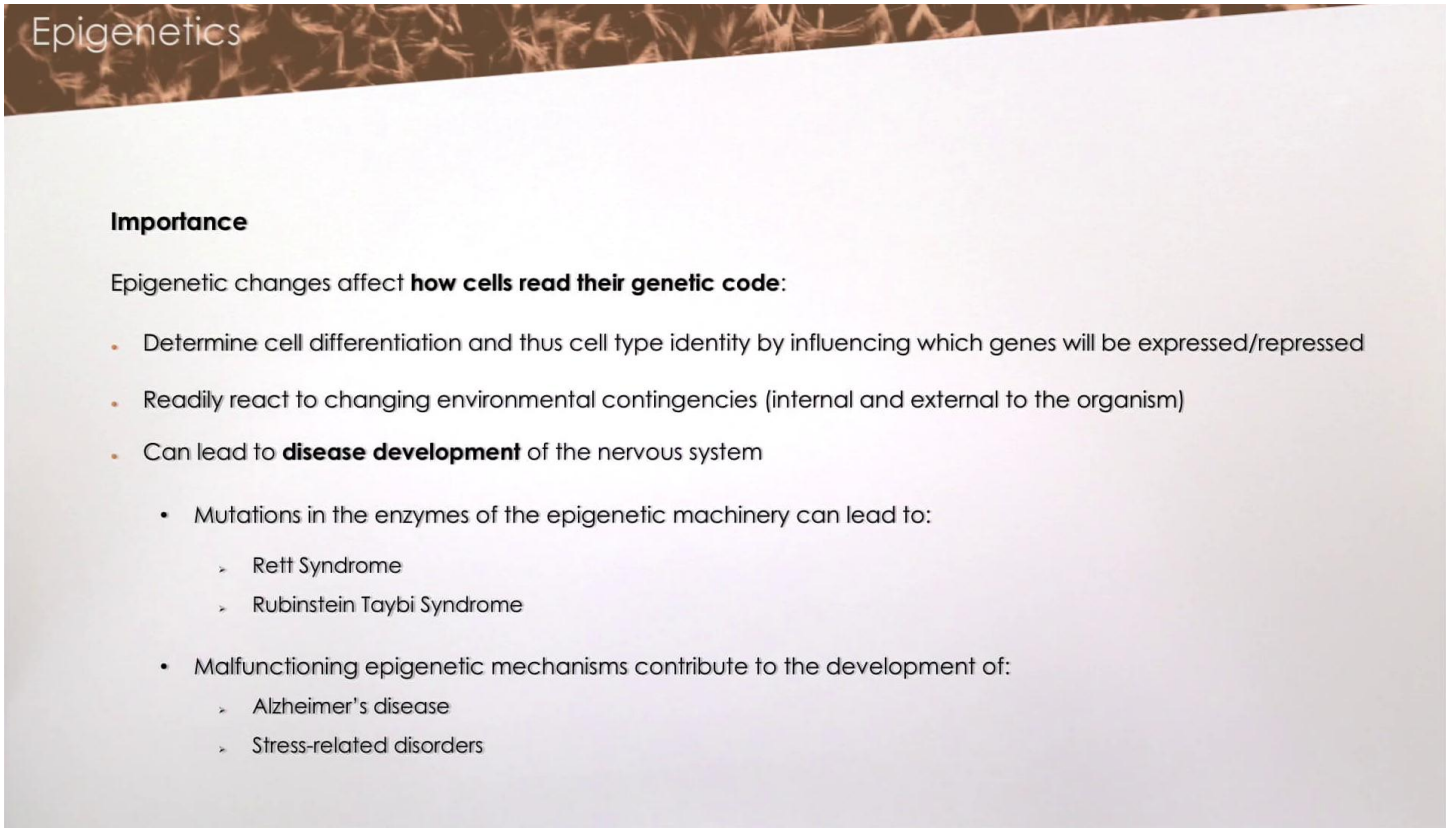


So epigenetic modifications can function bi-directionally. Together these epigenetic modifications define what is called an epigenetic code of gene expression.

Notes

Summary

5m 13s



The importance of these epigenetic codes is that the epigenetic changes affect how cells can read their genetic code. This will, for example, determine cellular differentiation and thereby cell type identity by influencing which genes will be expressed or not. Furthermore, these epigenetic codes can readily react to changing environments, both internal and external to the cell, and thereby react to a changing environment. With specific gene expression programs. Furthermore, if epigenetic codes are disturbed, this can lead to disease development in the nervous system. For example, mutations in the enzymes of the epigenetic machinery can lead to two neurodevelopmental disorders known as Rett Syndrome and Rubinstein-Taybi syndrome. In Rett Syndrome, we have a mutation in a methyl CPG binding protein that is called MCP2, whereas in Rubinstein-Taybi syndrome, we have a mutation in a so-called histone acetyltransferase. Furthermore, malfunctioning epigenetic mechanisms have been shown to contribute to the development of Alzheimer's disease and stress-related disorders.

Notes

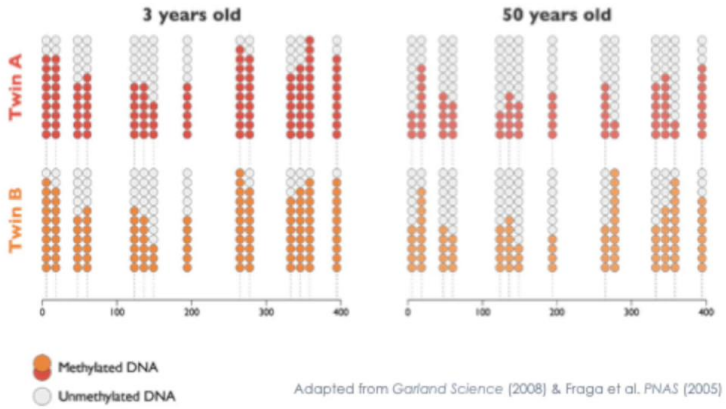
Summary

5m 27s

Epigenetic Inheritance

The **epigenetic code** in influenced by

- Developmental stages
- Biological age
- Environmental influences (e.g., lifestyle)
- Disease



The epigenetic code can react to changing environmental contingencies. Thereby, the epigenetic code can be influenced by different developmental stages, by the biological age of the person, by environmental influences such as lifestyle or smoking, or by the disease. The fact that the epigenetic code can be influenced by a changing environment is probably best identified with this example of Monozygotic twins. Here is a picture of these twin brothers taken when they were 50 years old, and one just by looking at them, wouldn't even guess that they are twins and it becomes obvious why this might be the case. At the bottom, we have the DNA methylation profile of the twin brothers when they were three years old and when they were 50 years old. What is depicted here is the methylation of different chromosomes. The black boxes indicate methylated sequences, whereas the white boxes indicate and unmethylated sequences. What we can see when they were three years old is that their methylation profiles between twin a on top and twin b on the bottom is that the methylation profile was roughly similar. However, when they were 50 years old, at the moment when this picture was taken, the methylation profile differed significantly.

Notes

Summary

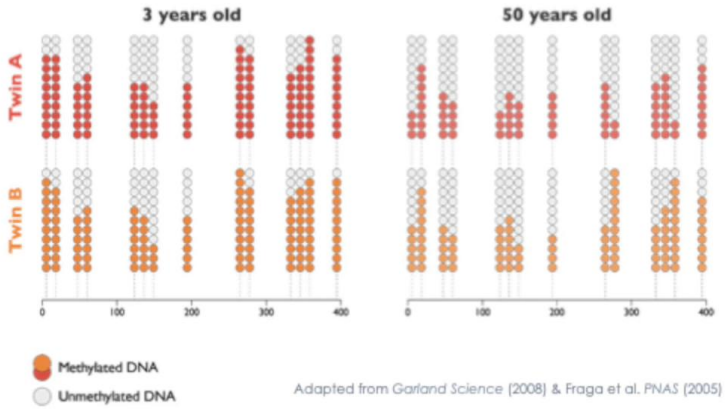
6m 47s

Epigenetic Inheritance

The **epigenetic code** in influenced by

- Developmental stages
- Biological age
- Environmental influences (e.g., lifestyle)
- Disease

Epigenetic codes define an "**epigenetic landscape**"

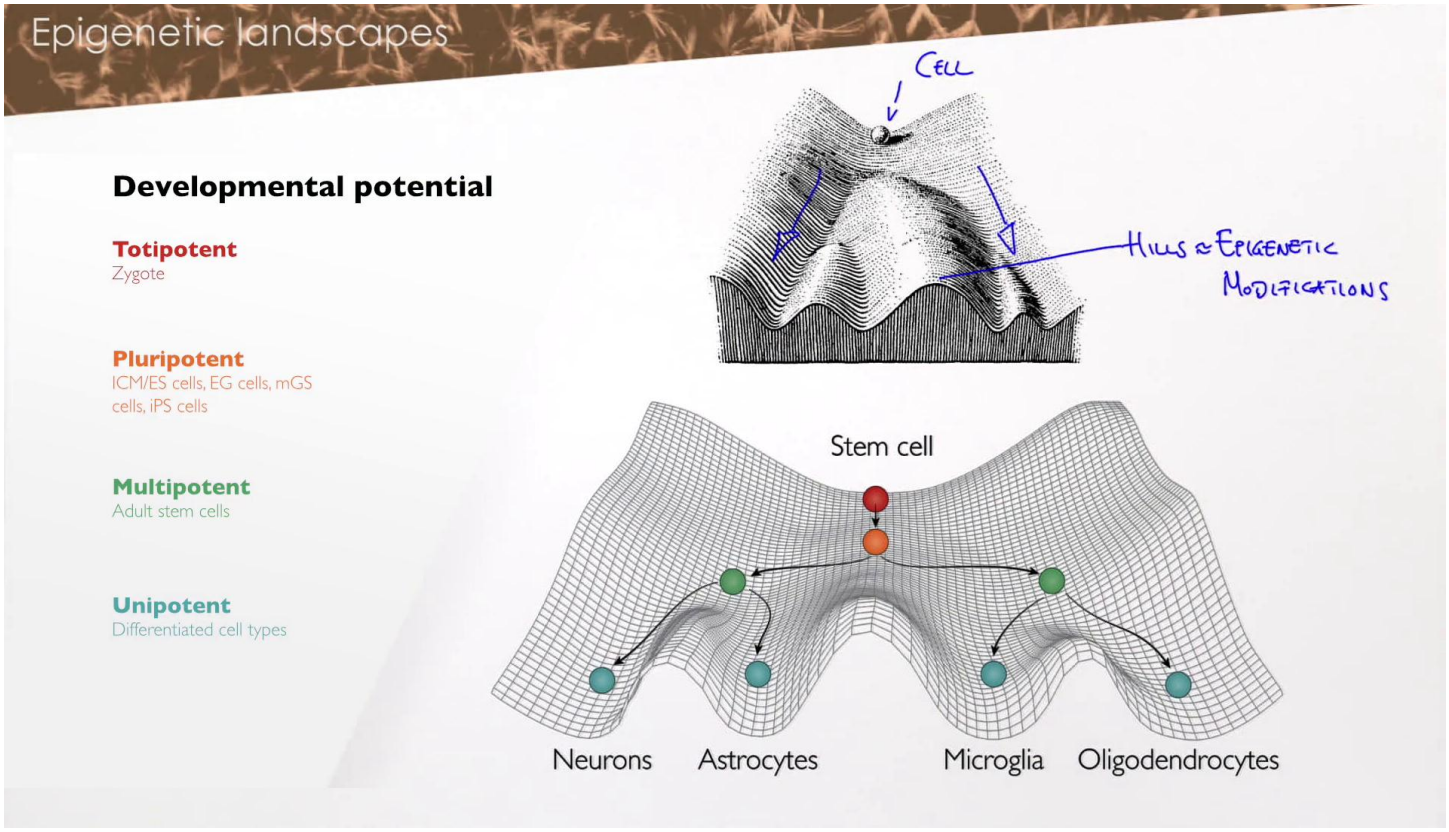


This is most likely due to different environments in which the 2 brothers were brought up. Now remember, these are Monozygotic twins, which means that they share the exact same genetic code, yet their epigenetic code has become different over the years.

Notes

Summary

8m 24s



Epigenetic codes are often also referred to as an epigenetic landscape, a term that was coined by the developmental biologist Konrad Waddington in 1957. What Waddington depicted up here is a cell that just like a ball that we would roll down a hill, can take different trajectories. You can take a trajectory to the left or you can take a trajectory to the right depending on how hilly the landscape is. It has to go through and what Waddington supposed was to be the case is that the hills are defined by epigenetic modifications. Waddington was a developmental biologist, so the way he pictured this was that on top of the hill, we would have a stem cell that is totipotent, such as a zygote. As the stem cell starts to roll down the hill, it loses its totipotency and will become pluripotent such as an embryonic stem cell, or even an induced pluripotent stem cell. As it rose further down the hill, as it becomes more and more differentiated, it will switch from a pluripotent to a multipotent state and ultimately to a fully differentiated or unipotent state, such as is the case for neurones, astrocytes, microglia or oligodendrocytes.

Notes

Summary

8m 46s

Epigenetic landscapes

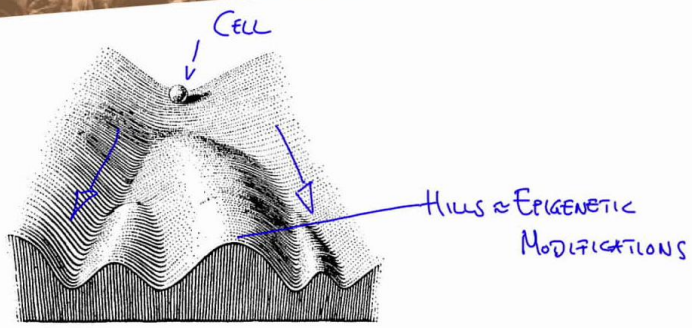
Developmental potential

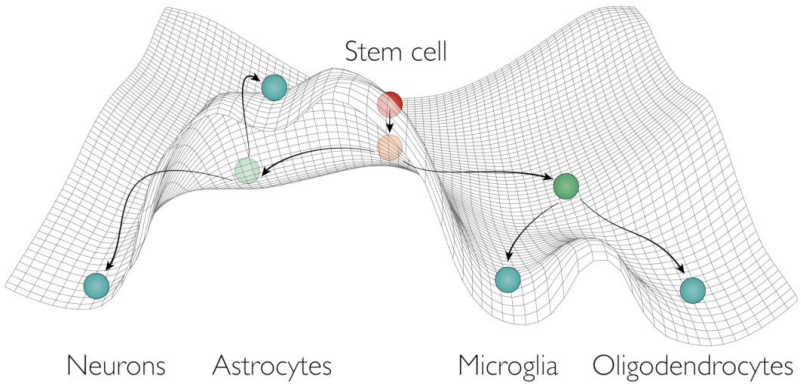
Totipotent
Zygote

Pluripotent
ICM/ES cells, EG cells, mGS cells, iPS cells

Multipotent
Adult stem cells

Unipotent
Differentiated cell types





So if we imagine that we are on the on the trajectory of a neurone differentiation, then this stem cell would be changed through development via epigenetic modifications to roll down to the left. Conversely, if we are in a non-neurone differentiation pathway, then the epigenetic boundaries, would be different and non-neurone specific.

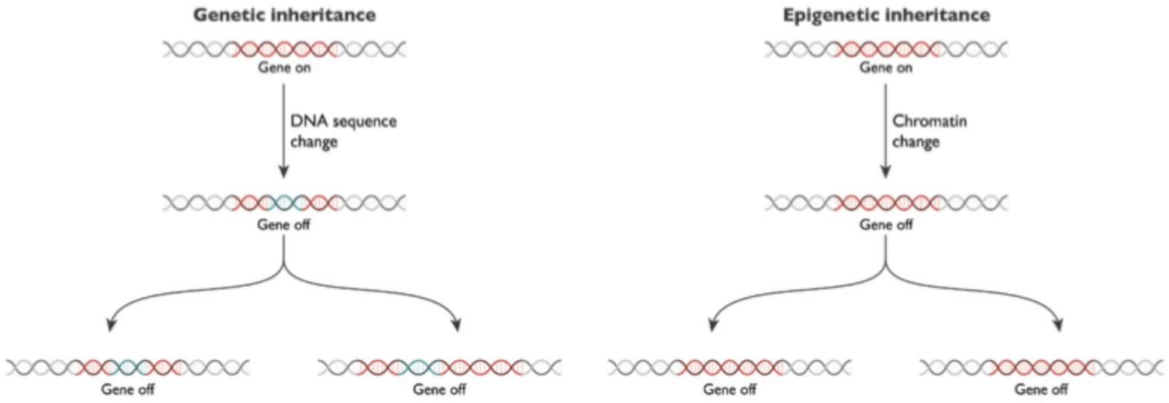
Notes

Summary

10m 17s

Epigenetic Inheritance

Epigenetic modifications, once acquired, can be **inherited** during development (mitosis)



So from this, it follows that epigenetic modifications once acquired can be inherited during development through a process called mitosis. So in addition to a genetic inheritance which is characterised by a DNA sequence change the kids transmitted through somatic cells to subsequent daughter generations. We also have an epigenetic inheritance that is a so-called chromatin state change that is brought about by histone posttranslational modifications or DNA methylation. This chromatin state change can then also be stably propagated through mitosis to subsequent data sets.

Notes

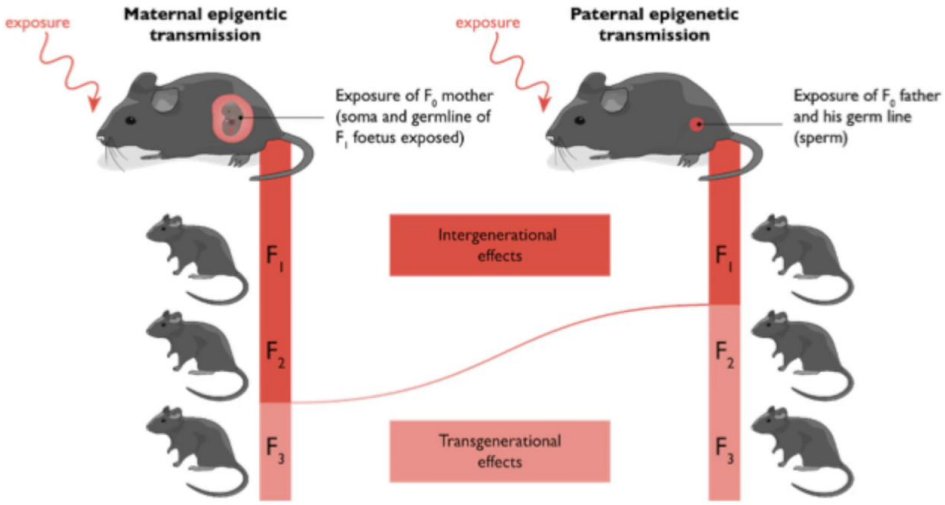
Summary

10m 49s

Epigenetic Inheritance

- Plants (*Z.mays*)
- Nematodes (*C.elegans*)
- Fruit flies (*D. melanogaster*)
- Mice (*M. musculus*)

but the underlying mechanisms are still poorly understood



Now, very interestingly, these epigenetic modifications, once acquired, can also be inherited across generations through a process called meiosis. This is known from plants, from mice, from nematodes such as C.elegans, from fruit flies such as drosophila, and also from rodents such as mice. Now, in order to be inherited across generations. The epigenetic mark that is installed by a given environmental stimulus, has to be able to be stably propagated through the process of meiosis. If we now consider the paternal epigenetic transmission that goes across generations, and if we say that the father, which would be our F0 generation, has been exposed to a specific environment. In which case both the father and his germline would be exposed to this environment. So if we really want to talk about transgenerational inheritance of epigenetic modifications, we will need to at least investigate the second generation. The F2 generation. If you now consider the maternal epigenetic transmission, then we appreciate that. If the mother is exposed to a changing environment and this mother is pregnant, then this stipulates that both the F0, which would be the mother, but also two subsequent generations, which are the F1, which would be the baby and the F2, which would be the all sides inside the unborn baby would be already affected.

Notes

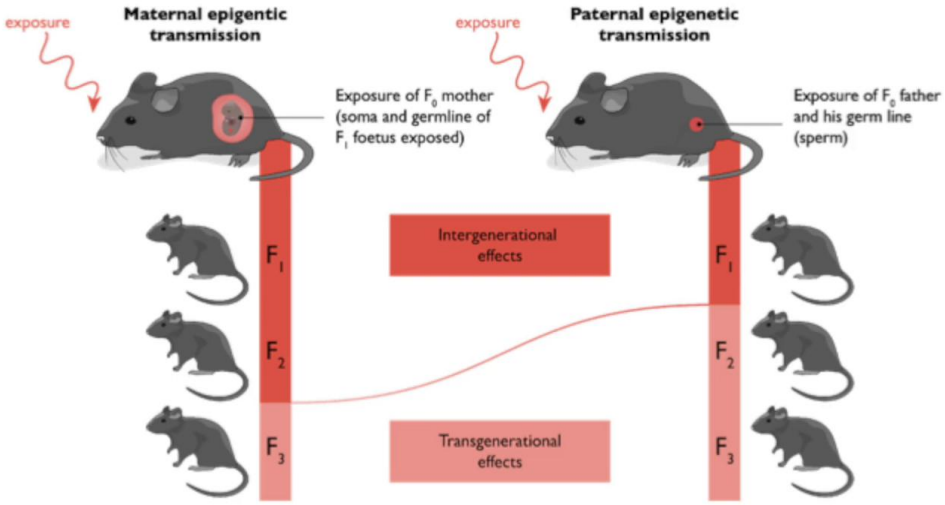
Summary

11m 35s

Epigenetic Inheritance

- Plants (*Z.mays*)
- Nematodes (*C.elegans*)
- Fruit flies (*D. melanogaster*)
- Mice (*M. musculus*)

but the underlying mechanisms are still poorly understood



This means for transgenerational effects to happen. On the paternal side, we have to study at least the second generation. Whereas on the maternal transmission side, we have to study at least the third generation. Although there are numerous examples that testify to the fact that epigenetic modifications can be inherited across generations. The underlying mechanisms are still poorly understood.

Notes

Summary

13m 23s