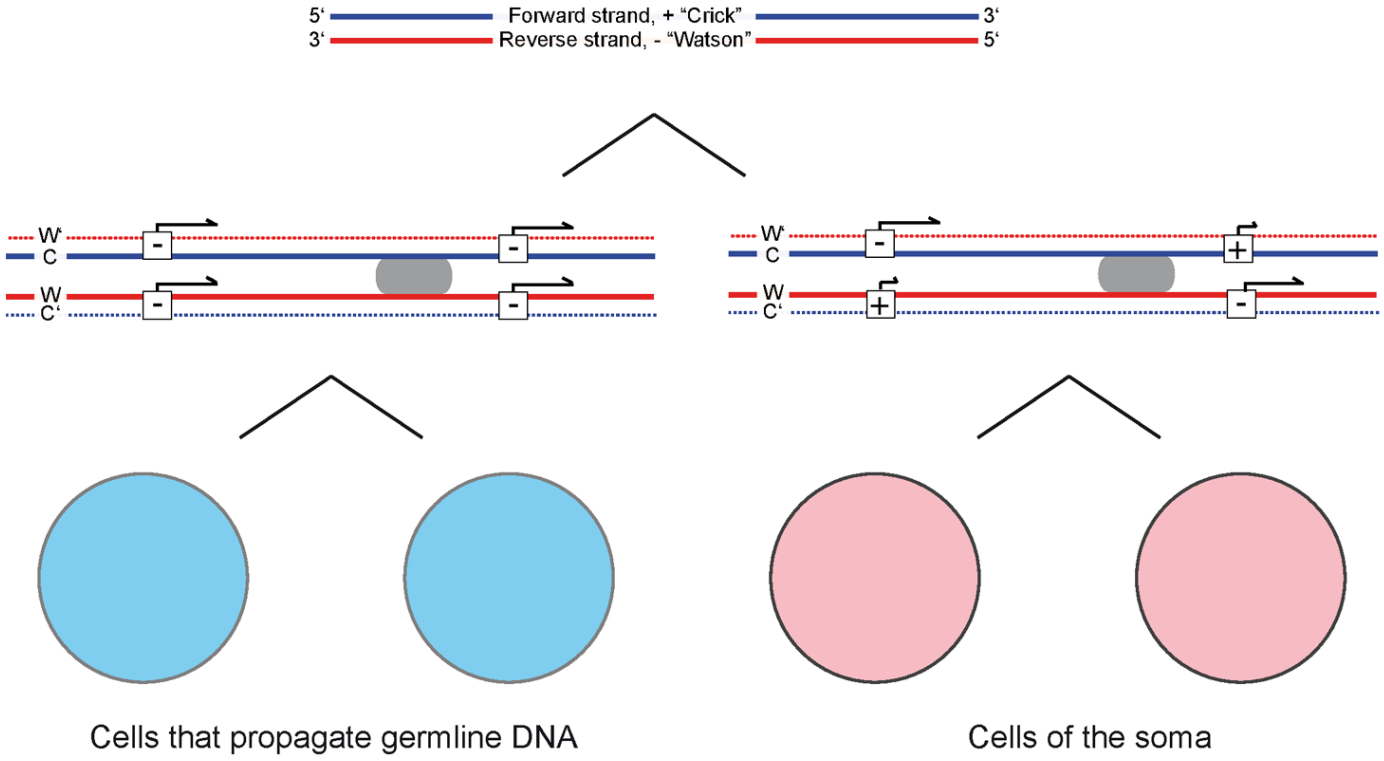
A new dimension in the study of life?

One of the key remaining questions in biology is how different cell types originate from single cells such a fertilized eggs or cells from early embryos. What factors drive cells to adopt one cell fate over another? Most of the studies in this area are focused on the genes that are expressed in different cell types and proteins that regulate the expression of those genes. But how do these factors drive asymmetric cell divisions during development? Apart from the cellular distribution of proteins and RNA, a specific modification of DNA, methylation of cytosine, is known to play a role in cell differentiation. Specifically, transcription of genes is typically suppressed if regulatory regions near genes are methylated. Studies on the regulation of DNA methylation and demethylation complement ongoing studies on the proteins and genes that are expressed in pluripotent cells upon induction of differentiation. But is that really all there is?



Model for how G4 structures in DNA could generate different gene expression patterns in cells according to the “silent sister” hypothesis. DNA typically consists of two strands, a “Watson” and a “Crick strand (top). Cells that propagate germline DNA in ciliates, flies and flatworms were shown to stain weakly with antibodies to G4 structures (bottom) in the paper by Hoffmann et al. Based on this observation it seems possible that the formation of G4 structures during DNA transactions such as replication and transcription is suppressed in cells of the germline compared to somatic cells. If G4 structures are not rapidly resolved during replication these structures could delay the deposition of epigenetic marks from the parental chromatid or could serve to recruit new epigenetic marks.

The resulting epigenetic differences between sister chromatids could trigger differences in gene expression between daughter cells as predicted by the silent sister hypothesis. The role of DNA methylation in this context is puzzling and intriguing. On the one hand it is known that cytosine methylation stabilizes the bond between guanine and cytosine nucleotides and thereby stabilizes duplex DNA. On the other hands cytosine methylation could also stabilize G4 structures. So it may be hard to predict how the dynamic equilibrium between duplex and quadruplex DNA is shifted upon methylation of cytosines in and around a specific gene without taking information of strands and G4 motifs, next to the expression of various proteins that may bind and resolve G4 structures into account. Of note: G4 motifs were shown to be not randomly distributed in the genome. Their specific enrichment of G4 motifs at genes that promote growth is in line with the proposed role in differentiation.

In a recent paper published in Nucleic Acid Research Hoffmann et al., report that cells with germline DNA in ciliates, flatworms and fruitflies have something in common: they all stain poorly with a monoclonal antibody specific for guanine quadruplex structures compared to more differentiated cells. This surprising finding raises a lot of questions such as what are guanine quadruplex structures? In duplex DNA guanine pairs with cytosine and thymidine pairs with adenosine. Interestingly, in single stranded guanine-rich DNA, another type of bonding between guanine bases can occur: four guanines can start exchanging electrons in a single plane called a guanine quadruplex (G4) quartet structure. The stability of G4 structures is expected to increase with the number of G4 planes. Many questions re G4 structures including the role of guanine-rich RNA in the formation of G4 structures remain unanswered. However, the notion that guanine-rich DNA can switch between the well-known duplex form that is essential for replication, transcription and recombination and higher order G4 structures which pose a problem for all these processes is intriguing and exciting. Could it be that cells that propagate the DNA for a species are better capable to suppress G4 structures compared to more differentiated cells? Long dismissed by many biologist as in vitro artifacts, G4 structures are known to readily form under physiological conditions. It was furthermore shown that specialized helicases are required to prevent instability of guanine–rich DNA. The notion that G4 could be more broadly involved in epigenetic regulation was predicted by the “silent sister” hypothesis. This connection is particularly intriguing in view of recent studies supporting this hypothesis from the group of Sale in Cambridge. Could a dynamic switch between duplex DNA and G4 DNA trigger differences between sister chromatids that play a role in the differentiation of pluripotent cells? Is there a role for DNA methylation in pushing this equilibrium one way or another? In the study by Hoffmann it was shown that G4 structures localize specifically to heterochromatin. Whether the formation of heterochromatin is triggered by G4 structures or induced upon condensation of DNA is currently now known. Indeed both situations could apply as G4 staining was found both in post-mitotic, condensed metaphase chromosomes as well as in dynamic bands of heterochromatin in polytene chromosomes of the fruit fly.

Sydney Brenner once said that progress of science depends on new techniques, new discoveries

and new ideas, provably in that order. The recent findings reported by Hoffmann open up a new dimension in studies of one of the most fascinating questions in biology: how is it possible that the same DNA can give rise, with clockwork precision, to a variety of different cell types.

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Guanine quadruplex structures localize to heterochromatin.
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