Programming cells: The importance of the envelope

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In a project that began with the retinal cells of nocturnal animals and has led to fundamental insights into the organization of genomic DNA, researchers from Ludwig-Maximilians-Universitaet (LMU) in Munich show how the nuclear envelope affects nuclear architecture - and gene regulation.

The double-stranded DNA molecules that make up the genetic material are wrapped around protein complexes to form compacted "chromatin". The active portion of the genome is less densely packed, and thus more easily accessible, than the inactive fraction, and is referred to as euchromatin. Euchromatin is typically located in the inner regions of the cell nucleus, while much of the inactive DNA in "heterochromatin" is associated with the inner face of the nuclear envelope. This type of chromatin organization is found in almost all higher organisms and may have been invented 500 million years ago.

But there is a curious exception to this generalization. In the retinal cells of nocturnal animals, the heterochromation is localized in the central area of the nucleus, as a research group led by LMU biologists Dr. Irina Solovei and Dr. Boris Joffe showed in a previous study. "This got us interested in the mechanisms that control the distribution of chromatin," says Professor Heinrich Leonhardt of LMU's Biozentrum. "How can the nuclear architecture in the rod cells of nocturnal animals be inverted in this way, and what determines the typical positioning of inactive chromatin on the outskirts of the nucleus in normal cells?" Leonhardt and his team have now completed an extensive study in search of the

answers.

A fundamental principle unveiled

With the help of targeted genetic manipulations in the mouse, Joffe and Solovei together with their colleagues show for the first time that there are two independent mechanisms for fixing heterochromatin to the inner face of the nuclear envelope. These mechanisms make use of two different components of the inner nuclear membrane as clamps – lamin A/C, and the so-called lamin-B receptor (LBR), which itself binds to B type lamins.

Normally the two components are used sequentially for this purpose. "In the course of differentiation, there is a switch from the LBR to lamin A/C, and there is always a least one type of tether available for attachment of heterochromatin to the nuclear periphery. But if both are missing, the inactive heterochromatin recoils like a severed elastic band and collapses in the center of the nucleus," explains Leonhardt. Moreover, the switch seems to be a fundamental principle of genome organization and cell differentiation in mammalian cells, as the researchers concluded from the study of 39 species and the analysis of diverse tissue types in nine genetic strains of mice.

Prospects for targeted therapies

Lamin proteins not only have a structural function but also have an impact on gene regulation. Thus LBR binds B type lamins and regulates stem-cell populations by promoting the expression of genes that are important for the proliferation of rapidly dividing stem cells. The lamin A/C gene on the other hand codes for a structural component of the nuclear envelope, and regulates cellular differentiation programs like e.g. the expression of muscle-specific genes in muscle cells. Mutations in this

gene result in so-called laminopathies – rare genetic diseases that are associated with a broad spectrum of clinical symptoms, including muscular dystrophy and progeria, a premature aging syndrome.

Joffe and Solovei suspect that mutations in lamin A/C affect the expression of specific genes during the maturation and differentiation of cells, with deleterious results for their function and for tissue integrity. This notion could explain the highly diverse and complex symptoms seen in patients with mutations in the lamin A/C gene - and it could open routes to the design of targeted therapies for laminopathies.

The new findings thus yield fundamentally new insights into how each of the many differentiated cell types in the body arises as the result of the precisely regulated expression of a specific complement of genes appropriate to each. "In the end, we have been brought from studies of night vision and an odd quirk of nature to the discovery of a fundamental regulatory mechanism: The nuclear envelope has a major say in development, and what kind of envelope our genetic material comes in makes a great deal of difference to our fate," Leonhardt concludes.

Provided by Ludwig Maximilian University of Munich