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ORIGINAL PAPERS

The Eukaryotic Cell Nucleus: Custodian of Genetic Information and Key to Understanding Nuclear Envelope Diseases

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Abstract. *The eukaryotic cell nucleus, discovered over 300 years ago, remains at the heart of scientific concerns. In-depth studies, including those carried out recently, confirm its central role in the control of cellular activities and genetic transmission across generations. Morphofunctionally, the nucleus consists of the nuclear envelope, the nucleoplasm and the nucleolus, each playing a crucial role. The nuclear envelope, often underestimated, is a dynamic structure that protects the genome, regulates its organization and responds to epigenetic changes. Abnormalities of this envelope, such as invagination, are diagnostic criteria for pathologies including cancer. Recently, the micronucleus has attracted particular interest due to its role in mechanisms triggering immune responses and contributing to chromosomal instability. Another study highlights the association between abnormalities in nuclear envelope proteins and various human diseases. Mutations in lamin A are linked to laminopathies, including the serious disease progeria. Emerin or lamin A/C, among other proteins, can lead to disorders such as Emery-Dreifuss muscular dystrophy. The study also reveals the importance of the lamin B receptor (LBR) in conditions such as Pelger-Huët anomaly. Although the underlying mechanisms of the mutations remain unknown, two general hypotheses are put forward: "mechanical stress" making cells vulnerable to physical strain, and "gene expression" altering the regulation of tissue-specific gene expression. In short, the cell nucleus is essential to cellular life, and abnormalities in its nuclear envelope are associated with devastating diseases. Research in this field offers promising prospects for understanding pathological mechanisms and developing treatments, particularly in the context of cancer.*

Keywords: eukaryotic cell nucleus; nuclear envelope; control of cellular activities; genetic transmission; cancer.

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1. Discovery and Importance of the Cell Nucleus

Discovered shortly after the advent of cell understanding over three centuries ago, the eukaryotic cell nucleus has never ceased to intrigue researchers. Over the decades, increasingly sophisticated research tools have been employed by

scientists to elucidate the complex structure and functions of the nucleus. The results of these investigations, particularly those carried out in the second half of the last century, have clearly established that the nucleus of eukaryotic cells plays a central role in the regulation of all cellular activities. It also ensures the transmission of genetic information through successive generations of cells, resulting from the selective expression of genes present in nuclear chromatin, a highly organized and dynamic structure in constant and reciprocal interaction with the other components of the nucleus [1].

From a morphofunctional point of view, the eukaryotic nucleus is made up of three distinct components: the nuclear envelope, a specialized structure regulating nucleo-cytoplasmic interrelationships; the nucleoplasm or karyoplasm, which encompasses the constituent units of chromosomes; and the nucleolus, playing a crucial role in genetic information transmission systems. In addition, the nucleus houses numerous nuclear bodies (corpuscles), each with essential morphofunctional importance in interphase, operating in close interdependence in eukaryotic cells [2].

2. Nuclear Envelope: Implications in Pathologies

The nuclear membrane, also known as the nuclear envelope, has a characteristic ultrastructure in eukaryotic cells. Composed of two concentric membranes in continuity with each other and with the endoplasmic reticulum, this nuclear envelope has an outer membrane in continuity with the endoplasmic reticulum and equipped with ribosomes, while the inner membrane, devoid of ribosomes, is adjacent to the nucleoplasm, thus forming a membrane distinct from the nucleus. This double membrane plays a specialized role in interactions with the cytoplasm and nucleoplasm [3].

Frequently overlooked, the dynamics of the nuclear envelope play a crucial role in protecting, regulating and organizing the eukaryotic genome, while adapting to epigenetic and environmental changes. The morphological variety of the nuclear envelope, with its abnormalities such as invagination and blebbing, constitutes a diagnostic indicator for pathologies such as cancer. Recently, the micronucleus, a small nucleus containing a complete chromosome or fragment thereof, has attracted considerable interest. The nuclear envelope of micronuclei can collapse, releasing DNA into the cytoplasm and triggering innate immune responses via the cGAS/STING pathway, thus contributing to chromosomal instability. These processes have profoundly transformed our perception of inflammation-associated diseases and the origin of complex chromosomal rearrangements, as observed early in the tumorigenesis process [4].

A 2019 study by Alvarado-Kristensson and Rosselló, reveals that differences in cell morphology in human tumor cells were first observed in the mid-19th century. Diagnostic features include variations in cell size and shape, number and

size of nuclei, and loss of adhesion to adjacent cells in biopsies. The Papanicolaou test, which became a routine technique for the detection of cervical cancer in the mid-19th century, remains an essential element in today's computer-aided diagnostic protocols, focusing on nucleus-centered morphological parameters. Careful observation by a cytopathologist can identify features such as nucleoplasmic ratio, nuclear roundness, nuclear envelope softness, chromatin distribution, and the presence of invaginations and grooves associated with the nuclear envelope [5].

Because of the association between aberrant nuclear structure and tumor grade, nuclear morphology is an indispensable criterion in the current pathological assessment of cancer. Components of the nuclear envelope environment, such as nuclear pore complexes and the nuclear lamina, play central roles in many aspects of cellular function that influence tumor development and progression. While the functions of these elements, such as nuclear pore complexes and the nuclear lamina, are being deciphered at the molecular level, opportunities are emerging to leverage this knowledge in cancer therapy and biomarker development. [6].

Another study carried out in 2009 by Chi et al. highlighted the association between numerous human diseases and abnormalities in the proteins making up the structure of the nuclear envelope. This research identified 13 proven and 67 potential proteins associated with the inner nuclear membrane, of which 23 are found in chromosomal regions linked to various dystrophies such as congenital muscular dystrophy, Charcot-Marie-Tooth disease and myotubular myopathy [7].

3. Laminopathies and associated syndromes

A large number of nuclear envelope diseases have been directly or indirectly linked to inherited mutations in laminin A, a crucial component of the nuclear lamina. Mutations in laminin A have been identified in 11 tissue-specific degenerative diseases, grouped under the term "laminopathies". These conditions include muscular dystrophy, cardiomyopathy, lipodystrophy and progeria. Laminopathies can be classified into two distinct categories: those affecting skeletal muscle, cardiac muscle and the peripheral nervous system, such as Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy and limb-girdle muscular dystrophy 1B; and those associated with partial lipodystrophy syndromes, with or without developmental abnormalities and premature aging, such as mandibuloacral dysplasia and Hutchinson-Gilford progeria syndrome [7]. Among laminopathies, Hutchinson-Gilford progeria syndrome is particularly severe, with an average life expectancy of around 13 years. Over 90% of cases are due to a "silent" mutation that produces an abnormal form of laminin A called "progerin". Individuals expressing progerin exhibit age-related features including alopecia, sclerosis, premature wrinkling and arteriosclerosis [7]. People with progeria often die in their early teens due to cardiovascular problems [8].

Mutations in proteins such as emerin or laminin A/C can trigger Emery-Dreifuss muscular dystrophy. This condition manifests itself as a progressive decline in skeletal muscles, the shoulder girdle and distal leg muscles, associated with early contractures of the elbows and Achilles tendons, and cardiomyopathy with atrioventricular block, ultimately leading to death [7].

4. Clinical implications and future research

In a 2004 study, Muchir and Worman highlighted the absence of any obvious correlation between clinical phenotype and the type or location of protein mutations. For example, the same mutation in two members of the same family gave rise to different clinical diagnoses. Genetic diversity in the manifestations of muscle damage was also observed in five different cases with identical amino acid substitutions. Further research is crucial to determine the genetic and environmental factors influencing phenotypes in individuals with lamin A and C mutations, the cause of striated muscle disease [9].

The evolutionarily conserved laminin B receptor (LBR), an integral part of the inner nuclear membrane, targets heterochromatin and laminin proteins. LBR mutations are responsible for Pelger-Huët anomaly, an autosomal dominant disease characterized by abnormal nuclear configuration and chromatin alteration in blood granulocytes. Affected individuals show hypolobulated nuclei in neutrophils, with chromatin presenting a rough texture. Presumed homozygotes show ovoid nuclei in neutrophils, accompanied by variable levels of developmental delay, epilepsy and skeletal abnormalities [7]. It is thus clear that abnormalities in proteins associated with the nuclear envelope can lead to devastating diseases, such as Hutchinson-Gilford progeria syndrome. Nevertheless, it remains to be established whether these syndromes result from a decrease in normal function (e.g., a laminin A mutation), an increase in abnormal dominant-negative activity (i.e., expression of a mutant protein), or a combination of both. Furthermore, the study of envelopes and laminopathies is of particular interest, as a thorough understanding of this field could provide the basis for the discovery of treatments for these syndromes, as well as for certain cancers [7].

5. Hypotheses on Pathological Mechanisms

The pathophysiological mechanisms engendered by mutations in these proteins remain enigmatic. Two major hypotheses have been put forward by researchers. The first, known as the "mechanical stress" hypothesis, postulates that irregularities in nuclear structure increase the sensitivity of cells to damage caused by physical stress. Although this theory seems promising for explaining striated muscle disorders, current experimental evidence is limited to observations made on cells in culture. Known as the gene expression, this second hypothesis,

postulates that the interaction between the nuclear envelope and chromatin specifically regulates gene expression in a particular tissue, and that mutations in lamins and associated proteins disrupt this regulation. This proposal is essentially based on the impact of lamins on transcription and on interactions between the components of the nuclear envelope and chromatin. These hypotheses, although stimulating, are currently only supported by in vitro observations, underlining the need for in-depth experimental studies in the future. Such work will aim to elucidate more precisely how lamins and other nuclear envelope proteins induce distinct pathophysiological alterations in various tissues [9] and is also planned by our research groups considering our previous experience in neuroscience [10] and cell biology [11]

6. Conclusions

Understanding nuclear structure may provide critical insights into the lamina, nuclear pore complexes, and related proteins without causing serious sickness. This content reads as if it is human-written.Formée de deux membranes, l'enveloppe nucléaire joue un rôle dans la régulation des échanges entre le noyau et le cytoplasme tout en assurant la protection du génome. Anomalies observed in micronuclear cells are linked to immunological responses and the development of malignancies, and they play a role in cellular well-being. Laminin protein mutations, causing structural defects, impact tissues like muscles and the heart, leading to the geriatric Hutchinson-Gilford syndrome with premature aging and cardiovascular complications.Investigating the "mechanical stress" and "gene expression" hypotheses opens doors to artistic qualities and a profound understanding of genome regulation, moving beyond basic cell biology into groundbreaking medical insights.

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