H. The nucleus and interactions with the cytoskeleton

I. The nucleus

I.1. Definition

The nucleus is the largest organelle in the cell (approximately 10%) and is easily visible under an optical microscope. The nucleus is a cellular compartment that exists only in eukaryotes and is present in all cells except red blood cells, keratinocytes in the superficial layers of the epidermis, and thrombocytes. It contains DNA in the form of chromosomes, a nucleolus, nucleoplasm, and nuclear matrix. It is the site of DNA replication, DNA transcription into RNA, and mRNA maturation. The nucleus temporarily disappears during the process of cell division, only to be reconstituted in the daughter cells

I.2. Function

The nucleus not only contains the essential cellular DNA, but is also the site of continuous transformations, particularly for synthesized RNAs. It is a cellular organelle whose functions are:

- To store the nuclear genome and protect genetic information;
- Storing the machinery necessary for chromosome replication and the expression of the information contained in genes

I.3. Nucleus structure

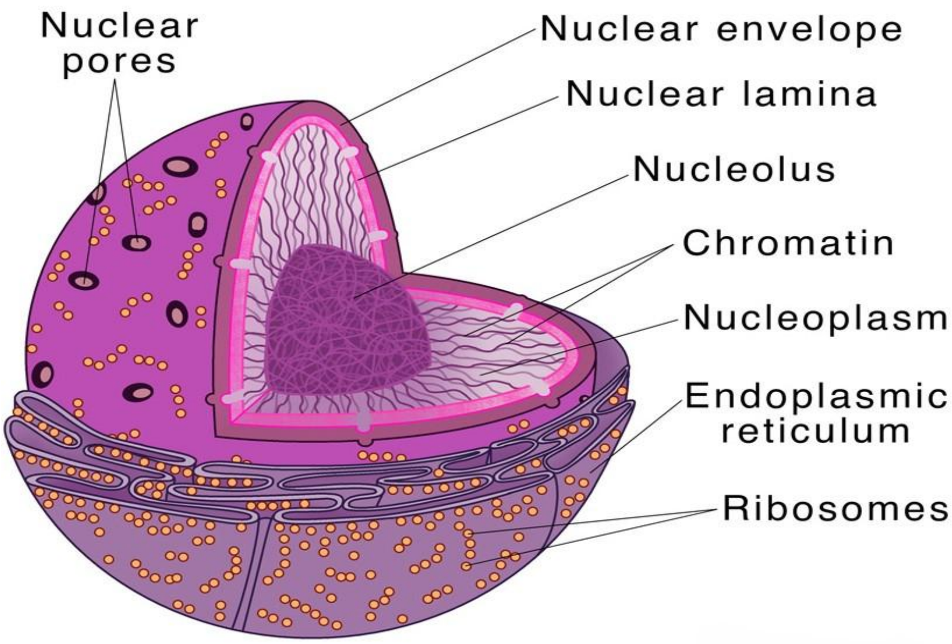

Figure III.1. Nucleus structure

I.3.1. Nucleoplasm

This is a liquid phase containing soluble proteins and mineral salts. The nucleoplasm also contains dissolved nucleotides and a significant amount of Mg^{2+}et Ca^{2+}.

I.3.2. DNA

DNA is associated with basic proteins: histones, which play an important structural role, enabling DNA compaction, and non-histones.

I.3.3. RNA

It is found in the form of ribosomal RNA, in significant quantities in the nucleolus, associated with proteins. It is also found in the form of pre-messenger RNA.

I.3.4. The nucleolus

Area of transcription of ribosomal RNA (rRNA) genes. It is a more or less spherical structure located in the nucleus, not delimited by a membrane. The number varies depending on the cell type, generally 1 or 2 nucleoli per nucleus or several (growing oocytes); it may be absent (sperm). It disappears during prophase and reforms during telophase, persisting throughout interphase.

I.3.5. The nuclear envelope

This is a barrier between the nuclear and cytoplasmic compartments with selective permeability. The nuclear envelope is a specialised part of the endoplasmic reticulum. It is formed of two membranes, each 6 nm thick, with a trilamellar, asymmetrical and fluid mosaic structure. They are separated by a cavity or perinuclear space, 10 to 30 nm thick, which is continuous with the cavity of the endoplasmic reticulum. The outer nuclear membrane carries ribosomes on its cytosolic side, and the inner nuclear membrane is associated on its nucleoplasmic side with a thin electron-dense layer called the lamina densa, which corresponds to a network of intermediate filaments consisting of lamins. It provides rigid structural support to the nuclear envelope and serves to anchor chromatin to the periphery of the nucleus.

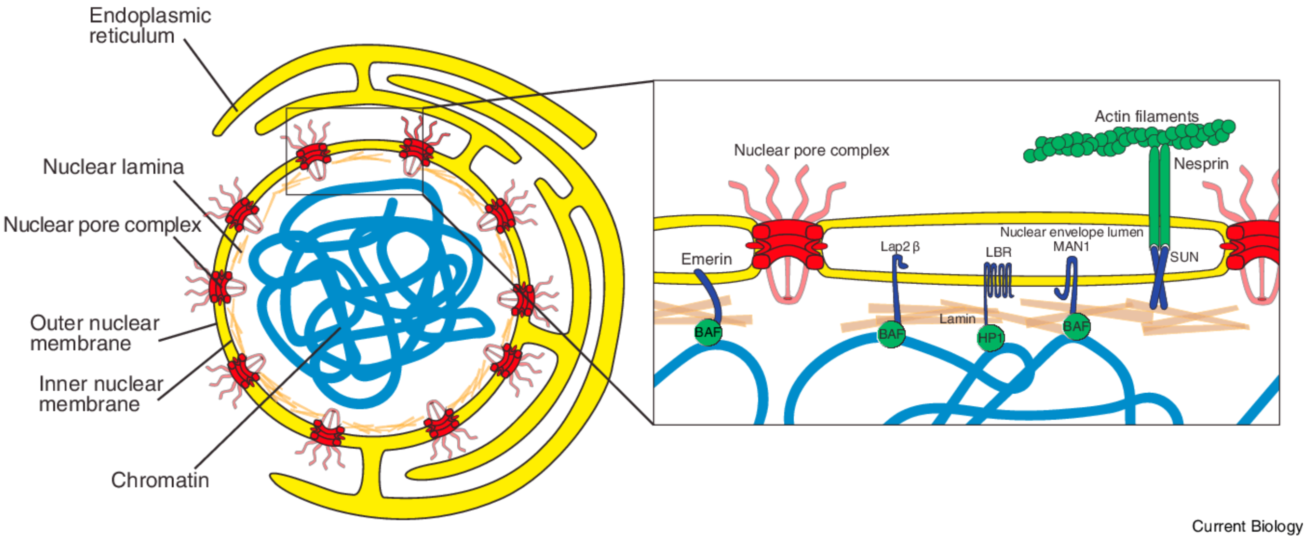

Figure III. 2. Schematic representation of the nuclear envelope

- **Nuclear Pore**

The nuclear envelope is a selective barrier with areas of interruption called nuclear pores. Their number varies depending on the type of cell, but above all on the physiological activity of the cells. They form a complex structure known as the nuclear pore complex (NPC).

The NPC consists of two large rings, each 120 nm in diameter, the cytosolic ring and the nucleoplasmic ring, which delimit a central orifice or central transporter 30 nm in diameter. Each of the two rings is formed by an assembly of eight radial arms that protrude into the central orifice, thus delimiting eight lateral channels. A third small ring is located in the nucleoplasm. There appears to be a very stable interconnection between the NCPs and the lamina densa, which serves as their anchor.

Passive transport of soluble molecules occurs through the lateral channels, while active transport of larger molecules occurs through the central channel or transporter. The nuclear envelope also allows the import and export of various molecules through the NPCs and double membranes. It thus controls and regulates exchanges between the cytosol and the nucleoplasm.

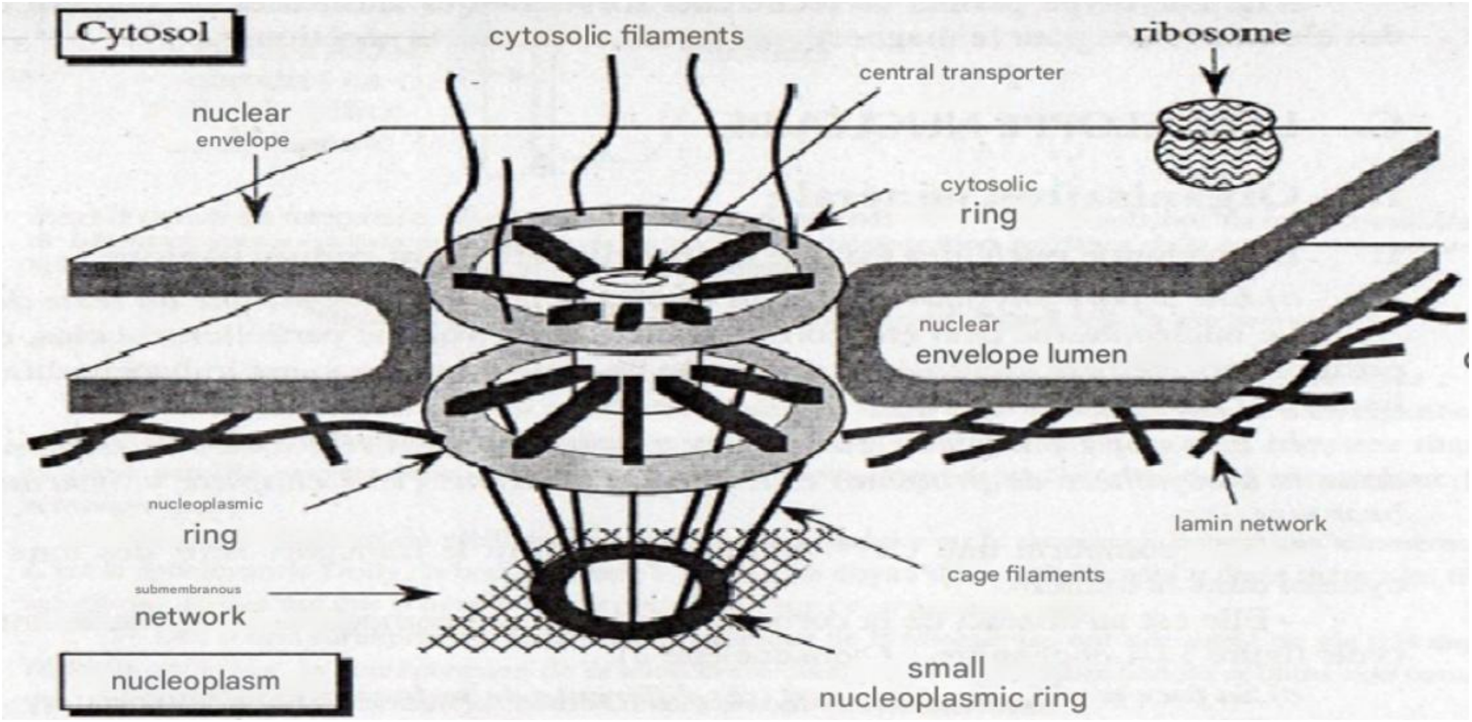

Figure III. 3. The nuclear pore complex

II. Links between the cytoskeleton and the nucleus

The main physiological roles of the cytoskeleton—maintaining cell integrity, migration, and molecular transport—clearly explain its strong interactions with the cell membrane. However, it seems surprising in this context that the cytoskeleton is also closely linked to the cell nucleus. The nucleus is physically connected to the cytoskeleton, a fundamental characteristic for the transmission of mechanical forces required for multiple nuclear and chromosomal functions. A stable connection between the nucleus and the cytoskeleton is required for a wide variety of physiological processes, such as cell migration and nuclear positioning.

The nucleoplasm contains the Lamin network, an intermediate filament underlying the nuclear membrane. Anchored to the membrane are nuclear pores and proteins of the LINC complex: SUN and Nesprin proteins. In the cytoplasm, Nesprins directly or indirectly connect the filaments of the three cytoskeletons. The ‘giant’ Nesprin 1/2 connects the actin cytoskeleton, Nesprin 4 has a kinesin-binding domain that allows it to bind to microtubules, and Nesprin 3 binds to intermediate filaments via plectin.

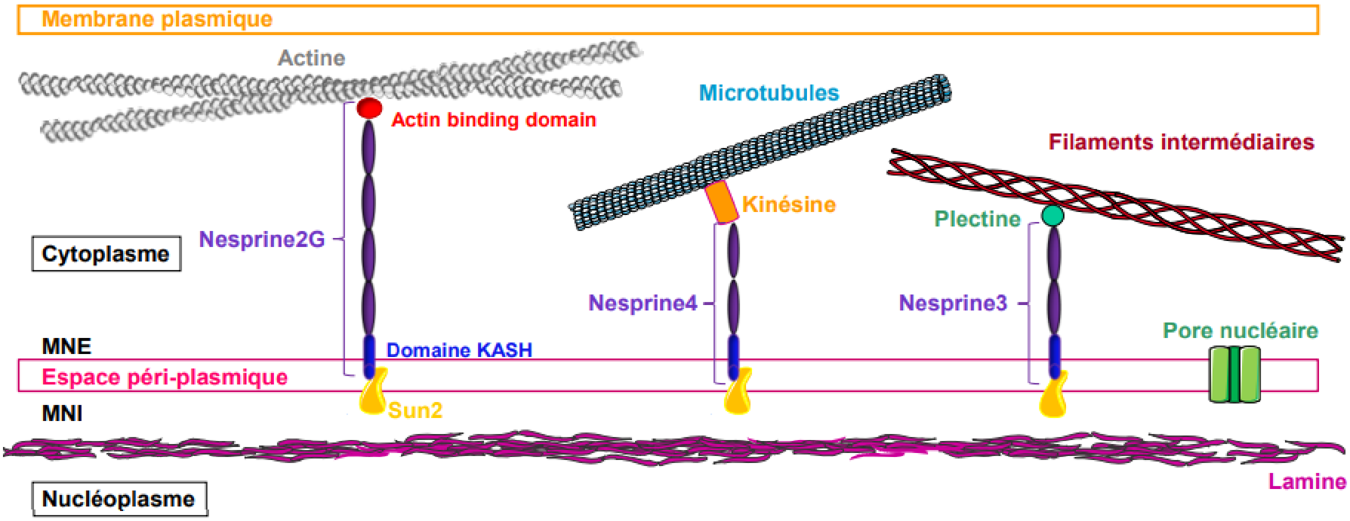

Figure4. Schematic representation of the nuclear envelope and the components of the LINC complex

II.1. Composition and varieties of LINC complexes and their connection to cytoskeletons

LINC complexes are composed of a multitude of proteins whose function may be redundant, and these complexes are connected to the three cytoskeletal proteins, which are themselves interconnected. Table 1 below presents only the three major components: laminins, nesprins and SUN proteins.

Table1. Summary of possible LINC complexes and their components

The nucleus is connected to the cytoskeleton by the LINC complex. In simple terms, Lamin, SUN and Nesprin proteins connect the nucleus to the cytoskeletons. The connection to actin is direct but requires additional proteins for interaction with microtubules or intermediate filaments.

Nucleoplasm	Perinuclear Space		Cytoplasm		Function
	SUN	Nesprin	Intermediate	Cytoskeleton	
Lamin A/C-B1	SUN1/2	Nesprin1/2	Not required	Actin	- Nuclear anchoring - Mechanotransduction
Lamin A/C-B1	SUN1/2	Nesprin3a	Plectin	Keratins	Nucleus-intermediate filament coupling (during actin depolymerization)
Lamin A/C-B1	SUN1/2	Nesprin4	Kinesinel	Microtubules	Epithelial polarity
Lamin A/C-B1	SUN1/2	Nesprin1/2	Dynein/Dynactin or Kinesinel	Microtubules	Neuronal migration

II.2. Lamins

Lamin proteins belong to the intermediate filament family, organised into networks and located on the nucleoplasmic side. They are the major constituents of the nuclear lamina, which organises the LINC complex. Lamin proteins determine the shape and size of the nucleus and the positioning of nuclear pores, and act as ‘shock absorbers’ to protect the nucleus during deformation.

In mammals, two types of laminins are expressed: type A laminins encoded by the LMNA gene, which mainly produce the proteins laminins A and C, and type B laminins encoded by the LMNB1 and LMNB2 genes, which produce laminins B1 and B1, respectively.

II.3. Nesprins

Nesprins (nuclear envelope spectrin repeat proteins) are characterised by a central region of variable size composed of spectrin domains, the number of which can vary greatly, and one or more KASH (Klarish/ANC-1/Syne homology) domains at the C-terminus for anchoring to the nuclear envelope. At the N-terminal of Nesprins, there are motifs that interact with different cytoskeletons. The most widely described are Nesprins 1 and 2, which have an actin-binding domain, Nesprin 3, which binds to intermediate filaments via plectin, and Nesprin 4, which interacts with microtubules via kinesin.

II.4. SUN proteins

SUN proteins are located in the perinuclear space and cross the inner membrane to interact with lamin. KASH domain proteins (including nesprins) bind to SUN1 or SUN2 proteins, allowing them to anchor to the nuclear envelope.

There are other components of the LINC complex that can substitute for SUN proteins. Torsin1A, in particular, can take on the role of SUN proteins in conditions where they are absent, thanks to its ability to bind to KASH domain proteins.