4.6. Pathobiochemistry of the Nucleus

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The nucleus is at the focal-point of cellular life in eukaryotic organisms, featuring an extended portfolio of various cellular events far beyond the replication and transcription of DNA. Due to the strategic position of nuclear structures, many nucleus-related pathobiochemical features have already been described in previous chapters on signal transduction, metabolism and individual pathological states. The current chapter therefore focuses on the relationship of the cell nucleus to other cellular compartments (mostly the cytoplasm) and summarizes the changes occurring in various pathological conditions.

Structure of the Cell Nucleus and its Pathology

In the evolution of advanced monocellular organisms, became separated genetic material, that is, DNA, by a complex protein-membrane structure approximately 1.5 billion years ago. This had a number of advantages: Since DNA was protected by a separate compartment, (1) DNA-length could be extended, and the increasing danger of DNA breaks by cytoskeletal movements could thus be avoided. An extra level of DNA protection could be achieved by lowering the redox potential of the nuclear compartment below the already reduced cytoplasm.

(2) The separation of RNA and protein synthesis provided additional options for regulation. These extra regulatory events are the 'maturation' of primary RNA transcripts, their transport rate, the spatial and temporal organization of their nuclear transport, and of that of regulatory proteins. Concentration gradients of various ions and small molecules provided an additional layer of regulatory complexity. Moreover, the complex structure of the nuclear pore complex (described below) serves as an 'organization center' during mitosis, whe the whole nucleus has to be disassembled and reassembled again.

(A) The major structural elements of the cell nucleus are shown on *Fig. 1*. The following characteristics of nuclear structure should be highlighted:

(1) *The nucleus is not separated from the rest of the cellular organelles*. The double membrane separating the nucleus from the cytoplasm is connected to the membrane of the endoplasmic reticulum, and the cell nucleus is also tightly connected to the cytoskeletal structure.

(2) *The cell nucleus is not uniform*. It consists of a nucleolus, as well as euchromatin and heterochromatin structures, consisting of DNA organized into a looser, active or a tighter, inactive form, respectively. The nucleus also contains a large number of 'centers' and 'granules'. The exact nature, function, dynamics and connections of these centers and granules are the subject of intensive research. Many enzymes, lipids and small species, such as calcium ions, are distributed in a highly uneven fashion in the cell nucleus.

(3) *The nucleus*, contrary to the figure shown below, *is not static*. During replication and transcription processes the structure of the nucleus changes continuously. Core histones, for example, have a residence half-life of only a few minutes in the nucleosomal structure. Moreover, a complete disassembly-reassembly cycle is performed at each mitotical event. These are remarkable features given thatthe nucleus has an extremely compact structure in which the accomplishment of such gross rearrangements is difficult.

(B) The structure of the cell nucleus is grossly rearranged in malignant cells. As special features the polymorphism of the chromatin structure (hyperchromasia) and the proliferation of the nucleolar volume have all been observed during tumor development. The extension of nucleolar volume can explained by the fact that ribosomal RNA synthesis and