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DNA–membrane complexes, mitochondria and aging

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Abstract

The results of extensive in vitro studies of DNA–lipid complexes allowed us to propose a model for the structure of such complexes and their involvement in the formation of DNA–membrane complexes (DMC). DMC seem to form the basis for such cellular structures as Bayer's junctions and nucleoid of bacteria, the nuclear pores, annulate lamellae and nucleoid of eucaryotes. The role of DMC in gene expression is discussed. Numerical density of mitochondria during cell aging correlates with the density of bacteria in batch culture. It is concluded that aging is caused by the unlimited growth of mitochondria and their subsequent degradation. The role of DMC in mitochondrial DNA damage at aging is discussed. The way of increasing the life span by controlling the density of mitochondria in a cell volume is likewise discussed. DMC formed between any two intracellular membranes can serve the basis for the membrane continuum in a cell.

Keywords: DNA; DNA–membrane complexes; Mitochondria; Aging

1. Introduction

The coexistence of three main cellular components—proteins, nucleic acids and lipids—assumes the existence of three types of interactions between them: protein–nucleic acids, lipid–proteins and lipid–nucleic acids.

However, the existence of DNA–lipid interactions has been questioned by most biologists to date. It is therefore necessary to discuss some aspects of DNA–lipid interactions and their role in cell functioning and in the formation of various cellular structures.

2. DNA–lipid complexes in vitro

IR spectroscopic analysis of DNA–lipid complexes (total fraction of lipids of a rat liver) showed that DNA denaturates in the presence of these lipids [1]. However, it is possible that denaturation of DNA could be caused by drying–rehydration during the procedure used for preparing DNA–lipid complexes for IR-spectroscopy experiments. Calorimetric investigation of the complex polyA*polyU-phosphatidylcholine liposomes in the absence of divalent cations revealed minor changes in the melting profile of a lipid and polynucleotide [2]. Thus, despite the existence of the interactions between DNA and liposomes composed of zwitterionic or negatively charged phospholipids, these interactions do not lead to significant changes in the structure of complexes or their components.

In a paper by Budker et al. [3] and in our work [4], it has been shown that specific interactions between zwitterionic phospholipids and polynucleotides take place in the presence of divalent metal cations (Me^{2+}). These complexes may play an important role in a cell.

Briefly, the results of the investigation of DNA–phosphatidylcholine–Me^{2+} (triple complexes) can be presented as follows:

(1) DNA forms complexes with three main lipids: phosphatidylcholine (PC), phosphatidylethanolamine (PE) and sphingomyelin (SM). Addition of other lipids to these complexes caused the increase or decrease of the energy of these interactions [4].
(2) The ability of divalent cations to form complexes with DNA and PC correlates with the degree of binding of these cations to PC [4].
(3) Liposomes fuse (either partially or completely) in the presence of Me^{2+} and DNA, i.e. DNA acts as fusogene [5].
(4) DNA is partially unwound in triple complex [3,4].

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(5) The ^{31}P-NMR method revealed a strong change in a signal connected with phosphate groups of PC, which implies the formation of triple complexes between phospholipids, DNA and Mg^{2+} [6].
(6) A cooperative character of Mn^{2+} binding in the DNA–PC complex has been shown [5].

3. The model of triple complexes and their role in the formation of cellular structures

It is known that, at the end of the anaphase, nuclear pores are formed simultaneously with the assembly of a new nuclear envelope. The membrane vesicles, which appear due to the breakdown of the old nuclear envelope and sarcoplasmic reticulum, are involved in the process of new nucleus assembly [7]. Apparently, the assembly of nuclear pores in the interphase is realized in a different way [8].

We suggested the following way of formation of interphase pores (Fig. 1). The interaction of chromatin DNA, which is in the form of nucleosomes, with inner nuclear membrane results in the invagination of this membrane in the direction of the cytoplasm. This leads to a contact between two nuclear membranes (Fig. 1a).

The histones do not prevent the interaction of DNA with the membrane since they are known to interact with both negatively charged [9] and neutral phospholipids [10]. Thus, it is possible that DNA (chromatin) is capable of penetrating into lipid bilayers. DNA helix unwinds in lipid environment and forms a prepore (Fig. 1b). This process is accompanied by a fusion of two membranes and the formation of a true nuclear pore (Fig. 1c) [11].

The process of nuclear pore formation in the late anaphase from membrane vesicles at the moment of chromatin decondensation [12,13] is presented in Fig. 2 (II). It is seen that:

- the fusion of two vesicles takes place when DNA (or DNA–RNA hybrid) is localized between vesicles. The DNA plays a role of fusogene;
- unwinding DNA or DNA–RNA hybrid on equator of the large vesicle appeared from two fused vesicles;
- there is fusion of eight vesicles with the large vesicle, which is encircled on equator with single-stranded DNA and DNA–RNA hybrids, the formation of prepore;
- there is fusion of remaining vesicles with a prepore membrane on its perimeter with the formation of fragments of a nuclear envelope with pores;
- there is fusion of fragments of the nucleus envelope and vesicles in a closed nuclear envelope.

The data indicating the possibility of the formation of a nuclear envelope with pores in an extract *Xenopus laevis* in the absence of DNA [14] seem to be in contradiction with our model. However, the presence of a number of double-stranded RNA in the ooplasm, as well as the presence of nonchromosomal DNA in a cytoplasm of many cells [15] that can initiate the formation of pore complexes, makes this argument inconsistent. The confirmation of our model is based on recent data on the connection of chromatin DNA with nuclear envelope [16].

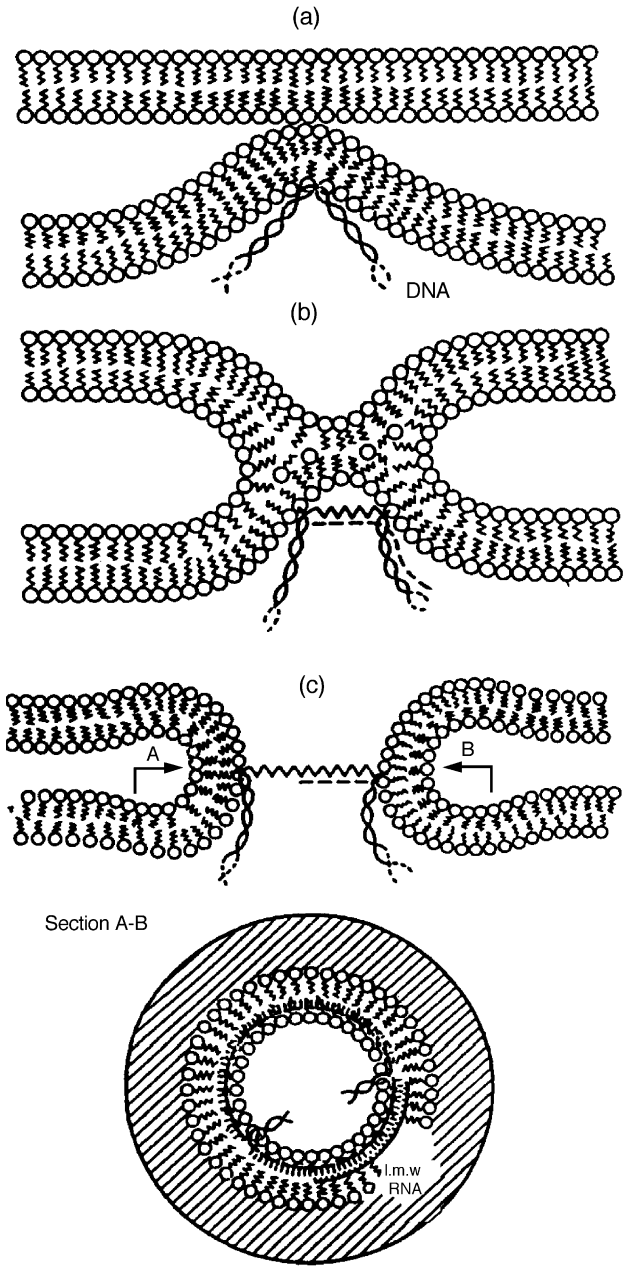

Fig. 1. Scheme of the interphase DMC formation (for details, see the text).

4. DMC, mitochondria and aging

Mitochondria could be involved in aging process. The theory of aging based on a role of mitochondria will be

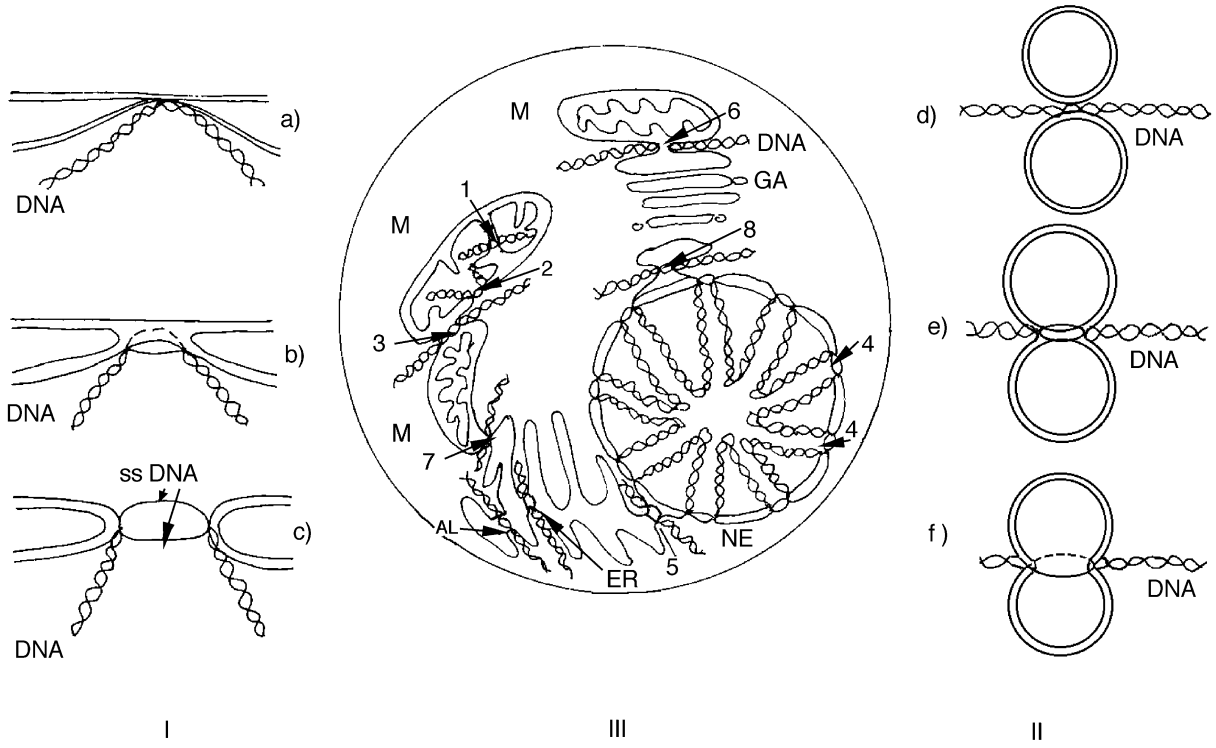

Fig. 2. The model of interphase (I), anaphase-telophase (II) nuclear pores assembly and intermembrane continuum (III).

regarded in the context of reactive oxygen species-induced damage of mitochondrial DNA, their membranes and decreasing activity of respiratory enzymes [17]. We believe that one of the important factors of mitochondria functioning and responsible for their degeneration at aging is the DMC [8]. A fraction of DMC of mitochondria was prepared almost simultaneously with DMC of bacteria by the same M-band method [18]. The fact that mitochondrial membranes interact with DNA in vitro in the presence of divalent metal cations [3] confirms that the complexes of DNA with the mitochondrial membrane can be formed in vivo. Morphologically, such contacts may look like Bayer's [19] junctions of procaryotes, i.e. they represent sites of partial or complete fusion of inner and outer mitochondrial membranes. Such zones of junction of two types of membranes have been revealed by electronic microscopy [20,21]. Moreover, according to our opinion, such type of interactions can respond to the formation of contacts between outer membranes of some mitochondria resulting in their association. The partial or complete fusion of any neighboring cytoplasmic membranes under the effect of DNA can initiate the formation of contacts and pores between them. This process thus resulted in a formation of united endocellular membrane continuum. The existence of such intermembrane contacts has been shown recently [22]. Nuclear, mitochondrial or cytoplasmic DNA [15] participates in the formation of such contacts. Thus, contacts may be formed between intramitochondrial membranes (cristae, cristae and the inner membrane of mitochondria, outer and inner membranes of mitochondria). The loss of DNA in mitochondria results in considerable changes in their structure and damage of intra- and intermitochondrial continuum of membrane [23]. The structure of such contacts is shown in Fig. 2(III). The changes in the lipid composition of mitochondrial membranes at aging play an important role in this process. The main lipid that is responsible for the formation of DMC in mitochondria may be cardiolipin. Cardiolipin binds to DNA through a bridge of Me^{2+}. The level of this lipid in the inner mitochondrial membrane is considerably reduced on aging [24]. The DNA damage in the form of point mutations and deletion of major regions of mitochondrial DNA on aging is shown [25]. Many years ago, in the system DNA–liposomes, it was shown that the DNA damage is induced by oxidized lipid [26]. This fact is in line with our hypothesis that DMC are the main target that is damaged at aging. This is due to the fact that any sites of DNA are in direct contact with lipids and their peroxides.

5. Dimensional limitation of life span

The analysis of the problem of the origin of eucaryotic cell from primary eucaryotes and eubacterias and in the symbiosis of mitochondria and eucaryotic cells [27] allows to discuss the mechanisms of aging from unconventional point of view. Possible reason of aging result in degeneration of mitochondria is due to the violation of their interaction with a cell nucleus [28,29]. However, we will discuss this

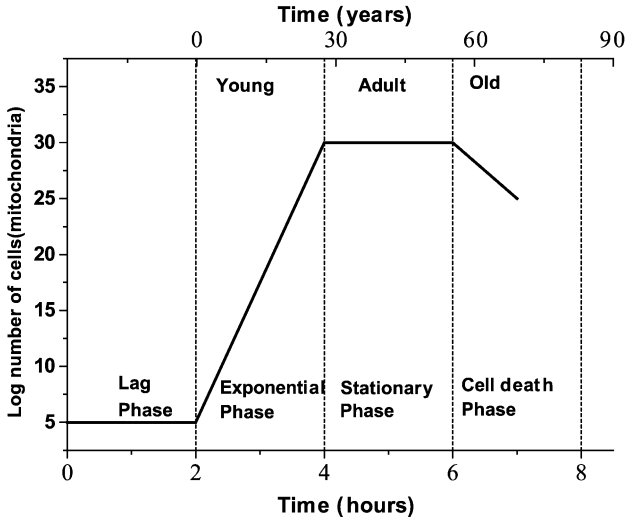

Fig. 3. Phase of mitochondria growth in a cell (for details, see the text).

problem from the microbiological point of view. Specifically, there is analogy between the behavior of mitochondria and bacterial cells in batch culture [30]. We considered a cell as a partially closed reactor in which bacterial cultures (mitochondria) grow. It is known that in batch culture, the bacteria growth curves have distinct phases. The first is lag phase and happens when the growth of bacteria is very low. The exponential growth phase or logarithmic phase turns into stationary phase leading to the phase of cell death. Similar phases can be found in the development of mitochondria in a cell. Morphometric data obtained by means of electron microscopy confirmed this observation [31,32]. The dependence of the number of mitochondria per unit volume of a cell (numerical density: N_v) on the age of organism correlates with the curves of bacterial culture growth (Fig. 3).

This parameter appreciably increases for adult animals in comparison with young ones and considerably falls with aging, sometimes, even lower than N_v of a young animal. It should be noted that a cell is not closed, but an open system, permanently exchanging with the environment. Nevertheless, our comparison is reasonable because cell division decreases with age or absolutely terminates, and thus approaching the model that we consider.

In food-restricted experimental animals, the curves of culture growth are characterized by the elongation of exponential growth phase. Perhaps it can explain the extension of life span of these animals at these conditions [33]. One unexpected conclusion consists in destroying a part of mitochondria (preferably defective and low active) and leaving a space for the growth of normal mitochondria. It results in the improvement of energetic cell and its renewal. The ways of such destruction can be different (antibiotics, various inhibitors of respiration, etc.). Wide application in medicine of antibiotics and other drugs that influence the activity and division of mitochondria [34] is one possible factor that increase the life span of man. It is also possible to destroy mitochondria with the help of apoptotic factors [35] and the uncouplers (for example, fatty acids as natural "mild uncouplers") [36]. For regularly divided cells, the degradation of mitochondria was not shown. This suggests that aging is determined by the failure of cells of differentiated organism to divide regularly. This results in the overproduction of mitochondria in cells and their subsequent damage. Uncontrolled by nucleus, the division of mitochondria (mitochondrial cancer?!) leads to cell death, damage of organ functions and death of all organism. The most suitable way to fight aging can be limitation in food or special diet. Our theory is in accordance with the correlation between species-specific metabolic rate ("rate of living") and life span [37].

The limitations in nutrition can be reduced to change the stereotypes of our lifestyle, when an increasing number of countries provoke their inhabitants to overeating. The reasonable diet can be useful, prevents diseases and lengthens our life.

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