From cryo-TEM study of lipid-DNA- complexes to nuclear pore assembly and regulation of gene expression

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The lipid-DNA interactions have been studied by biophysicists for more than 40 years. DNA forms complexes with lipids both in vitro, and in vivo. There are interactions between DNA and lipids, organized in ordered supramolecular structures of liposome type, besides direct interactions between DNA and lipids being in the dissolved condition. The examples are interactions in vitro between DNA and cationic liposomes and ternary complexes (TC): DNA zwitterionic liposomes - Me²⁺ [1, 2].

At present, ternary complexes (TC): DNA - zwitterionic lipids – Mg²⁺ are considered as trivial supplement to complexes of DNA–cationic lipids (lipoplexes). Most studies deal with DNA-cationic surfactants interactions, while TC which are more complex and close to nature, are poorly investigated. The principle concept of the TC formation is that the addition of divalent cations to zwitterionic liposomes transforms them into cationic liposomes which interact with DNA then. Our studies of TC with cryo-TEM technique keeping the native structure of the complex showed that this concept is not true.

Many our cryo- TEM data showed that the bilayers of liposomes in TC come close together, showing, however, no signs of fusion (Fig.1). This is so-called adhesive type of interaction or aggregation. If the fact of liposome aggregation liposomes in TC is without question, the problem of DNA-induced fusion of liposomes needs consideration. The comparative study of the liposome size before and after TC formation confirmed the fusion of liposomes to the size around 100 nm (Fig.2). After this size the liposomes stop to fuse and begin to form adhesive contacts.

On the base of these in vitro studies we proposed that interaction between lipids of membrane vesicles in a cell and chromatin DNA can be the first stage of a nuclear envelope and pore complex assembly. Membrane vesicles forming the nuclear envelope with pores in a cell are analog of liposomes (Fig.3). The author has proposed the general mechanism of DNA-membrane complexes (DMC) formation with participation of three-stranded hybrids: DNA-low molecular weight RNA and lipids bilayer of membrane vesicles which form the nuclear envelope [1]. The model allows explaining structure of bacterial and eucaryotic nucleoid, nuclear matrix, and also specificity of an attachment of certain sites of DNA to a membrane.

The structure of interphase chromatin cannot be considered without taking into account its interaction with nuclear membrane in the region of nuclear pores. This is the reason for the enhanced transcriptional activity of the genes neighboring the DNA-membrane contacts. The sequence of an attachment and detachment of sites of DNA - nuclear envelope is programmed in the course of cellular differentiation and is invariable for the differentiated cells. According to our DMC model presence of single-stranded DNA in their structure determine sequence of nucleoporins binding to ssDNA and high frequency of transcription initiation on these sites of genome. That increase of a transcription of genes located close DMC and lower transcriptional activity of the genes inside of nucleus [3]. Therefore it is easy to explain the high level of a transcription near to nuclear pores observed in many recent experiments.

It is obvious, that drugs interacting with single-stranded DNA in DMC area will influence on the transcription of nearby genes. That is possible relate to the anticancer substances, some hormones and drugs interacting with a nuclear envelope at nuclear pore level.

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References


Fig.1 a) DOPC liposomes aggregation in TC, bar-50nm; b) =a)+ BaCl$_2$ DNA staining, bar 100nm.

Fig.2 a) DOPC liposomes (hemi)-fusion in TC, bar-50nm; b) multilayered structures in TC, bar-100nm.

Fig.3. The model of first stage of nuclear pore formation (before nucleoporins participation).