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Review Article

The Genome of the Primitive Eukaryote Dinoflagellates: Organization and Functioning

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ABSTRACT

Marie-Odile Soyer-Gobillard (1996) The genome of the primitive eukaryote dinoflagellates: organization and functioning. *Zoological Studies* **35**(2): 78-84. Dinoflagellates are unicellular primitive eukaryotes, as shown by ultrastructural, biochemical and molecular studies. Most are phytoplanktonic and are considered to be an important link in the trophic chain. Several species are able to produce dangerous toxins and/or to anarchically proliferate in their aquatic environment.

These cells are distinguished by features of their chromatin, nuclear apparatus and mitotic system. From a molecular point of view, they are the only known eukaryotes in which the chromatin is totally devoid of histones and nucleosomes. Their chromosomal nucleofilaments are organized into a right-handed double helical bundle in a hierarchy of 6 levels of organization, this architecture being maintained by divalent cations and structural RNAs. Their chromosomes are permanently compacted in the nuclear envelope which persists throughout the typically eukaryotic cell cycle. Their genome is composed of an enormous quantity of DNA (1 to 10 times the human genome and 200 to 2 000 times the *Saccharomyces* genome) and its base composition is unique. Previous work using ^{3}H adenine incorporation showed that RNA transcription occurs on extrachromosomal nucleofilaments.

By means of electron microscopy (EM) and immunocytochemistry, we recently demonstrated that genetically active DNA is located in the periphery of the chromosomes where Z-DNA sequences and a specific basic nuclear protein (HCc, p14) are located, the main body being composed of highly repeated sequences in a B-DNA conformation. Enzymatic digestions of genomic *Crypthecodinium cohnii* DNA followed by hybridizations either with a cDNA or an rDNA gene also led to the conclusions that active chromatin is peripherally located. In the nucleolus, both B- and Z-DNA as well as the HCc protein are found in the nucleolar organizing region (NOR) while the rRNA coding sequences were detected by in situ hybridization in the periphery of the NOR where EM shows that chromosome nucleofilaments are partially unwound. So, a local unwinding of the peripheral loop nucleofilaments, favored by the presence of Z-DNA sequences, and of the topoisomerase II homologue appears essential for the completion of the transcription process.

Key words: Chromosomes, Nucleus, Nucleolus, rRNA genes, Dinoflagellates.

INTRODUCTION

For over 10 years, dinoflagellate protists have drawn the attention of protozoologists, cell biologists and toxicologists. Widespread not only in the phytoplankton of fresh and marine waters but also in the benthos, these organisms are autotrophic or heterotrophic, free or parasitic, and they constitute an important link of the food chain. Both toxic and non-toxic dinoflagellates can also anarchically proliferate in sea water, causing important economic problems (red tides, ciguaterra.) (for reviews, see Spector1984, Taylor 1987).

Dinoflagellates are also early eukaryotes whose molecular phylogeny has been well studied. Recent investigations suggest that they emerged close to the typical eukaryotes, yeasts and ciliates (Lenaers et al. 1991) althought some ultrastructural and biochemical data show several prokaryotic characteristics in addition to the original eukaryotic ones (Herzog et al. 1984).

THE NUCLEUS

The peculiar nature of the dinoflagellate nucleus has been documented for a long time (for a review, see Raikov 1987). In most species, there is a permanent condensation of the chromatin in well-defined chromosomes (from 4 to 200, depending on the species, Spector 1984a) which do not decondense during the G1-Phase. Another characteristic of these chromosomes is the total absence of longitudinal differentiation at either the Q, G or C banding (Haapala and Soyer 1974).

Dinoflagellate mitosis named dinomitosis by E Chatton (1920), is particularly original. The nuclear envelope is present throughout the cell cycle (Soyer 1969a,b 1972, Triemer and Fritz 1984) which is clearly eukaryotic (Bhaud et al. 1991 1994) and the microtubular mitotic spindle is totally extranuclear passing through the nuclear envelope by means of cytoplasmic channels (Perret et al. 1991 1993). The segregation of the chromosomes during mitosis occurs in direct contact with the nuclear envelope (Kubai and Ris 1969, Soyer and Haapala 1974a,b). Interestingly, the presence of lamins, which are immunologically related to vertebrate lamins, has been demonstrated in the nuclear matrix, near the nuclear envelope of *Amphidinium carterae* (Minguez et al. 1994). These lamins probably play an important role during chromosome division.

Recently, the complete microtubular system of the heterotrophic dinoflagellate *Crypthecodinium cohnii* was described throughout the cell cycle after confocal laser scanning fluorescence microscopy observations and labelling with anti-β-tubulin (Perret et al. 1993). This system has allowed us also to observe that the sub-cortical microtubular system does not depolymerize during mitosis, in contrast to higher eukaryotic cells. Linked to the microtubular mitotic system and to the flagellar roots is the centrosomal region, composed of numerous Golgi bodies and several specific proteins. One of these was recently identified as an HSP70-related protein associated with the centrosome from dinoflagellates to human cells (Perret et al. 1995). In the case of this closed mitosis (dinomitosis), the centrosomes determine the orientation of the nuclear envelope and of the microtubular mitotic spindle during mitosis.

Light-microscopic observations of the autotrophic dinoflagellate *Prorocentrum micans*, after silver-staining of the argyrophilic proteins of the nucleolus organizing region (Ag-NOR staining), has shown the presence of nucleolar material throughout the vegetative cell cycle and in particular during all the mitotic stages. This is in contrast to most higher eukaryotes, in which nucleoli disappear at the end of the prophase and are reconstituted in daughter cells during the telophase (Salamin-Michel et al. 1990, Soyer-Gobillard and Géraud 1992).

CHROMOSOMES AND CHROMATIN

At the electron microscopic (EM) level, ultrathin sections of dinoflagellate chromosomes reveal the characteristic arch-shaped organization of the nucleofilaments (Bouligand et al. 1968, Soyer and Haapala 1974a; Fig.1A,B), which resemble some bacterial nucleoids (Gourret 1978). Although the pattern of dinoflagellate DNA synthesis is typically eukaryotic (Bhaud and Soyer 1986, Bhaud et al. 1994), they are the only eukaryotes totally devoid of histones and nucleosomes (Herzog and Soyer 1981, Rizzo 1991) as in prokaryotes. Chromosome spreading and observation in EM (Haapala and Soyer 1973, and for a review see Spector 1984b) reveal a double-twisted helix organization, the architecture being maintained by the presence of the divalent cations Ca^{2+} and Mg^{2+} (Herzog and Soyer 1983) and structural RNAs (Soyer and Haapala 1974b, Soyer and Herzog 1985). The bundles of nucleofilaments are supertwisted with 6 hierarchical levels of organization (Herzog and Soyer 1983, Herzog et al. 1984). Other charac-

teristics of the dinoflagellate chromatin are: (1) the presence of an unusual base, hydroxymethyl uracil, in a high proportion (Herzog et al. 1982 1984), which substitutes more than 60% of the thymines in the autotrophic dinoflagellate *Prorocentrum micans* as well in the heterotrophic *Noctiluca scintillans*; and (2) the presence of repeated sequences in their DNA (Britten and Kohne 1968).

The lack of nucleosome-like structures has been demonstrated in many dinoflagellate species as well as the absence of histones. Nevertheless, the presence of specific nuclear basic proteins has been documented in several species (for reviews, see Rizzo 1987 1991). Recently, analysis of the amino acid composition of the major basic nuclear protein HCc (p14) of the heterotrophic *Crypthecodinium cohnii* (Sala-Rovira et al. 1991) has revealed that it differs markedly from other known DNA-binding proteins such as histones. HCc antigens were immunolocalized and mainly detected at the periphery of the permanently condensed chromosomes as well as in the nucleolar organizing region (NOR) (Géraud et al. 1991). These results suggest that these basic, non-histone proteins are involved at some level in the regulation of gene expression.

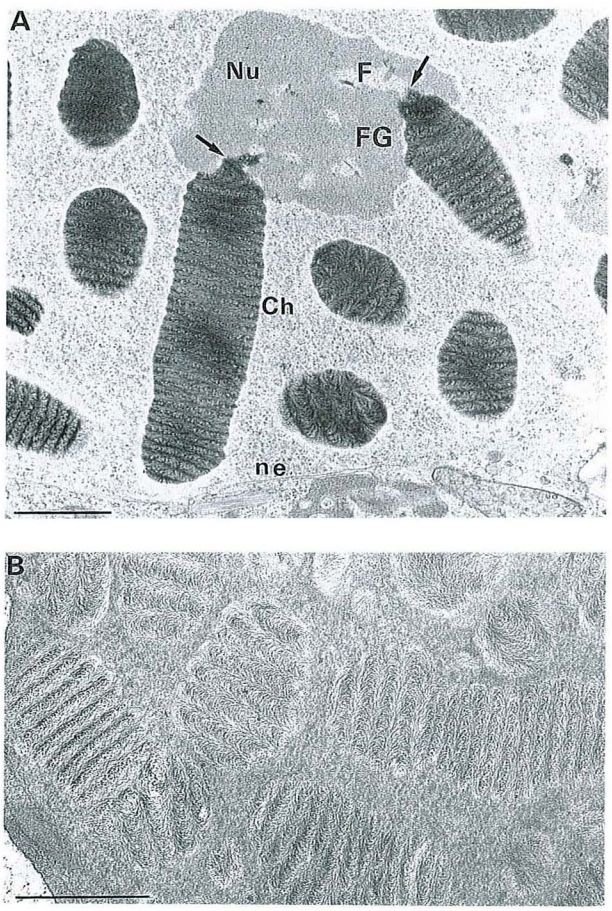

Fig. 1. EM of Dinoflagellate (*Prorocentrum micans*) nuclei.
A. Fast-freeze fixed, freeze-substituted *P. micans* cell in late telophase. In this high-magnification micrograph, 2 chromosomes are visible with their unwound telomeric parts (arrows) generating a nucleolus which is comprised of only fibrillar (F) and fibrillo-granular (FG) regions. Bar, 1 μm. Ch: chromosome; ne: nuclear envelope; nu: nucleolus.
B. Arch-shaped *P. micans* chromosomes prepared with a conventional EM fixation technique (Soyer 1977). Bar: 1 μm.

The presence of chromosomes in a permanently condensed state throughout the cell cycle raises the question of how such a structure can be transcribed and replicated. Soyer and Haapala (1974b) described extra-chromosomal loops evidenced after in situ pronase pre-treatment. They proposed a model in which a local untwisting of the supercoiling in these loops could allow transcription to occur. More recently, Sigee (1984) demonstrated the location of the active chromatin in these same regions using tritiated adenine incorporation and autoradiography.

This result has been recently confirmed by Anderson et al. (1992). After mild restriction endonuclease digestions of intact nuclei of *Crypthecodinium cohnii*, two categories of molecules of low and high uncut molecular weight DNA fragments were revealed. Digestions of extracted and purified genomic DNA produced predominantly low molecular weight fragments. Southern blots of these two types of digestions were screened (1) with a single *C. cohnii* cDNA; (2) with heterologous dinoflagellate ribosomal DNA; and (3) with a total *C. cohnii* cDNA library. Preferential hybridizations of the probes with the low molecular weight fragments support the view that active chromatin is located at the periphery of the chromosomes and that the main body of the dinoflagellate chromosomes is composed of structural or silent DNA.

The absence of histones, the stabilization of the DNA supercoiling by divalent cations, the presence of rare bases and the high G and C content (Herzog et al. 1982) are factors known to facilitate local transitions between the two DNA categories (B- and Z-DNA) coexisting in the chromosomes. Indeed, various studies have demonstrated the stabilization of the left-handed DNA structure (Z-DNA) by negative supercoiling (for a review, see Jovin et al. 1987), Z-DNA sequences reducing or suppressing the superhelicity of circular DNA molecules.

We have detected and immunolocalized B-DNA (right-handed double helix) (Fig. 2A) and Z-DNA conformations (Soyer-Gobillard et al. 1990) in the

nucleus of the dinoflagellate *Prorocentrum micans* (Fig. 2B,C). We have shown that Z-DNA sequences are located at the periphery of the chromosomes by means of mono- and polyclonal antibodies, of fluorescent optical microscopy on squashed or cryosectioned cells and in EM. Double labellings have also evidenced the presence of B-DNA extrachomosomal loops (Fig. 2D), and the nucleolar organizing region (NOR) contains DNA in B- and Z configurations. The B- to Z-reversible transitions are a dynamic phenomenon and the Z-DNA sequences allow the unwinding of the peripheral supercoiled nucleofilaments to permit the functioning of the active chromatin.

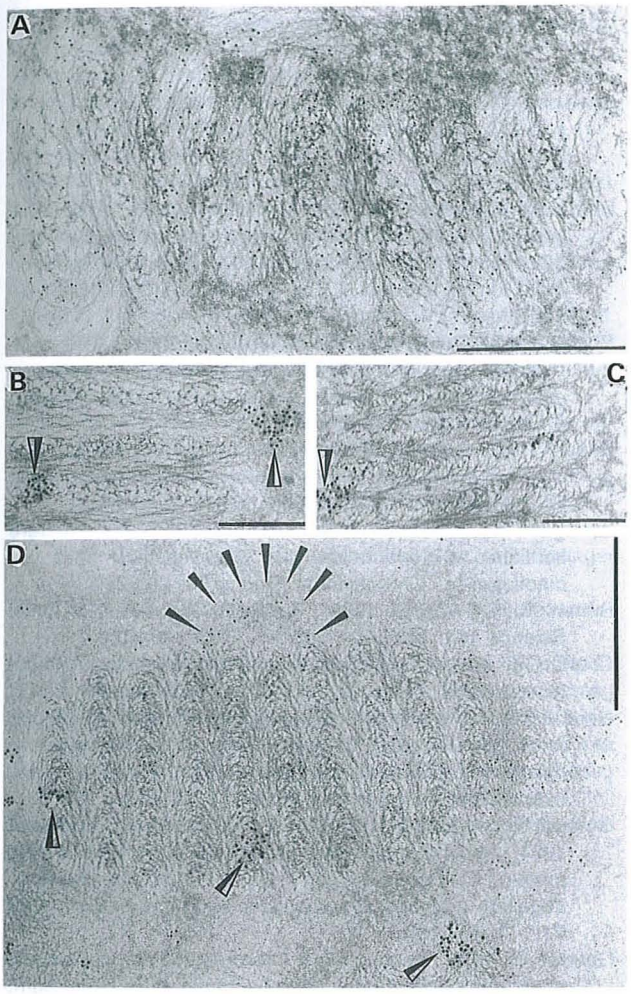

Fig. 2. Immunodetection in EM of B- and Z-DNA sequences in the chromosomes of *Prorocentrum micans*.

A. High magnification of a longitudinal section of a *P. micans* chromosome after polyclonal anti-B-DNA immunolabeling. Many 5-nm gold particles are localized on the nucleofilaments in the arch-shaped configuration. Bar: 0.5 μm.

B, C. Z-DNA was detected in *P. micans* chromosomes after treatment by a 1/25 dilution of polyclonal anti-Z-DNA as the 1st antibody and a 1/20 dilution of GAR-7 nm as the 2nd antibody. Some 7-nm gold particles are visible on the nucleofilaments located within the chromosome and on its periphery. Bars: 0.25 μm.

D. Double labeling of B- and Z-DNA in nuclei treated by a 1/25 dilution of polyclonal anti-B-DNA antibody and a dilution of anti-Z-DNA followed by 1/20 GAHu-5 nm and GAR-7 nm gold particles, respectively. Bar: 0.5 μm.

NUCLEOLUS AND RNA TRANSCRIPTION

EM observations after conventional or fast-freeze fixation revealed that during the interphase several functional nucleoli with 3 compartments (NORs, fibrillo-granular and preribosomal granular compartments) are present in the nucleus (Fig. 1A). Nucleogenesis occurs through the formation of prenucleolar bodies around lateral or telomeric unwound nucleofilaments extruding from the chromosomes as seen on the drawing Fig. 3. Several chromosomes can contribute to the formation of one nucleolus as seen in Fig. 1A and Fig. 3.

We have hybridized rRNA coding sequences of *Prorocentrum micans* on RNase-treated cryosections of the same dinoflagellate. DNA-DNA hybrids were detected either by fluorescent avidin or by indirect immunogold procedures in EM. Coding sequences of ribosomal genes were detected both

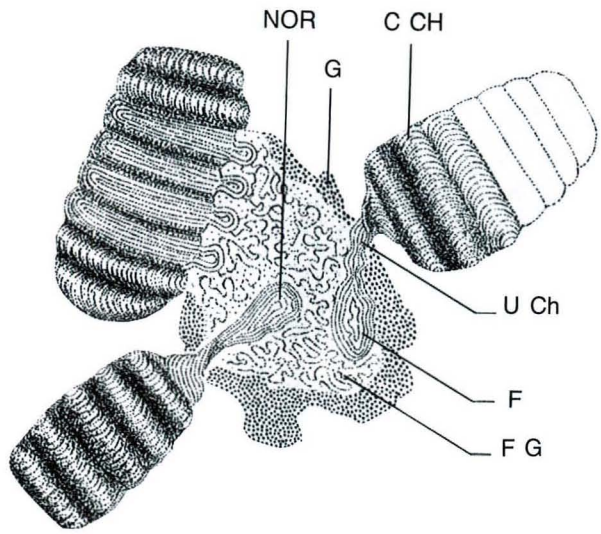

Fig. 3. Schematic representation based on EM observations of nucleolar chromosomes of *Prorocentrum micans*, showing the unwinding of nucleofilaments located in the telomeric or lateral regions. Several chromosomes are contributing to the formation of the new nucleolus. C Ch: condensed chromosome; U Ch: unwound chromosome region; NOR: nucleolar organizing region; F: fibrillar region; FG: fibrillo-granular region; G: granular region.

at the periphery of the nucleolar organizer region (NOR) which corresponds to the unwound part of the nucleolar chromosomes and in the proximal part of the fibrillo-granular region (Géraud et al. 1991). These results suggest that rRNA gene transcription predominantly occurs at the periphery of the NOR where the coding sequences are located.

CONCLUSION: DINOFLAGELLATE CHROMOSOMES, A MODEL FOR THE STUDY OF CHROMOSOME FUNCTIONING

We have summarized and represented most of these results in a model (Fig. 4) in which it is clear that the DNA-binding basic proteins and the rRNA coding sequences that constitute the major part of the active chromatin are located at the periphery of the unwound telomeric or non-telomeric region of the chromosomes whether nucleolar or not. The unwinding of the peripheral nucleofilaments is facilited by the presence of left-handed (Z-DNA) sequences while the structural part of the chromosome is mainly composed of B-DNA.

This leads to the conclusion that dinoflagellate cells constitute an excellent model for the study of the functional structure of the eukaryotic nucleolus as well as for the study of chromosome functioning.

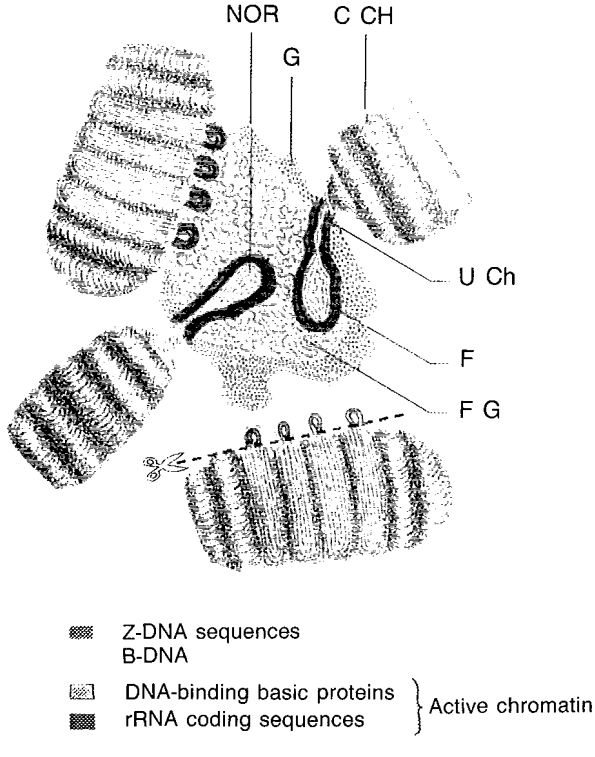

Fig. 4. Schematic representation of the localization of the active chromatin on nucleolar and non-nucleolar chromosomes.

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原始眞核生物—渦鞭藻之基因組：組成與功能

Marie-Odile Soyer-Gobillard[1]

顯微結構、生化及分子上的研究皆顯示渦鞭藻是單細胞原始的眞核生物。它們大多數是浮游植物且被認爲是食物鏈重要的一環。有些種類可以產生有毒的毒素，並可隨意的在水生環境中增殖。

這些細胞可由它們染色質的特徵，細胞核的結構及有絲分裂的系統來辨識。以分子上的觀點，它們是唯一已知的眞核生物，具有缺乏組織蛋白及細胞質單體的染色質，它們染色體的核纖維會形成一束右旋性雙股螺旋，同時藉著兩價離子及結構性的RNA來逐步排列成六個層級的結構體。它們的染色體永遠被緊密的包裹在細胞核模內且維持至典形細胞週期的完成。它們的基因組是由巨大數量的DNA組成（人類基因組的1-10倍及酵母菌基因組的200-2 000倍）且有特殊的鹽基成份。前人以^{3}H標定的腺嘌呤納入法的研究結果顯示，RNA之轉錄發生在染色體外之核纖維上。

藉著電子顯微鏡及免疫細胞化學的研究，我們最近證明遺傳上活躍的DNA是在染色體的外圍，在那裡有Z-DNA序列及一特殊的鹼性細胞核蛋白質(HCc, p14)，而整體上是由高度重複之序列以B-DNA形狀組成。由酵素剪切*Crypthecodinium cohnii* DNA及後續的cDNA或rDNA基因之雜合反應結果所得之結論是活躍的染色質位於外圍區域。在核仁，B-DNA, Z-DNA及HCc蛋白質可以在核仁組織區域(NOR)被偵測到，而rRNA密碼序列以原位雜合反應在NOR之外圍區域被偵測到，同時電顯結果顯示染色體核纖維有部分被解開，因此解開核纖維外圍環狀區域有助於Z-DNA 序列的存在而 topoisomerase Ⅱ 相似物似乎是完成轉錄過程所必需的。

關鍵詞：染色體, 核細胞, 核仁rRNA基因, 渦鞭藻。

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