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REVIEW PAPER

The Isochores as a Fundamental Level of Genome Structure and Organization: A General Overview

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Abstract The recent availability of a number of fully sequenced genomes (including marine organisms) allowed to map very precisely the isochores, based on DNA sequences, confirming the results obtained before genome sequencing by the ultracentrifugation in CsCl. In fact, the analytical profile of human DNA showed that the vertebrate genome is a mosaic of isochores, typically megabase-size DNA segments that belong to a small number of families characterized by different GC levels. In this review, we will concentrate on some general genome features regarding the compositional organization from different organisms and their evolution, ranging from vertebrates to invertebrates until unicellular organisms. Since isochores are tightly linked to biological properties such as gene density, replication timing, and recombination, the new level of detail provided by the isochore map helped the understanding of genome structure, function, and evolution. All the findings reported here confirm the idea that the isochores can be considered as a "fundamental level of genome structure and organization." We stress that we do not discuss in this review the origin of isochores, which is still a matter of controversy, but we focus on well established structural and physiological aspects.

Keywords Base composition · Invertebrates · Isochores · Vertebrates · Unicellulars

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Introduction to Isochores

The ultracentrifugation in Cs_2SO_4 density gradients in the presence of sequence-specific ligands (e.g., Ag^+) was shown to lead to a high resolution of mammalian DNAs according to base composition much before genome sequencing (Corneo et al. 1968). These findings offered new perspectives in the study of the organization of eukaryotic genomes, taking the place of DNA reassociation kinetics based on the separation of single- and double-stranded DNA on hydroxyapatite (Bernardi 1965; Britten and Kohne 1968). More than 50 years ago, calf thymus DNA, the standard eukaryotic DNA, was shown to be remarkably more heterogeneous in base composition than bacterial DNAs (Meselson et al. 1957). Interestingly, high-resolution ultracentrifugation of this DNA showed a discontinuous compositional heterogeneity of the main band, consisting of three families of DNA molecules, also separating the GC-rich satellites (Filipski et al. 1973). The families of DNA molecules were then shown in the other mammalian genomes (including the human genome) explored and were defined as fairly homogeneous DNA stretches (Macaya et al. 1976; Thiery et al. 1976) called isochores (Cuny et al. 1981) for compositionally equal landscapes. The first family was then resolved into two families, L1 and L2; the second and the third families were called H1 and H2, respectively; and another quantitatively small family, H3 was identified (Zerial et al. 1986), neglecting the satellite DNAs (~2% of the genome) and ribosomal DNAs (~0.5% of the genome). The isochore families were characterized by their increasing GC levels from L1 to H3.

Twenty-five years after these findings, also thanks to the availability of the complete sequence of the human genome, different computational approaches have been used to disprove or redefine isochores (Eyre-Walker and

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