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Fractality of chromatin

The extension of the fractal concept towards biology and medicine has improved our understanding of functional properties and the dynamics of physiological phenomena in living organisms Fractals are very useful to characterize properly the complexity of tissues by describing relevant underlying design principles [1]. Fractality has evolutionary advantages. Structures with fractal features can be built by simple, iterative programs. Fractal banching is a simple and efficient way for the construction of complex connections resulting in short distances for transport. Fractal foldings of membranes permit to create a large surface area within a very small volume. Power law organization of physiological systems increase the capacity of adaptation in the case of changes in the environment [1]. Therefore we can expect that fractality can also be found in the organization of the genome and the epigenome. Several investigators showed the presence of self-similarity in DNA sequences. Experimental data support the concept of a fractal organization of chromatin. In intact interphase chicken erythrocytes, spectra obtained by small angle neutron scattering. revealed a constant fractal dimension of the protein component, and a biphasic DNA organization, with a fractal dimension on lower scales and a different one on the larger scales [2]. Fractal structures can be created in polymers by iterative processes for instance by repeated folding during condensation. Thus a polymer can be packed in a small volume without entanglements, facilitating rapid unravelling when necessary. Recent experiments suggest that this process applies also to chromatin leading to a genome organization in form of a spatial segregation of open and closed chromatin with knot-free fractal globule formations[3]. All these studies support the concept of a fractal nature of DNA, nuclear chromatin and the surrounding nucleoplasmic space, i.e. a fractal organization of the nucleus. Morphologists, using light and electron microscopy, are demonstrating indirect evidence for the fractal organization of chromatin for nearly two decades . They differentiate basically two distinct chromatin conformations: the uncondensed euchromatin and the much denser and darker heterochromatin, which is usually considered to be transcriptionally less active. Alterations of the nuclear architecture reflect genomic and non-genomic changes, which are very common in tumor cells. Genomic changes may be point mutations translocations, or amplifications or alterations of the chromosomal position. Furthermore malignant tumors show widespread epigenetic changes including global hypomethylation, as well as focal hypermethylation of multiple CpG island gene regulatory regions. Hypomethylation is associated with decondensing of the chromatin structure and induces chromosomal instability. A more aggressive behaviour is usually observed in genetically unstable neoplasias with an increasing number of genetic or epigenetic changes. Therefore unstable tumors are expected to show a more complex chromatin rearrangement, with a mixture of many chromatin areas with varying density (lighter and darker), equivalent to a higher fractal dimension in the computerized image analysis[1]. Clinico-pathologic studies demonstrated that an increased fractal dimension of chromatin at diagnosis was an independent adverse prognostic factor for survival of patients with different

malignant neoplasias, such as multiple myeloma , squamous cell carcinoma of the oral cavity squamous cell carcinoma of the larynx , and malignant melanoma of the skin [4-7]. Therefore we may conclude that the complexity of the chromatin architecture in neoplastic cells may reveal important prognostic information. In summary, fractal characteristics of the nucleus are essential for its function and are reflected in its chromatin structure, which may accompany pathologic processes , such as carcinogenesis and tumor progression.

References

[1] Metze K. Fractal dimension of chromatin and cancer prognosis. Epigenomics,2: 601-604 (2010)

[2] Lebedev DV, Filatov MV, Kuklin AI, Islamov AKh, Kentzinger E, Pantina R, Toperverg BP, Isaev-Ivanov VV: Fractal nature of chromatin organization in interphase chicken erythrocyte nuclei: DNA structure exhibits biphasic fractal properties. FEBS Lett 579:1465-1468(2005).

[3] Lieberman-Aiden E, Van Berkum NL, Williams L, Imakaev M, Ragoczy T, Telling A, Amit I, Lajoie BR, Sabo PJ, Dorschner MO, Sandstrom R, Bernstein B, Bender MA, Groudine M, Gnirke A, Stamatoyannopoulos J, Mirny LA, Lander ES, Dekker J: Comprehensive mapping of long-range interactions reveals folding principles of the human genome. Science 326: 289-293(2009).

[4] Delides A, Panayiotides I, Alegakis A, Kyroudi A, Banis C, Pavlaki A, Helidonis E, Kittas C: Fractal dimension as a prognostic factor for laryngeal carcinoma. Anticancer Res (2005) 25, 2141-2144 (2005).

[5] Goutzanis L, Papadogeorgakis N, Pavlopoulos PM, Katti K, Petsinis V, Plochoras I, Pantelidaki C, Kavantzas N, Patsouris E, Alexandridis C: Nuclear fractal dimension as a prognostic factor in oral squamous cell carcinoma. Oral Oncol 44, 345-353(2008).

[6] Metze K, Ferro DP, Falconi MA, Adam RL, Ortega M, Lima CP, De Souza AC, Lorand-Metze I: Fractal characteristics of nuclear chromatin in routinely stained cytology are independent prognostic factors in patients with multiple myeloma. Virchows Archiv 2009

[7] Bedin V, Adam RL, de Sá BC, Landman G, Metze K : Fractal dimension of chromatin is an independent prognostic factor for survival in melanoma. BMC Cancer 10, 260 (2010) .