Introduction into Nuclear Structure

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Far field optical light microscopy with its unique capability for contactless, non-destructive imaging inside thick transparent specimens such as cell nuclei has contributed widely to the present knowledge of the three-dimensional (3D-) architecture of the human genome in the cell nucleus. Visual microscopy observations and quantitative light optical analyses, especially confocal data, in combination with molecular labelling procedures, have revealed a highly structured nuclear genome organisation suggesting the existence of "chromatin folding" and "chromatin positioning" codes. Such informations have been used in "Scientific Computing" approaches of human nuclear genome structure. Computer modelling based on experimental observations allowed to predict a variety of light microscopically detectable features of nuclear genome structure.

A serious problem for the extension of "large scale" and "mesoscale" light microscopical studies of nuclear genome organization to nuclear genome nanostructure analysis is the limited resolution. Due to the thickness of human cell nuclei in the order of several micrometer, far field methods have to be used if the cell is to remain three-dimensionally (3D) conserved. In recent years, various light optical approaches to overcome this impasse have been described. Examples are 4Pi-microscopy (pioneered by Stefan Hell, Goettingen/Heidelberg); Spectral Precision Distance Microscopy (SPDM), or Spatially Modulated Illumination (SMI) microscopy. These and other novel approaches allowed to increase the optical, the topological, and the size resolution to the range of few tens of nm (about 1/10 to 1/20 of the exciting wavelength applied). Their use will allow to close the gap between the resolution achieved by ionizing radiation imaging and low photon energy microscopy.

Together with novel developments in molecular fluorescence labelling approaches, light optical "nanoscopy" is expected to provide a platform technology for a highly advanced study of the complexity of mammalian nuclear genome structure, down the few nucleosome level. The experimental "nanoscopic" results obtained may be combined with biocomputing approaches of these structures. Eventually, such studies may essentially contribute also to improve strategies for the reprogramming of the genome in mammalian cells, such as adult stem cells.

In summary, a "tool set" of experimental and theoretical approaches is emerging to analyse and understand cell nuclear structure on a quantitative level, allowing to establish a "nuclear genome biophysics".