“Single-molecule epigenetics: Multivalent interactions govern dynamic assembly of heterochromatin”

Epigenetic processes are involved in organism development and, if dysregulated, in disease. A major mechanism involves post-translational modifications (PTMs) of histone proteins, the basic building blocks of chromatin. Mechanistically, histone PTMs function by providing specific binding platforms for effector proteins, which enact gene repression, activation or modulate the chromatin state. Importantly, as effector proteins often contain multiple histone PTM binding modules, multivalent interactions between effector proteins and modified chromatin fibers have been proposed as a fundamental mechanism of chromatin signaling: Multivalent engagement of several PTMs may increase effector affinity and enable the simultaneous read-out of PTM combinations, thereby fine-tuning a biological response. These processes are however not well understood on a mechanistic level. Nevertheless, a quantitative understanding is of utmost importance for a greater understanding of epigenetic regulatory processes, especially in light of the promise of epigenetic therapies, e.g. for certain cancers.

Therefore, we established a method, combining chemical chromatin synthesis, protein chemistry and single-molecule imaging which allows us to measure how individual multivalent chromatin effectors dynamically interact with their cognate histone mark in chromatin fibers.

Employing this methodology, we have shown that HP1a, a fundamental component of silent chromatin, employs multivalent recognition of histone 3 tri-methylated at lysine 9 (H3K9me3) to increase its residence time at chromatin loci. Moreover, multivalency also results in a greatly increased association rate compared to monomeric, and thus monovalent HP1a. Thus, by increasing association kinetics, effector multivalency results in high affinity, while maintaining a dynamic chromatin state.

Date & time: Thursday, August 13, 2015 at 05:00pm
Location: Lecture Hall Y44-H-05, UZH Irchel

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