セミナーのお知らせ

8 月 28 日 (金) 14:00-15:00 すずかけ台キャンパス B2 棟 B426 大会議室

Regulation of histone H3.3 supply and loading on chromatin

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In the interphase nucleus, chromatin is organized in distinct domains that accommodate the regulation of DNA replication and gene expression. These domains vary in their histone content and post-translational modifications. Histone H3 consists of several isoforms, one of which, histone H3.3, is deposited into distinct chromatin domains by dedicated chaperones including HIRA, ASF1A, ATRX and DAXX. We will discuss recent findings from our laboratory on the role of histone chaperones, chromatin proteins and sub-nuclear structures in the regulation of H3.3 supply and loading on chromatin.

Genome-wide studies show that epitope-tagged H3.3 is enriched in active genes and promoters and in a subset of H3K27me3-marked regions [1]. A pool of newly synthesized H3.3 is recruited to PML bodies by DAXX, where it encounters several H3.3 chaperones before being loaded on chromatin. This suggests a role of PML bodies as 'triage centers' for H3.3 [2]. In Pml-null cells, neo-synthesized H3.3 is rapidly incorporated into chromatin, notably in sites that are found to associate with PML in wild-type cells, and in compact chromatin domains, a process reversed by re-introduction of PML (unpublished results). This indicates that PML imposes site-specificity in the deposition of H3.3 into chromatin. Imaging and biochemical studies show that DEK regulates both wide-spread HIRA-mediated deposition of H3.3, and DAXX/ATRX-dependent ectopic H3.3 accumulation in heterochromatin domains. In embryonic stem cells, loss of DEK delocalizes PML, ATRX and H3.3 from telomeres and induces a fragile telomere phenotype. From these studies, we propose a role of PML bodies and DEK as guardians of chromatin, controlling chromatin integrity by restricting wide-spread deposition of H3.3 by dedicated chaperones. Our results also suggest that telomere stability relies on proper histone H3.3 supply regulated by PML and DEK.

Selected Publications

[1] Delbarre et al 2010. Mol Biol Cell 21, 1872-1884
[2] Delbarre et al 2013. Genome Res. 23, 440-451
[3] Ivanauskiene et al 2014. Genome Res. 24, 1584-1594

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