セミナーの案内

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講演タイトル：

Interaction of histone H3 K9 and the nuclear envelope

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Interaction of histone H3 K9 and the nuclear envelope

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Heterochromatin comes in several forms and becomes the dominant form of chromatin as cells terminally differentiate. At least one class of heterochromatin is positioned adjacent to the nuclear lamina. To determine if this positioning is necessary for normal differentiation, we have visualized developmentally controlled promoters in *C. elegans.* The position of low-copy integrated transgenes containing developmentally regulated promoters (*myo*-3::mCh or *pha*-4::mCh-H2B) and arrays of LacO sites, were examined during development. In early embryos, inactive tissue-specific promoters were randomly distributed throughout the nuclear volume. During cellular differentiation, transgene position depended strictly on transcriptional status: repressed tissue specific promoters were shifted to the nuclear periphery, while active promoters were sequestered internally. In contrast, large heterochromatic arrays were sequestered at the periphery even in embryonic nuclei.

Heterochromatic transgene arrays were then used to screen for factors involved in chromatin silencing and peripheral anchoring. This screen showed that co-depletion of two H3K9 histone methyltransferases, MET-2 (SetDB1 homolog) and SET-25 (G9a-like) releases heterochromatin silencing and peripheral anchoring. Genetic and biochemical analysis suggests that the two HMTs act in a sequential order and show the peripheral anchoring of heterochromatin is a direct consequence of mono- and di-methylation on H3K9. Silencing of the array requires H3K9 trimethylation. In genome-wide mapping experiments by DAM-ID we can show that specific chromosomal regions and chromosome arm extremities lose their peripheral anchoring in the double *met-2 set-25* mutant, confirming the importance of this mechanism for the C elegans genome.

We further tested the role of lamin in H3K9methylated chromatin anchoring, by analyzing a dominant point mutation linked to human Emery Dreyfuss Muscular Dystrophy introduced into array-carrying worms. Loss of worm lamin derepresses and delocalizes heterochromatic arrays, whereas the gain of function point mutated lamin interfered with the release of active muscle-specific promoter arrays, uniquely in muscle cells . This correlates with muscle-specific expression defects, morphological disruption of actin fibers and sarcomeres, and muscle dysfunction. Forward genetic screens are now identifying proteins at the interface between lamin and H3K9me marks on heterochromatin.