Abstract – Mechanisms of heterochromatin exclusion by the nuclear pore protein TPR

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In most mammalian cell types, heterochromatin accumulates at the nuclear periphery and associates with the nuclear lamina. On the other hand, the vicinity of nuclear pores is always devoid of heterochromatin. TPR (translocated promoter region) - a nucleoporin from the nuclear basket of the nuclear pore complexes - is necessary for heterochromatin exclusion, but the mechanisms by which TPR excludes heterochromatin are completely unknown. To address this question, we artificially target TPR to a heterochromatin domain and assess subsequent chromatin reorganization. As a model of a heterochromatin domain, we use mouse pericentric heterochromatin which forms clusters called chromocenters. TPR targeting to chromocenters leads to two different phenotypes. On one hand, we observe enlargement of chromocenters in a small fraction of the cells, which suggests chromatin reorganization. On the other hand, in the majority of the cells, TPR accumulates as a shell around the chromocenters, showing mutual exclusion between TPR and heterochromatin, which might mimic heterochromatin exclusion at nuclear pores. Both phenotypes were associated with a decreased enrichment of the repressive histone mark H3K9me3 indicating that TPR can modify chromatin composition. We further identified the TPR Domain that is necessary and sufficient for heterochromatin-TPR mutual exclusion. In the future we aim to address the physical properties underlying heterochromatin-TPR exclusion. This work will therefore shed light on a new mechanism of chromatin organization by nuclear pores.