Polycomb repression and RNA polymerase in neural tube development

Jieun Jeong[1], Yuichi Nishi[2], Andrew P. McMahon[2]
[1]University of Pennsylvania School of Medicine, Philadelphia, PA [2]Keck School of Medicine, USC, L.A., CA

I. INTRODUCTION

Embryo development involves differentiation of tissues that starts from embryonic stem cells. The emerging tissues send and receive signaling molecules and in response differentiate further, and the proper timing and spatial characteristics of each stage are important for correct development. This requires precise control of the expression of key transcription factors that in turn control gene expression in their respective cell types. Here we establish new aspects of activity of polycomb repression complexes, PRC, which are involved in this process. Activity of PRC complexes forms additional layer of control for genes that are activated/deactivated with making/removing epigenetic modifications at promoter regions such as H3K4me3 and H3K27ac. It was shown previously that PRC-2 complex induces tri-methylation of lysine 27 of histone H3, epigenetic mark H3K27me3, and this modification recruits PRC-1 complex which makes further epigenetic changes that may prevent the conversion of RNA polymerase II (pol2) to a conformation that produces gene transcripts. This prevents gene expression. Alternatively, PRC histone modifications induce pol2 form that does produce gene transcripts but orders of magnitude less efficiently than the standard productive form. It was also shown previously that PRC activity is more frequent in early cell development where it affects 20-25% of genes, and that most genes repressed by PRC are eventually expressed.

II. PURPOSE AND HYPOTHESIS

For most genes the expression level is determined by the cell without PRC activity by regulating the activation through H3K4me3, H3K27ac etc., which opens the question of the benefit of an extra level of regulation. We show that PRC allows to recruit pol2 to genes without expressing them. When PRC activity is being reduced, the expression of gene increases as pol2 changes to productive forms. The speed of that increase depends on the amount of pre-loaded pol2. The differences in that speed for different genes are particularly important when two master transcription factors are simultaneously stimulated and they repress each other, and in the stable state only one of two factors is expressed. In the development of the neural tube, this situation is present for Nkx2-2 and Olig2, the key factors of two adjacent layers in the neural tube, pV3 and pMN (motor neurons), and possibly with other boundaries between the layers.

III. CONCLUSIONS

In the development of neural tube, neural tube cells initially represent EB type with high levels of Oct4. With a certain combination of signals, EB cells eliminate Oct4, activate Sox2 and stimulate expression of Pax6. Then Shh signal from the notochord creates Pax6-free layers on the ventral side, FP, pV3, pMN, pV2

Qualitative narrative of Balaskas et al. At the beginning of the EB to NEB transition, three key factors (Pax6, Olig2, Nkx2.2) have low levels. Pax6 increases first, activated by RA. Next, in the ventral layers Olig2 increases in response to Shh ➔ Gli1, while Nkx2-2 is repressed by Olig2 and Pax6. Olig2 represses Pax6 which decreases. However, Olig2 is a less effective repressor of Nkx2-2 than Pax6. When the net impact of Gli1 (activator from Shh pathway), Oli2 and Pax6 (repressor) is sufficient to stimulate Nkx2-2, the latter responds rapidly, thus eliminating Pax6 and Olig2 from pV3 (but not from pMN)

This system relies on combinations of activating impact of Gli1 and repressors and we hypothesize that these signals independently regulate pol2 recruitment and PRC activity. Redundant mechanisms of gene control levels enable different types of responses to simultaneous activation and repression and precise control of patterns formed in the tissue. We observe that Nkx2-2 has the highest levels of pol2/H3K36me3 (ratio), Pax6 is intermediate and Olig2 has the lowest. We conjecture that this determines the speed of reaction of these genes to activating signals as needed by dynamic control of gene expression.