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BioSim Talk 2025 #3

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July 18, 2025 (Friday), 16:30-18:00

Institute for Protein Research,
The University of Osaka (Suita Campus)
2th floor conference room (large)

Analysis of interactions between the two candidates for 22q11.2 deletion syndrome in fibroblasts

CRKL and *TBX1* are two candidate genes for the 22q11.2 deletion syndrome, the most frequently observed deletion syndrome in humans. The two genes genetically interact as compound heterozygosity in mouse models generating a spectrum of phenotypes closely resembling the human syndrome, thus providing strong support for the hypothesis that the two genes are central to the pathogenesis of heterozygous deletions found in approximately 90% of syndromic patients. It has been, however, challenging to pinpoint the nature of the interaction, as CRKL (CRK-like) is an adapter protein known to function downstream of tyrosine kinases, while TBX1 (T-Box 1) is a DNA binding protein. On one hand, we showed that these two genes interact between different tissues during mouse development. On the other, it is possible that they may also cooperate within a single type of cell. To address the latter possibility, we have constructed mouse embryonic fibroblast models. RNA-seq and Tbx1 ChIP-seq analyses revealed highly similar expression profiles tied to CRK/CRKL and TBX1 groups as well as Tbx1 ChIP peak associated genes, reinforcing the hypothesis that the CRK family genes and TBX1 share functional pathways such as regulation of cell-matrix adhesions. Interestingly, TBX1 binding to its target site per se is not sufficient for binary decisions for up or down regulation, thus suggesting an importance of the binding context for Tbx1-dependent outcome. Our study indicates that Tbx1 binding motifs are highly homologous to Tbx20-binding consensus. Interestingly, some of the TBX1 binding peaks have sequences that can accommodate Tbx1 DNA binding domain as dimers/oligomers, as predicted by AlphaFold simulations. These results suggest an important role of Tbx1 in regulating its target genes as a core member of the regulatory complex and indicate that CRKL and TBX1 cooperate for cellular phenotypes at the gene regulation level.

Link for online participation via Zoom:
Meeting ID: 897 7872 8259, Passcode: 890505
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