Modelling the impact of double X-dosage on signalling pathways implicated in pluripotency

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X-chromosome inactivation (XCI) is a process in mammals which enables dosage compensation between XX and XY individuals. The process of XCI has been found to be closely coupled to the transition of ground pluripotent state of cells of the ICM to the differentiated state during embryonic development. It has been shown that the presence of two active X-chromosomes (XaXa) in female cells inhibits this transition and affects the activity of several signal transduction pathways which may be important for differentiation of the stem cells (Schulz et. Al, 2014). I plan to study the differences in signalling in cells with one or two active X-chromosome by combining systematic perturbation data set with mathematical modelling. My poster will focus my approach to study the interplay and cross-talk of five signalling pathways that have been found to play major role in the maintenance of pluripotency in mouse embryonic stem cells(mESCs), namely (i) Lif-Stat3 (ii) Wnt- beta-catenin (iii) Bmp4-Smad1-Id (iv) Fgf4-Mek-Erk and (v) Igf-Akt signalling cascades. The effect of activation and inhibition of each of these pathways on important signalling intermediates and endpoints will be measured in mESCs that have one or two active X-chromosomes but are otherwise genetically identical. The signalling intermediates would be measured using the Luminex platform, which performs multiplexed phosphorylation analysis. Additionally, expression of pluripotency markers Sox2, Oct4, Nanog and differentiation markers like Tuj1, Sox1, Brachyury will be measured. This multi-dimensional data set, along with a literature-derived starting network, will be used to reconstruct the best-fit network through a semi-quantitative modelling approach (Klinger et al., 2013). The output networks for the two kinds of cells would be compared to identify the differences in cell signalling in them and hypothesize the point(s) in the network via which double dose of active X-chromosomes mediate their effect on cell signalling cascades implicated in maintenance of pluripotency.

References

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