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Understanding epigenetic reprogramming by X chromosome reactivation

Irene Cantone

University of Naples Federico II, Italy

Erasure of epigenetic memory is required to convert somatic cells towards pluripotency.

Reactivation of the inactive X chromosome (Xi) has been used to model epigenetic reprogramming in mouse, but human studies are hampered by Xi epigenetic instability and difficulties in tracking partially reprogrammed iPSCs. Recently, I have established a cell fusion reprogramming system that recapitulates features of human naïve pluripotency and enables tracing early chromatin changes. This system revealed that loss of XIST and H3K27me3 from the human Xi precedes and is required for Xi transcriptional reactivation ahead of cell division (Cantone et al., Nature Comm 2016). Interestingly, single-cell RNA-FISH and allele-specific RNA sequencing analyses revealed that reprogramming-mediated human Xi reactivation was partial and selective for a specific subset of genes. Selective Xi reactivation was not limited to gene loci residing within specific chromatin domains (e.g. H3K27me3 or H3K9me3 domains) neither influenced by proximity to XIST locus.

Reactivation was instead associated with stochastic Xi expression ahead of reprogramming, as shown by single cells and isogenic fibroblast clones (Cantone et al., Genome Biology 2017). Notably, stochastic Xi transcription is stabilized in some clonal lineages suggesting that single-cell transcriptional variability might underlie heritable gene reactivation even in heterochromatic contexts. Implications for targeted Xi gene reactivation during human pluripotent reprogramming and in somatic cells will be discussed as a concept for modelling and therapy of human X-linked diseases

Biography

Irene Cantone has completed his PhD at the age of 25 years from Telethon Institute of Genetic and Medicine and postdoctoral studies from MRC London institute of Medical Sciences. She has been awarded Marie-Curie, EMBO and Human Frontiers Science Programme long-term fellowship. She is currently a Professor at the University. She has published more than 15 papers in reputed peerreviewed journals (e.g. Cell, Nature Structural Molecular Biology, Nature Communication and Genome Biology) and has been serving as an editorial board member of PLOS and Nature journals