Translational research: molecular diagnostics and therapeutics

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Epigenetic Reprogramming in somatic, pluripotent and disease cells
Epigenetic modifications are used to maintain cell identity and are erased when cells are reprogrammed towards distinct fates. My lab investigates the molecular mechanisms underlying the loss of epigenetic memory by using the reactivation of genes along the inactive X chromosome (Xi) as exemplar. To this, we are developing two lines of research:

1.Tracing X chromosome reactivation during human pluripotent reprogramming.

The presence of two active X chromosomes is a hallmark of pluripotency, highly unstable in culture. By using cell fusions, I was able to reverse human Xi silencing and revealed a hierarchy of chromatin and transcriptional events[3]. Notably, cell fusion-mediated reprogramming encompasses a spectrum of human pluripotency[2]. To investigate the molecular determinants of distinct reprogramming states, we are now investigating transcriptional and epigenetic reprogramming at the single cell level.

2. X chromosome reactivation in sex-biased diseases.

Recently, I have shown that loss of XIST and H3K27me3 from the Xi is necessary to Xi reactivation[3]. Similar chromatin changes have been observed in lymphocytes from female-biased autoimmune diseases. We are now investigating whether the same chromatin structure characterizes a range of sex-biased diseases. Understanding X chromosome reactivation in disease will enable us to identify novel diagnostic biomarkers and therapeutic targets.

1. Genetics and Epigenetics of Sex Bias: Insights from Human Cancer and Autoimmunity.
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2. Allele-specific analysis of cell fusion-mediated pluripotent reprograming reveals distinct and predictive susceptibilities of human X-linked genes to reactivation.
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3. Ordered chromatin changes and human X chromosome reactivation by cell fusionmediated pluripotent reprogramming.
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Rougeulle C, Vallot C, Heard E, Chaligne R, Merkenschlager M, Fisher AG. Nat Commun. 2016 Aug 10;7:12354. doi: 10.1038/ncomms12354. PMID: 27507283

4. Epigenetic programming and reprogramming during development.
Cantone I, Fisher AG. Nat Struct Mol Biol. 2013 Mar;20(3):282-9. doi: 10.1038/nsmb.2489. Epub 2013 Mar 5. PMID: 23463313

5. A yeast synthetic network for in vivo assessment of reverse-engineering and modeling approaches.
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