第 346 回つくば分子生命科学セミナー

TSUKUBA MOLECULAR LIFE SCIENCE SEMINAR

演題：Functional interactions between Nanog and Esrrb in pluripotent cells

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日時：2012 年 3 月 22 日（木）17:00-18:00

会場：医学学系棟４階４８２室

要旨：

Embryonic stem (ES) cell pluripotency is sustained by a network of transcription factors centred around Oct4, Sox2 and Nanog. While Oct4 and Sox2 protein levels are relatively stable, ES cells fluctuate between states of high Nanog expression, associated with high self-renewal efficiency, and low Nanog expression, associated with an increased propensity to differentiate. However, the mechanisms by which Nanog functions remain unclear and in particular Nanog target genes are uncharacterised.

Using a range of cell lines expressing differing Nanog levels we identified putative Nanog target genes. We then used *Nanog*$^{-/-}$ cells expressing a tamoxifen-inducible Nanog-ERT fusion protein to identify genes directly responsive to Nanog nuclear relocalisation. Prominent amongst Nanog-responsive genes is Estrogen-related receptor b (Esrrb). Nanog binds directly to *Esrrb,* enhances binding of RNAPolII to the *Esrrb* promoter and stimulates transcription. In the presence of Nanog, transcription of the 50kb *Esrrb* gene requires 15 minutes. In the absence of Nanog, transcription takes longer, due to a less rapid release of RNAPII from the *Esrrb* promoter.

We next determined the functional relevance of Esrrb expression for ES cells. Overexpression of Esrrb in ES cells results in cytokine-independent self-renewal and maintenance of pluripotency. Remarkably, this activity is retained in *Nanog*$^{-/-}$ ES cells. Esrrb exhibits a strong reprogramming capacity that surpasses Nanog. Consistent with the functional placement of Esrrb downstream of Nanog, Esrrb overcomes the reprogramming barrier created by Nanog deletion. Together these data identify Esrrb as a critical downstream mediator of Nanog function.

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