

Opposing Effects of TFIID Subunits on Embryonic Stem Cells Maintenance and Proliferation

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Abstract

Embryonic stem cells (ESC) have the unique features of self-renewal and pluripotency, properties that can generate every cell type. Differentiated cells derived from ESC have therapeutic potential for many human diseases. Therefore, elucidating the molecular basis of ESC pluripotency is important not only for understanding the principles of mammalian cell differentiation and development but also for clinical applications. The maintenance of ESC pluripotency and self-renewal is controlled by a complicated transcriptional program that activates genes supporting pluripotency while repressing developmental genes. TAF4 and TAF4b are ubiquitous and cell type specific TFIID subunits, respectively. We found that TAF4b is highly expressed in embryonic stem cells (ESC) and is down regulated upon induction of differentiation. Knockdown of TAF4b by siRNA is accompanied by changes that are consistent with differentiation which are not seen upon TAF4 knockdown. In addition, retinoic acid-induced differentiation is accelerated in the absence of TAF4b while it is significantly delayed by knocking down TAF4. Likewise, TAF4b supports and TAF4 inhibits ESC proliferation and cell cycle progression. Our findings suggest that switching on the differentiation program is TAF4 dependent whereas maintaining the 'stemness' state is TAF4b dependent. We have determined the genome-wide changes of gene expression of embryonic stem cells (ESC) in which TAF4b has been knocked down and we are currently analyzing and validating the data. Preliminary findings suggest that TAF4b downregulated genes are particularly enriched with cell cycle regulation and overlap genes controlled by c-myc, a factor known to be central for ESC maintenance and self-renewal. The up-regulated group is enriched with genes associated with neuronal differentiation. Together with the group of Yuki Yamaguchi and Hiroshi Handa we are currently investigating whether the inhibitory effect of TAF4b on gene expression is linked to transcription elongation control mediated by DSIF and NELF.