Embryonic stem cells (ESCs) are valuable tools for regenerative medicine, being capable of self-renewing in culture indefinitely while retaining their pluripotency, i.e., the ability to generate any cell of the adult organism. At the heart of these capabilities is a complex transcriptional network, which carefully guards an uncommitted state, yet permits ESCs to remain poised for differentiation. So far, many ESC transcription factors, including the core pluripotency proteins, Oct4, Sox2 and Nanog (OSN), have been identified and extensively characterized. These molecules participate in highly interrelated pathways to activate their own expression, as well as downstream self-renewal regulators, via co-recruitment to enhancer regions in the vicinity of these genes. However, we know much less about the individual roles played by each of these factors within multi-protein complexes, the identity of their potential coregulators, or how they functionally connect to the general transcription and chromatin remodeling machineries. In this context, we recently investigated the protein-protein interactions, or how they functionally connect to the general transcription and chromatin state as well as providing a scaffold upon which to recruit the basal transcription machinery itself (Fig. 1A). Furthermore, we have discovered that Ncoa3 interacts with CBP to the Nanog locus, thus ensuring the maintenance of active histone modifications at this gene. Overall, these results point toward a crucial role for Ncoa3 in potentiating transcription and/or reprogramming of primordial germ cells (PGCs) in vivo.

Our collective findings lead onto a key question: what is the functional role for Esrrb and Ncoa3 underlying their essential nature in the ESC network? Genome-wide, both ESC and PGC-relevant target genes are also enriched for marks of active enhancers, H3K4me1/H3K27ac and p300 recruitment, suggesting a link between the presence of Esrrb-Ncoa3 and transcriptional activation. Moreover, we demonstrated that Ncoa3 interacts with RNA polymerase II itself and is required for the association between Esrrb and the general transcription machinery. Complementing our data, a concurrent study reports that Ncoa3 also recruits the chromatin-modifying proteins CARM1 and CBP to the Nanog locus, thus ensuring the maintenance of active histone modifications at this gene. Overall, these results point toward a crucial role for Ncoa3 in potentiating transcription in ESCs by locally facilitating an “open” chromatin state as well as providing a scaffold upon which to recruit the basal transcription machinery itself (Fig. 1A). Loss of Esrrb/Ncoa3 upon differentiation or shRNA-mediated depletion would therefore inhibit the transcription of ESC-associated genes, consequently triggering a collapse of the network and the exit of self-renewal (Fig. 1B).

In conclusion, these findings establish Ncoa3 as a key member of pluripotency transcriptional machinery, which carefully guards an uncommitted state, yet permits ESCs to remain poised for differentiation.
transcriptional circuitries, emphasizing the importance of this coactivator not just in somatic and cancer cells, but also in early developmental contexts. An interesting future avenue is to characterize the upstream signaling pathways that may regulate Ncoa3 in pluripotent cells, as this molecule is a well-known target for numerous post-translational modifications. Accordingly, increased Ncoa3 stability notably correlates with GSK3 inhibition in ESCs.\(^8\) Ncoa3 modification in response to one or more external signaling pathways could therefore alter its protein stability, cellular location or even its transcriptional activity, thus serving as an elegant way to fine-tune the cellular state of ESCs and iPSCs.

**Figure 1.** Proposed model depicting the role of Esrbb and Ncoa3 at ESC-specific enhancers. (A) In pluripotent cells, Esrbb binds to ERR response elements (ERREs) at active enhancer regions, which also contain bound core proteins such as Nanog and Oct4 (not shown). AF-2-mediated recruitment of Ncoa3 is, in turn, essential for Esrbb activity, with Ncoa3 binding both epigenetic and basal transcription machinery complexes to bring about strong activation of target genes. (B) Upon conditions where Esrbb and/or Ncoa3 proteins are downregulated (faint color), their loss might lead to alterations in chromatin structure and destabilization of RNA polymerase II (RNAPol2), thus triggering differentiation.

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