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The transcriptional regulator CBX2 and ovarian function: A whole-genome and whole transcriptome approach

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It is now well established that *CBX2* is indispensable for testis development in humans and mice. However, the role of this polycomb protein in the ovary remains largely undefined. To address this issue and understand its function in human ovaries, I firstly adopted a hypothesis-driven approach and evaluated the expression of known female genes, i.e. *FOXL2*, *RSPO1* and *WNT4* in human pre-granulosa cells after forced expression and RNA interference of *CBX2* isoforms and vice-versa. I also conducted a comprehensive and unbiased genome-wide analysis based-Dam methylase identification (DamID) and RNA sequencing strategies to identify *CBX2* responsive candidate genes in the ovary, as a hypothesis-generating approach. The two isoforms appeared to be functionally distinct: *CBX2.1* has been confirmed to be a pro-male factor, whereas *CBX2.2* might be partly pro-female most likely via the interaction with *RSPO1* and through the regulation of ovary developmental markers (i.e. *OCT-4*, *AMH* and *ESR2*). Besides having a sex-determining role, both *CBX2* isoforms might act as regulatory agents protecting granulosa cells from uncontrolled growth and proliferation by influencing *WNT4* and *RSPO1* signaling pathways. In the second part of this project, *CBX2* regulated-genes were identified, but focus was on gonads-specific genes reportedly involved in sex development and disorders of sex development (DSD). Functional enrichment analysis revealed *CBX2's* involvement in several molecular pathways in developmental processes. Notably, I found out that *CBX2.1* and *CBX2.2* are ahead of genes contributing to folliculogenesis and steroidogenesis (i.e. *ESR1*, *NRG1*, *PTGER2*, *TGFβ*, *BMP2*, *FSHR*, *STARD6* and *NTRK1/2*). In addition, *CBX2*-related-genes involved in PCOS like *AMH*, *AKR1C1*, *RSPO2* and *DKK1* were confirmed. Other genes were linked to premature ovarian failure (POF) (*POF1B*, *BMP15* and *HOXA13*) and pituitary hormone deficiency (i.e. *LHX4* and *KISS1*). PcG proteins have been identified as being important proteins in tumorigenesis due to their potential to repress tumor suppressor genes and regulate genes related to stemness and differentiation. This is not surprising given the well-proven tight connection between development and cancer. In accordance to what was hypothesized above, *CBX2* isoforms might protect granulosa cells from uncontrolled growth by affecting oncogenic markers like *NRG1*, *FZD7*, *TGFα*, *AMIGO2* and *RSPO3*. Consistent with this, our findings identified group of genes with specific actions in the networks regulating sex development and eventually helped clarifying the rank of CBX2 regulator in the female regulatory events.

Jury:

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