APC (Adenomatous Polyposis Coli) Is Essential for Maintaining the Integrity of the Seminiferous Epithelium

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Sertoli cells provide the microenvironment necessary for germ cell development and spermatogenesis; disruption of Sertoli cell morphology or function can lead to germ cell aplasia, which is observed in testicular dysgenesis syndromes. Mutation of the adenomatous polyposis coli (APC) gene has been associated with various human cancers, including testicular cancer, but its involvement nonmalignant testicular pathologies has not been reported. We have developed a mouse model (APC<sup>cko</sup>) that expresses a truncated form of APC in Sertoli cells. Despite normal embryonic and early postnatal testicular development in APC<sup>cko</sup> mice, premature germ cell loss and Sertoli cell-only seminiferous tubules were observed in mutant testes without affecting Sertoli cell quiescence, apoptosis, or differentiation, which were confirmed by the absence of both proliferating cell nuclear antigen, DNA strand breaks, and anti-Müllerian hormone, respectively. We show that mutant Sertoli cells lose their apical extensions, which would normally enclose germ cells during various stages of spermatogenesis, and were unable to maintain the blood-testis barrier because of disrupted expression of junctional proteins. We also observed an up-regulation of Snail and Slug, markers suggestive of epithelial-mesenchymal transition in the Sertoli cells, but tumorigenesis was not observed. No comparable phenotype was observed with Sertoli cell-specific loss-of-function mutations in β-catenin, leading us to speculate that truncation of APC in Sertoli cells results in progressive degeneration of the seminiferous tubules by a mechanism that disrupts the integrity of Sertoli cell junctions independently of APC-regulated β-catenin activities and leads to development of a Sertoli cell-only phenotype.

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Estrogen Sulfotransferase Inhibits Adipocyte Differentiation

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The estrogen sulfotransferase (EST) is a phase II drug-metabolizing enzyme known to catalyze the sulfoconjugation of estrogens. EST is highly expressed in the white adipose tissue of male mice, but the role of EST in the development and function of adipocytes remains largely unknown. In this report, we showed that EST played an important role in adipocyte differentiation. EST was highly expressed in 3T3-L1 preadipocytes and primary mouse preadipocytes. The expression of EST was dramatically reduced in differentiated 3T3-L1 cells and mature primary adipocytes. Overexpression of EST in 3T3-L1 cells prevented adipocyte differentiation. In contrast, preadipocytes isolated from EST knockout (EST<sup>+/−</sup>) mice exhibited enhanced differentiation. The inhibitory effect of EST on adipogenesis likely resulted from the sustained activation of ERK1/2 MAPK and inhibition of insulin signaling, leading to a failure of switch from clonal expansion to differentiation. The enzymatic activity of EST was required for the inhibitory effect of EST on adipogenesis, because an enzyme-dead EST mutant failed to inhibit adipocyte differentiation. In vivo, overexpression of EST in the adipose tissue of female transgenic mice resulted in smaller adipocyte size. Taken together, our results suggest that EST functions as a negative regulator of adipogenesis.

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A TSH-CREB1-miRNA Loop Is Required for Thyroid Cell Growth

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MicroRNA (miRNA) are an important class of regulators that participate in such biological functions as development, cell proliferation, differentiation, and apoptosis. The aim of this study was to elucidate the role of miRNA in cell proliferation using a unique cell system, namely thyroid cells that require thyrotropin for their growth. Here, we report the identification of a set of five specific miRNA (miR-1, miR-28-A, miR-290-5p, miR-296-3p, and miR-297a), whose down-regulation by thyrotropin is required for thyroid cell growth. In fact, overexpression of these miRNA negatively affects cell growth. We show that three of these miRNA target cAMP-responsive element binding protein (CREB)1, a thyrotropin-activated transcription factor, and that CREB1 binds the regulatory regions of the down-regulated miRNA. Hence, these data indicate that a synergistic loop involving thyrotropin, CREB1, and miRNA is required for thyroid cell proliferation.

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