12º COBRAPEM
Congresso Brasileiro Pediátrico de Endocrinologia e Metabologia
31 de maio a 03 de junho de 2017
Rio de Janeiro . RJ

Trabalhos Científicos

Título: Vitamin D Signaling In Pediatric Adrenocortical Tumors And Its Crosstalk With The Wnt/beta-Catenin Pathway In Adrenocortical Tumor Cells

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Resumo: Wnt/Beta-catenin pathway activation is an adrenocortical tumors (ACT) hallmark. We hypothesized that VDR and beta-catenin interact in adrenocortical cells and vitamin D signaling is impaired in pediatric ACT. AIM: We investigated the role of 1,25-dihydroxydevitaminD3 (VitD3)/VDR in ACT tumorigenesis and its interaction with beta-catenin and adrenocortical cell proliferation. METHODS: Clinicopathological features and VDR expression (qPCR and immunohistochemistry) were evaluated in 72 pediatric ACTs, 33 fetal and 12 pediatric adrenals. In vitro, we evaluated in NCI-H295 cells the effects of VDR activation by VitD3 (10-7M;48h) or inhibition (siRNA) on the expression of Wnt/beta-catenin and cell cycle markers (qPCR, immunoblotting and immunofluorescence), cell cycle (flow cytometry) and viability (MTS). RESULTS: VDR was expressed in the nucleus of fetal adrenal subcapsular cells (20th week). Immunostaining increased, extended to the cytoplasm and outspread throughout the cortex in late gestation and postnatal adrenals. In ACT, VDR was mostly cytoplasmic. Strong VDR immunostaining was associated with adenomas. VDR mRNA was underexpressed, especially in carcinomas. In vitro, VitD3 increased VDR expression and nuclear accumulation. VitD3/VDR arrested cells in GO/G1 phase and reduced the G1-S markers CCND1, CDK4, CCNE1 and CDK2. MYC, DKK3 and CTNNB1 expression reduced and beta-catenin immunofluorescence was impaired. Cell viability reduced after 96h. VDR knockdown increased CTNNB1/beta-catenin and DKK3. VitD3 resettled VDR expression and reduced MYC and CCND1. CONCLUSION: VDR effects adrenocortical cells differentiation and maintenance. VDR was underexpressed in pediatric ACT, mainly in carcinomas. VitD3/VDR and Wnt/beta-catenin interacted repressing beta-catenin and adrenocortical cell proliferation. VDR activation may emerge as a therapy for ACT.