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Thyroid

HPT-AXIS AND THYROID HORMONE ACTION

Mouse Thyroid Responds to Iodine Overload by Transcriptionally Enhancing the Keap1/Nrf2 Antioxidant Response and by Upregulating Nrf2-Dependent and Independent Inflammatory and Fibrosis Pathways.

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Nrf2 (Nfe2l2) is a transcription factor that regulates a series of cytoprotective and antioxidant enzymes. Its cytoplasmic inhibitor Keap1 senses the presence of oxidative or electrophilic stress though the interaction of sulfhydryl groups of its cysteines with reactive species and ceases to bind Nrf2. Thus, Nrf2 can transfer to the nucleus and induce its target genes. Follicular thyroid cells have physiologically high levels of reactive oxygen species as oxidation of iodine is essential for iodination of thyroglobulin and thyroid hormones synthesis. We have shown previously that Nrf2 pathway is active in thyroid and regulates the transcription of thyroglobulin. We thus hypothesized that the response of thyroid to iodine excess should comprise Nrf2-dependent and -independent pathways. To this end, 3 months-old male C57Bl6J WT or Nrf2 knockout (KO) mice were exposed to 0.05% sodium iodide in their water for 7 days. Thyroids were excised and used for RNA extraction; RNA-seq was performed by Exiqon, with a fold-change cutoff set at 2. Selected representative genes of the enriched pathways were quantified by real-time qPCR to validate RNA-seq results. Pathway analysis of the differentially expressed genes was performed using the Ingenuity Pathway Analysis (IPA) software. Pathways that were enriched with a p-value<0.05 were considered significant. 828 genes were differentially expressed in response to iodine exposure; 66% were upregulated, as were most of the highly enriched pathways (related to inflammatory-immune response, antioxidant response, xenobiotic metabolism, platelet activation and calcium signaling). About 300 genes were differentially expressed between WT and KO mice; highly enriched pathways were related to glutathione and xenobiotic metabolism, Ahr signaling and Nrf2 signaling and were all downregulated in KO mice. Analysis of the potential upstream regulators of these highly enriched pathways revealed that Nrf2 and NfkB are major regulators of the antioxidant and inflammatory response induction upon iodine exposure and that Tgfβ-Smad cascade regulates the induction of fibrosis signaling. Last, we performed an analysis limited to already known thyroid pathways. A few genes were enriched following this method; upregulation of Duoxa1 (hydrogen peroxide generator) and downregulation of Nis (sodium iodide symporter) upon iodine exposure, which are expected responses, and the downregulation of thyroglobulin and upregulation of Duoxa1 in KO mice that confirm our previous findings. In conclusion, Nrf2-driven cytoprotective response is upregulated after iodine overload along with induction of inflammatory pathways. Nrf2 regulates transcriptomic responses in the thyroid, including a small but significant part of the response to iodine challenge. Hence, Nrf2 can be considered a novel player in the frontiers of thyroid antioxidant response and thyroid economy.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

OTX2 Mutations in Congenital Hypopituitarism Patients

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The transcription factor *OTX2* is implicated in pituitary, ocular and craniofacial development. Mutations have been described in patients with variable congenital hypopituitarism (CH) ranging from isolated growth hormone deficiency (IGHD) to combined pituitary hormone deficiency (CPHD) with/without an ectopic posterior pituitary (EPP).We aimed (i) to establish the contribution of *OTX2* mutations in the etiology of CH in a sub-cohort of patients and to study their functional consequences and (ii) establish a detailed human *OTX2* expression profile in a hypothalamo-pituitary (HP) context. We screened 127 patients from national (n=103) and international centers (n=24) on the septo-optic dysplasia (SOD) spectrum with variable eye abnormalities. Eye abnormalities included micro/anophthalmia, retinal dystrophy and/or coloboma in 29 of these patients, with the rest having optic nerve hypoplasia (ONH). An EPP was reported on MRI in 35 patients. The cohort previously tested negative for mutations in *HESX1, SOX2, SOX3, PROKR2* and *GH1*. Transactivation assays involved a dual-luciferase reporter in murine hypothalamic GT1-7 neurons transiently transfected with *OTX2* constructs. *In situ* hybridization was performed to analyze human brain *OTX2* expression during embryogenesis. Seven heterozygous *OTX2* changes were identified: two chromosomal deletions spanning *OTX2* in patients with micro/anophthalmia, GHD and an EPP, with one patient having cerebellar hypoplasia. Three