early-onset colorectal cancer. Even before mechanisms of carcinogenesis are elucidated, caution using 17-OHPC and other endocrine-active pharmaceuticals in early pregnancy is warranted, especially in the absence of a clear short-term benefit, and given the possible effect on risk of cancer in adult offspring.

Endocrine Disruption

ENVIRONMENTAL ENDOCRINE DISRUPTION IN DEVELOPMENT AND DISEASE

Novel Assay for Detection of Progesterone Receptor-Interacting Endocrine Disruptors

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The presence of progesterone receptor (PR)-interacting compounds in the environment may have serious health consequences for humans and wildlife, but the methods for their detection and monitoring are limited. Here we report the development and testing of a cell line expressing a chimeric construct containing ligand-binding domain of progesterone receptor and green fluorescent protein-tagged domain of the glucocorticoid receptor (GFP-GR-PR) under tetracycline regulation. Unlike the constitutively nuclear PR, this chimera is cytoplasmic in the absence of the ligand and translocates to the nucleus in response to the hormone or its analogues. The GFP-GR-PR chimera maintains specificity for binding to progesterone and does not cross-react with GR-activating hormones. A concentration- and time-dependent translocation in response to progesterone confirmed picomolar sensitivity for detecting PR ligands. Importantly, the assay can detect both agonist and antagonist activities and thus can be used for screening environmental samples for contamination with endocrine disruptors and for drug development. Using this approach, we screened water samples collected at 23 sites along 2 major rivers in Virginia: Mattaponi and Rappahannock Rivers. We detected a low, but reproducible PR-binding activity in 34.8 % of the sites tested. The calculated progesterone equivalent concentration (EQ) in some of these sites reached ~ 0.8 ng/L. The assay provides an effect-based approach for screening PR-interacting endocrine disrupting chemicals regardless of whether they exert agonist or antagonist activities. Either one could be seriously disruptive for the health of humans and wildlife.

Endocrine Disruption

ENVIRONMENTAL ENDOCRINE DISRUPTION IN DEVELOPMENT AND DISEASE

Perchlorate and Nitrate Treatments Disrupt the Endoderm and Thyroid Development Through Epigenetic Mechanisms

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Nitrate and perchlorate competitively inhibit iodide uptake in thyrocytes and disrupt thyroid function in rodents and humans. Our previous data indicated that the intrauterine exposure to perchlorate or nitrate induced thyroid dysfunction in the offspring rats during adult life. Therefore, this study aimed to investigate the effects of these endocrine disruptors during the embryonic period on the endoderm and thyroid development. Additionally, it was also investigated the role of epigenetic modifications in the programming of gene expression of the evaluated tissues. For this purpose, CD1 pregnant female mice received filtered water (control) or filtered water supplemented with sodium perchlorate (0.3 or 1 ppm) or sodium nitrate (20 or 50 ppm). At gestational day 16.5 (GD16.5), the embryonic thyroid lobes were collected and processed for molecular analysis. Besides the *in vivo* model, the effect of these thyroid disruptors was also evaluated during the differentiation of mouse embryonic stem cells (mESc) into endoderm and thyroid cells. Endoderm cells differentiation was achieved through the treatment of mESc with several growth factors. During the entire protocol the cells were exposed or not to sodium perchlorate or sodium nitrate (10^{-5} or 10^{-7} M). The effects of perchlorate and nitrate were also evaluated during the differentiation of mESC into thyroid cells. For this purpose, mESC-derived endoderm cells were transiently transfected with Pax8/Nkx2.1 expressing vectors. During the endoderm-to-thyrocytes differentiation protocol, the cells were also exposed or not to perchlorate or nitrate (10^{-5} or 10^{-7} M). The results demonstrated that both thyroid disruptors reduced the mRNA and protein expression of several endoderm markers (Foxa1, Gata4, Sox17) in the mESc-derived endoderm cells. Moreover, perchlorate or nitrate treatment also reduced the expression of thyroid transcription factors (*Pax8, Nkx2.1, Foxe1*) and thyroid differentiation markers (*Slc5a5, Tpo, Tshr, Tg*) both in the embryonic thyroid lobes and in the mESc-derived thyrocytes. Epigenetic mechanisms related to transcription repression seem to be involved in the gene expression downregulation both *in vivo* and *in vitro*, since perchlorate and nitrate increased the mRNA expression of *Dnmt1, Dnmt3, Hdac* and reduced the expression of *Hat*. Additionally, the methylation of histone H3 was increased, and the acetylation status of this histone was decreased in perchlorate- or nitrate-exposed thyroid lobes and mESc-derived endoderm/thyroid cells. In conclusion, our data strongly suggest that the programming of thyroid dysfunction induced by intrauterine exposure to perchlorate or nitrate involve the disruption of the endoderm and thyroid development during embryonic life through epigenetic mechanisms.

Genetics and Development (including Gene Regulation)

FROM BENCH TO BEDSIDE: GENETICS, DEVELOPMENT AND CELL SIGNALING IN ENDOCRINOLOGY

A Novel Algorithm for Rare Disease Gene Prediction Based on Phenotypic Similarity

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Genetic studies have yielded only a limited number of genes clearly implicated in endocrine disorders, in large part due to two current knowledge gaps. First, genome