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Nonalcoholic Fatty Liver Disease, Liver Fibrosis, and Cardiometabolic Risk Factors in Adolescence: A Cross-Sectional Study of 1874 General Population Adolescents

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Context: The impact of adolescent nonalcoholic fatty liver disease (NAFLD) on health, independent of fat mass, is unclear.

Objective: The objective of the study was to determine the independent (of total body fat) association of ultrasound scan (USS)-determined NAFLD with liver fibrosis, insulin resistance, and dyslipidemia among healthy adolescents.

Design: This was a cross-sectional analysis in participants from a UK birth cohort.

Participants: One thousand eight hundred seventy-four (1059 female) individuals of a mean age of 17.9 years participated in the study.

Main Outcomes: USS assessed liver stiffness (shear velocity, an indicator of fibrosis) and volume, fasting glucose, insulin, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, alanine amino transferase, aspartate amino transferase, γ-glutamyltransferase, and haptoglobin.

Results: The prevalence of NAFLD was 2.5% [95% confidence interval (CI) 1.8–3.3] and was the same in females and males. Dual-energy X-ray absorptiometry determined total body fat mass was strongly associated with USS NAFLD: odds ratio 2.5% (95% CI 2.44–4.07) per 1 SD (−10 kg) fat mass. Those with NAFLD had larger liver volumes and greater shear velocity. They also had higher fasting glucose, insulin, triglycerides, low-density lipoprotein cholesterol, alanine amino transferase, aspartate amino transferase, γ-glutamyltransferase, and haptoglobin and lower high-density lipoprotein cholesterol. Most associations were independent of total body fat. For example, after adjustment for fat mass and other confounders, hepatic shear velocity [mean difference 22.8% (95% CI 15.6–30.5)], triglyceride levels [23.6% (95% CI 6.0–44.2)], and insulin [39.4% (95% CI 10.7–75.5)] were greater in those with NAFLD compared with those without NAFLD.

Conclusion: In healthy European adolescents, 2.5% have USS-defined NAFLD. Even after accounting for total body fat, those with NAFLD have more adverse levels of liver fibrosis and cardiometabolic risk factors.

Increased Brown Adipose Tissue Oxidative Capacity in Cold-Acclimated Humans

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Context: Recent studies examining brown adipose tissue (BAT) metabolism in adult humans have provided convincing evidence of its thermogenic potential and role in clearing circulating glucose and fatty acids under acute cold exposure. In contrast, early indications suggest that BAT metabolism is defective in obesity and type 2 diabetes, which may have important pathological and therapeutic implications. Although many mammalian models have demonstrated the phenotypic flexibility of this tissue through chronic cold exposure, little is known about the metabolic plasticity of BAT in humans.

Objective: Our objective was to determine whether 4 weeks of daily cold exposure could increase both the volume of metabolically active BAT and its oxidative capacity.

Design: Six nonacclimated men were exposed to 10°C for 2 hours daily for 4 weeks (5 d/wk), using a liquid-conditioned suit. Using electromyography combined with positron emission tomography with [11C]acetate and [18F]fluorodeoxyglucose, shivering intensity and BAT oxidative metabolism, glucose uptake, and volume before and after 4 weeks of cold acclimation were examined under controlled acute cold-exposure conditions.

Results: The 4-week acclimation protocol elicited a 45% increase in BAT volume of activity (from 66 ± 30 to 95 ± 28 mL, P < .05) and a 2.2-fold increase in cold-induced total BAT oxidative metabolism (from 0.725 ± 0.300 to 1.591 ± 0.326 mL·s⁻¹, P < .05). Shivering intensity was not significantly different before compared with after acclimation (2.1% ± 0.7% vs 2.0% ± 0.5% maximal voluntary contraction, respectively). Fractional glucose uptake in BAT increased after acclimation (from 0.035 ± 0.014 to 0.048 ± 0.012 min⁻¹), and net glucose uptake also trended toward an increase (from 163 ± 60 to 209 ± 50 nmol·g⁻¹·min⁻¹).

Conclusions: These findings demonstrate that daily cold exposure not only increases the volume of metabolically active
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Increased Placental Expression of Fibroblast Growth Factor 21 in Gestational Diabetes Mellitus

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Background: Fibroblast growth factor 21 (FGF21) can regulate glucose and lipid metabolism. The placenta actively synthesizes and secretes many hormones, but it is unknown whether this includes FGF21. This study aimed to analyze the placental expression of FGF21 in women with or without gestational diabetes mellitus (GDM).

Methods: FGF21 and peroxisome proliferator-activated receptor (PPAR)-α mRNA and protein expression were measured in the placentae of 20 women with and 18 without GDM. mRNA expression of PPARα, FGF receptors 1–4, the coreceptor β-klotho, and glucose transporter (GLUT)-1, -3, and -4 was investigated. Maternal and fetal circulating FGF21 levels were assessed in 10 mother-baby dyads per condition.

Results: FGF21 was expressed in the placenta and its mRNA expression increased in women with GDM [10.75 (interquartile range 3.28–125.6 AU)] vs control [0.83 (0.22–4.78), P < .001], as is its protein expression [GDM 2.89 (1.44–7.50) vs control [0.42 (0.05–1.98), P < .05]. PPARα mRNA but not protein expression was increased in GDM [2.94 (0.70–7.26)] vs control [0.99 (0.43–2.17), P < .05] and was positively correlated to FGF21 mRNA expression (r = 0.43, P < .01). Placental mRNA expression of FGF receptors and GLUT1 was unchanged, and β-klotho, GLUT3, and GLUT4 showed increased expression in GDM. Maternal circulating FGF21 levels were similar [GDM 323 (75–921) vs control 269 (49–731) pg/mL, P = .81]. FGF21 was undetected in fetal cord blood.

Conclusions: FGF21 is expressed in the placenta and its expression is increased in GDM. The absence of FGF21 in fetal cord blood suggests that neither placental FGF21 nor maternal circulating FGF21 is secreted into the fetal circulation. Placental FGF21 may be a regulator of placental metabolism.

Oxytocin, a New Determinant of Bone Mineral Density in PostMenopausal Women: Analysis of the OPUS Cohort

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Introduction: Oxytocin (OT), a neurohypophysial hormone regulated by estrogen and leptin, may play a role in bone metabolism in humans as suggested by animal studies. This study assessed the relationship between OT and bone status in a large population of postmenopausal women.

Subjects and Methods: Subjects were included in the Osteoporosis and Ultrasound study, a 6-year prospective study in a population-based cohort. Final visit data were used for this cross-sectional study. OT, leptin, and estradiol serum levels were measured in 1097 postmenopausal women and compared with bone mineral density (BMD), fractures, and the bone turnover markers (BTMs) procollagen type 1 N-terminal propeptide, bone alkaline phosphatase, and C-telopeptide of type 1 collagen.

Results: The median age was 70.8 years, 16% were osteoporotic, 48% were osteopenic, and 29% had at least one fracture. The OT serum level was related to spine (r = +0.12, P = .0002) and total hip BMD (r = +0.21, P < .0001) and with BTM (procollagen type 1 N-terminal propeptide: r = −0.13, P < .0001, bone alkaline phosphatase: r = −0.07, P = .02, C-telopeptide of...
type 1 collagen: $r = -0.18, P < .0001$). The relationship of OT with BMD was independent of BTM. After adjustment for confounding factors, the correlation between OT serum level and BMD remains significant at the hip in women with unmeasurable estradiol or leptin above the median value. There was no significant relationship between OT serum levels and fractures.

Conclusion: High OT levels are associated with high BMD, especially at the hip in women with low estradiol or high leptin serum levels. The mechanism may be explained by the effect of OT on bone turnover.

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**Estradiol-17β Upregulates Pyruvate Kinase M2 Expression to Coactivate Estrogen Receptor-α and to Integrate Metabolic Reprogramming With the Mitogenic Response in Endometrial Cells**

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Context: Proliferating cells reprogram their cellular glucose metabolism to meet the bioenergetic and biosynthetic demands and to maintain cellular redox homeostasis. Pyruvate kinase M (PKM) is a critical regulator of this metabolic reprogramming. However, whether estradiol-17β (E2) reprograms cellular metabolism to support proliferation of human primary endometrial stromal cells (hESCs) and the molecular basis of this reprogramming are not well understood.

Objectives: Our objectives were to study whether E2 induces reprogramming of glucose metabolism in hESCs and to investigate the potential roles of PKM2 in E2-induced metabolic reprogramming and proliferation of these cells.

Methods: The oxygen consumption rate and extracellular acidification rate were assessed by a Seahorse XF24 analyzer. PKM2 expression was assessed by real-time RT-PCR and immunoblotting.

Results: E2 induces a Warburg-like glucose metabolism in hESCs by inducing the expression of PKM. E2 also enhanced PKM splicing into the PKM2 isoform by upregulating the c-Myc-hnRNP axis. Furthermore, E2 induces PKM2 oxidation, phosphorylation, and nuclear translocation. In addition to its glycolytic function, PKM2 physically interacted with estrogen receptor-α (ERα) and functioned as an ERα coactivator. Small-molecule PKM2 activators ameliorated ERα transcriptional activity and abrogated the E2-induced hESC proliferation.

Conclusions: We show for the first time that E2-induced hESC proliferation is associated with a shift in glucose metabolism toward aerobic glycolysis, and the molecular basis for this metabolic shift is linked to the effects of E2 on PKM2. In addition, PKM2 acts as a transcriptional coactivator for ERα and small-molecule PKM2 activators inhibit ERα transcriptional activity and reduce E2-induced cell proliferation.

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**Cell Cycle Deregulation and TP53 and RAS Mutations Are Major Events in Poorly Differentiated and Undifferentiated Thyroid Carcinomas**

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Background: Anaplastic thyroid carcinomas (ATCs) are among the most lethal malignancies, for which there is no effective treatment.

Objective: In the present study, we aimed to elucidate the molecular alterations contributing to ATC development and to identify novel therapeutic targets.

Design: We profiled the global gene expression of five ATCs and validated differentially expressed genes by quantitative RT-PCR in an independent set of tumors. In a series of 26 ATCs, we searched for pathogenic alterations in genes involved in the most deregulated cellular processes, including the hot spot regions of RAS, BRAF, TP53, CTNNB1 (β-catenin), and PIK3CA genes, and, for the first time, a comprehensive analysis of components involved in the cell cycle [cyclin-dependent kinase (CDK) inhibitors (CDKI); CDKN1A (p21^CIP1); CDKN1B (p14^ARF, p16^INK4A); CDKN2B (p15^INK4B); CDKN2C (p18^INK4C)], cell adhesion (AXIN1), and proliferation (PTEN).

Mutational analysis was also performed in 22 poorly differentiated thyroid carcinomas (PDTCs).

Results: Expression profiling revealed that ATCs were characterized by the underexpression of epithelial components and the up-regulation of mesenchymal markers and genes from TGF-β pathway as well as the overexpression of cell cycle-related genes. In accordance, the up-regulation of the SNAI2 gene, a TGF-β-responsive mesenchymal factor, was validated. CDKN3, which prevents the G/S transition, was significantly up-regulated in ATCs and PDTC and aberrantly spliced in ATCs. Mutational analysis showed that most mutations were present in TP53 (42% of ATCs; 27% of PDTCs) or RAS (31% of ATCs; 18% of PDTCs). TP53 and RAS alterations showed evidence of mutual exclusivity ($P = .0354$). PIK3CA, PTEN, and CDKI mutations were present in 14%–20% of PDTCs, and in 10%–14% of ATCs. BRAF, CTNNB1, and AXIN1 mutations were rarely detected.

Conclusion: Overall, this study identified crucial roles for the TP53, RAS, CDKI, and TGF-β pathway, which may represent feasible therapeutic targets for ATC and PDTC treatment.

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**1,5-Anhydroglucitol in Saliva Is a Noninvasive Marker of Short-Term Glycemic Control**

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Context: In most ethnicities at least a quarter of all cases with diabetes is assumed to be undiagnosed. Screening for diabetes...
using saliva has been suggested as an effective approach to identify affected individuals.

Objective: The objective of the study was to identify a non-invasive metabolic marker of type 2 diabetes in saliva.

Design and Setting: In a case-control study of type 2 diabetes, we used a clinical metabolomics discovery study to screen for diabetes-relevant metabolic readouts in saliva, using blood and urine as a reference. With a combination of three metabolomics platforms based on nontargeted mass spectrometry, we examined 2178 metabolites in saliva, blood plasma, and urine samples from 188 subjects with type 2 diabetes and 181 controls of Arab and Asian ethnicities.

Results: We found a strong association of type 2 diabetes with 1,5-anhydroglucitol (1,5-AG) in saliva ($P = 3.6 \times 10^{-11}$). Levels of 1,5-AG in saliva highly correlated with 1,5-AG levels in blood and inversely correlated with blood glucose and glycosylated hemoglobin levels. These findings were robust across three different non-Caucasian ethnicities (Arabs, South Asians, and Filipinos), irrespective of body mass index, age, and gender.

Conclusions: Clinical studies have already established 1,5-AG in blood as a reliable marker of short-term glycemic control. Our study suggests that 1,5-AG in saliva can be used in national screening programs for undiagnosed diabetes, which are of particular interest for Middle Eastern countries with young populations and exceptionally high diabetes rates.

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CLM3, a Multitarget Tyrosine Kinase Inhibitor With Antiangiogenic Properties, Is Active Against Primary Anaplastic Thyroid Cancer in Vitro and in Vivo

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Context and Objective: We have studied the antitumor activity of a pyrazolo[3,4-d]pyrimidine compound (CLM3) proposed for a multiple signal transduction inhibition [including the RET tyrosine kinase, epidermal growth factor receptor, and vascular endothelial growth factor (VEGF) receptor and with antiangiogenic activity] in primary anaplastic thyroid cancer (ATC) cells, in the human cell line 8305C (undifferentiated thyroid cancer), and in an ATC-cell line (AF).

Design and Main Outcome Measures: CLM3 was tested in primary ATC cells at the concentrations of 5, 10, 30, and 50 μM; in 8305C cells, in AF cell, at 1, 5, 10, 30, 50, or 100 μM; and in AF cells in CD nu/nu mice.

Results: CLM3 significantly inhibited the proliferation of 8305C and AF cells, also inducing apoptosis. A significant reduction of proliferation with CLM3 in ATC cells ($P < .01$, ANOVA) was shown. CLM3 increased the percentage of apoptotic ATC cells dose dependently ($P < .001$, ANOVA) and inhibited migration ($P < .01$) and invasion ($P < .001$). The AF cell line was injected sc in CD nu/nu mice, and tumor masses became detectable 15 days later. CLM3 (50 mg/kg per die) significantly inhibited tumor growth (starting 16 d after the beginning of treatment). CLM3 significantly decreased the VEGF-A expression and microvessel density in AF tumor tissues. Furthermore, CLM3 inhibited epidermal growth factor receptor, AKT, and ERK1/2 phosphorylation and down-regulated cyclin D1 in 8305C and AF cells.

Conclusions: The antitumor and antiangiogenic activity of a pyrazolo[3,4-d]pyrimidine compound (CLM3) is very promising in anaplastic thyroid cancer, opening the way to a future clinical evaluation.

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Adiposity and Glycemic Control in Children Exposed to Perfluorinated Compounds

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Objective: Our objective was to explore whether childhood exposure to perfluorinated and polyfluorinated compounds (PFCs), widely used stain- and grease-repellent chemicals, is associated with adiposity and markers of glycemic control.

Materials and Methods: Body mass index, skinfold thickness, waist circumference, leptin, adiponectin, insulin, glucose, and triglyceride concentrations were assessed in 8- to 10-year-old children in 1997 in a subset of the European Youth Heart Study, Danish component. Plasma PFC concentrations were available from 499 children. Linear regression models were performed to determine the association between PFC exposure and indicators of adiposity and markers of glycemic control.

Results: There was no association between PFC exposures and adiposity or markers of glycemic control in normal-weight children. Among overweight children, an increase of 10 ng perfluorooctane sulfonic acid/mL plasma was associated with 16.2% (95% confidence interval [CI], 5.2%–28.3%) higher insulin concentration, 12.0% (95% CI, 2.4%–22.4%) higher β-cell activity, 17.6% (95% CI, 5.8%–38.0%) higher insulin resistance, and 8.6% (95% CI, 1.2%–16.5%) higher triglyceride concentrations, and an increase of 10 ng perfluorooctanoic acid/mL plasma was associated with 71.6% (95% CI, 2.4%–187.5%) higher insulin concentration, 67.5% (95% CI, 5.5%–166.0%) higher β-cell function, 73.9% (95% CI, 0.2%–202.0%) higher insulin resistance, and 76.2% (95% CI, 22.8%–153.0%) higher triglyceride concentrations.

Discussion: Increased PFC exposure in overweight 8- to 10-year-old children was associated with higher insulin and triglyceride concentrations. Chance findings may explain some of our results, and due to the cross-sectional design, reverse causation cannot be excluded. The findings therefore need to be confirmed in longitudinal studies.

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Abstracts Translational Highlights from The Endocrine Society Journals Endocrinology, March 2014, 155(3):1168 –1173

Low-Density Lipoprotein Cholesterol Is Associated With Fracture Risk in Diabetes Patients: A Nested Case-Control Study
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Aim: Diabetes mellitus is associated with an increased risk of fractures, which is not explained fully by bone mineral density and common risk factors. The aim of this study is to investigate the association of medication and biochemical markers on the risk of fracture in a diabetes population.

Methods: This was a nested case-control study based on Danish diabetes patients from the Danish National Hospital Discharge Registry. The cases of the study were diabetes patients with a fracture (n = 24 349), and controls were diabetes patients with no fracture (n = 132 349). A total of 2816 diabetes patients were available for an analysis of patient characteristics, comorbidities, biochemical parameters, and drug usage.

Results: Patient age at the time of diabetes diagnosis, a diagnosis of previous fracture, an alcohol-related diagnosis, total cholesterol level, and the usage of antidepressants, antiepileptics, and insulin all increased the odds of fracture. Low-density lipoprotein cholesterol levels decreased the odds of fracture, in which the level of 3.04–5.96 mmol/L was optimal with regard to fracture risk.

Conclusion: Low-density lipoprotein cholesterol may add to the understanding of fractures in diabetes patients, and it may be added to current fracture risk models in diabetes patients.

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Obestatin Levels Are Associated With C-Peptide and Antiinsulin Antibodies at the Onset, Whereas Unacylated and Acylated Ghrelin Levels Are Not Predictive of Long-Term Metabolic Control in Children With Type 1 Diabetes
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Context and Objective: Ghrelin secretion is altered at the onset of type 1 diabetes. Contemporary regulation of acylated ghrelin (AG), unacylated ghrelin (UAG), and obestatin (OBST) remains undefined in this disease. It is unknown as to whether they could be good predictors of changes in glucose and metabolic control.

Design, Setting, and Subjects: This was a longitudinal study conducted in a tertiary care center. AG, UAG, and OBST were measured at baseline and after 2 years of follow-up in 51 children and adolescents with a history of type 1 diabetes extending beyond 1 year. A total of 33 healthy matched subjects were used as controls.

Results: Age-, puberty-, and body mass index-adjusted UAG levels were lower (P < .005) and OBST levels were higher (P < .009) in children with type 1 diabetes, with respect to controls. AG levels were similar to controls, but all ratios of the three peptides are altered in diabetic patients. OBST (P < .05) was negatively correlated with C-peptide (P < .05) and insulin (P < .008) at the onset of diabetes. In diabetic patients, baseline AG and UAG levels were negatively correlated with insulin dosage in the short and long term (P < .001). AG, but not OBST, was positively correlated with C-peptide levels 2 years after diagnosis (P < .05). Overall, the peptides were not predictive of glucose and metabolic control.

Conclusions: UAG, AG, OBST, and their ratios are differently regulated in children with type 1 diabetes, suggesting a role in the metabolic balance of the disease, with insulin a likely regulator of AG and UAG. The peptides do not appear to be good long-term predictors of glucose control, with further investigations needed to explain whether OBST could be a precocious predictor of islet dysfunction.

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Regulation of IL-1 Receptor Antagonist by TSH in Fibrocytes and Orbital Fibroblasts
Bin Li and Terry J. Smith

Context: The IL-1 family plays important roles in normal physiology and mediates inflammation. The actions of IL-1 are modulated by multiple IL-1 receptor antagonists (IL-1RA), including intracellular and secreted forms. IL-1 has been implicated in autoimmunity, such as that occurring in Graves’ disease (GD) and its inflammatory orbital manifestation, thyroid-associated ophthalmopathy (TAO). We have previously reported that CD34+ fibrocytes, monocyte-lineage bone marrow-derived cells, express functional TSH receptor, the central antigen in GD. When activated by TSH, they produce IL-6, IL-8, and TNF-α. Moreover, they infiltrate the orbit in TAO in which they transition into CD34+ fibroblasts and comprise a population of orbital fibroblasts (OFS). Little is known currently about any relationship between TSH, TSH receptor, and the IL-1 pathway.

Objective: The objective of the study was to determine whether TSH regulates IL-1RA in fibrocytes and OFs.

Design/Setting/Participants: Fibrocytes and OFs were collected and analyzed from healthy individuals and those with GD in an academic clinical practice.

Main Outcome Measures: Real-time PCR, Western blot analysis, reporter gene assays, and cell transfections were measured.

Results: TSH induces the expression of IL-1RA in fibrocytes and OFs. The patterns of induction diverge quantitatively and qualitatively in the two cell types. This results from relatively small effects on gene transcription-related events but a greater influence on secreted IL-1RA and intracellular IL-1RA mRNA stabilities. These actions of TSH are dependent on the intermediate induction of IL-1α and IL-1β.

Conclusions: Our findings for the first time directly link activities of the TSH and IL-1 pathways. Furthermore, they identify novel molecular interactions that could be targeted as therapy for TAO.

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Endocrine Reviews

The Na\(^+\)/I\(^-\) Symporter (NIS): Mechanism and Medical Impact

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The Na\(^+\)/I\(^-\) symporter (NIS) is the plasma membrane glycoprotein that mediates active I\(^-\) transport in the thyroid and other tissues, such as salivary glands, stomach, lactating breast, and small intestine. In the thyroid, NIS-mediated I\(^-\) uptake plays a key role as the first step in the biosynthesis of the thyroid hormones, of which iodine is an essential constituent. These hormones are crucial for the development of the central nervous system and the lungs in the fetus and the newborn and for intermediary metabolism at all ages. Since the cloning of NIS in 1996, NIS research has become a major field of inquiry, with considerable impact on many basic and translational areas. In this article, we review the most recent findings on NIS, I\(^-\) homeostasis, and related topics and place them in historical context. Among many other issues, we discuss the current outlook on iodide deficiency disorders, the roles of AhR signaling in breast carcinoma. The status of AhR including wound healing assay, invasion assay, and matrix metalloproteinase (MMP) proteins asso-
ciated with AhR in breast carcinoma cells were also firstly identified. These results demonstrated that AhR in breast carcinoma cells is considered a newly defined histological prognostic parameter of the breast cancer patients and effects of AhR activation on proliferation and MMPs expression may be related to the relatively good clinical outcome of AhR-positive breast cancer patients.

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Hormones and Cancer

Aryl Hydrocarbon Receptor in Breast Cancer—A Newly Defined Prognostic Marker

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Aryl hydrocarbon receptor (AhR) has been reported to exert various anticancer effects upon breast carcinoma cells in vitro but its details have remained largely unknown. Therefore, we first examined the AhR status in 90 invasive ductal carcinoma patients using immunohistochemistry. We then performed in vitro studies including wound healing assay, invasion assay, and matrix metalloproteinase (MMP) protein array in order to further elucidate the roles of AhR signaling in breast carcinoma. The status of AhR immunoreactivity was inversely correlated with histological grade (P\(_\mu\)=\(\mu\)0.0135) and Ki-67 labeling index (LI; P\(_\mu\)=\(\mu\)0.0087) of the patients. In addition, results of both uni- and multivariate analyses revealed that AhR in carcinoma cells turned out an independent prognostic factor with a protective relative risk (P\(_\mu\)=\(\mu\)0.0179). An administration of 10 nM 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a ligand of AhR, significantly decreased Ki-67 Li in an AhR-dependent fashion in MCF-7, T47D, ZR75-1, and MDA-MB-231. Wound healing and invasion assays performed in T47D and ZR75-1 further demonstrated that 10 nM TCDD inhibited estrogen-induced migration and invasion of cells. MMP proteins associated with AhR in breast carcinoma cells were also firstly identified. These results demonstrated that AhR in breast carcinoma cells is considered a newly defined histological prognostic parameter of the breast cancer patients and effects of AhR activation on proliferation and MMPs expression may be related to the relatively good clinical outcome of AhR-positive breast cancer patients.

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Prostatic Receptor Expression and Breast Cancer: Relationships with Tumor Characteristics among Pre- and Post-menopausal Women in a Population-Based Case–Control Study from Poland

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Previous studies have found an association between elevated circulating prolactin levels and increased risk of breast cancer. Prolactin stimulates breast cancer cell proliferation, migration, and survival via binding to the cell-surface prolactin receptor. The association of prolactin receptor expression with breast tumorigenesis remains unclear as studies that have focused on this association have had limited sample size and/or information about tumor characteristics. Here, we examined the association of prolactin receptor expression with tumor characteristics among 736 cases, from a large population-based case–control study of breast cancer conducted in Poland (2000–2003), with detailed risk factor and pathology data. Tumors were centrally reviewed and prepared as tissue microarrays for immunohistochemical analysis of prolactin receptor expression. Association of prolactin receptor expression across strata of tumor characteristics was evaluated using \(\chi^2\) analysis and logistic regression. Prolactin receptor expression did not vary by menopausal status; therefore, data from pre- and post-menopausal women were combined in the analyses. Approximately 83 % of breast cancers were categorized as strong prolactin receptor staining. Negative/low prolactin receptor expression was independently associated with poorly differentiated (P\(_\mu\)=\(\mu\)1.2\(\mu\)\(\mu\)0.005) and larger tumors (P\(_\mu\)=\(\mu\)0.0005). These associations were independent of estrogen receptor expression. This is the largest study to date in which the association of prolactin receptor expression with tumor characteristics has been evaluated. These data provide new avenues from which to explore the associations of the prolactin/prolactin receptor signaling network with breast tumorigenesis.

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