hypertension, especially in young patients, due to their malignant potential and the effects of catecholamine secretion on the cardiovascular system.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY II

PAPP-A Inhibition - a Novel Anti-Obesity Therapeutic Approach

Akhila Ramakrishna, MD, Cheryl A. Conover, PhD.
Mayo Clinic, Rochester, MN, USA.

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Background: Adipose tissue is a heterogeneous endocrine organ with tremendous capability for expansion. The antithetical pathogenicity of visceral adipose tissue (VAT), compared to subcutaneous adipose tissue (SAT), has been linked to the metabolic stress of enlarging mature adipocytes and a limited ability to recruit new adipocytes. One of the major distinguishing features of VAT preadipocytes is the high expression of Pregnancy Associated Plasma Protein–A (PAPP-A) when compared to SAT. PAPP-A is a zinc metalloprotease that is secreted, and can associate with the cell surface in an autocrine or paracrine fashion. It is the only known physiological IGFBP-4 (Insulin-like Growth Factor Binding Protein) protease. It cleaves the IGF/IGFBP-4 complex, releasing IGF, making it more bio-available for receptor engagement and downstream signaling. The role of IGFs in adipogenic differentiation is well established. While there is quantitative depot-specific variability in PAPP-A expression among preadipocytes, mature adipocytes do not express any PAPP-A. These findings suggest that there may be a relationship between PAPP-A inhibition and adipogenic differentiation and maturation. Similar to human VAT, PAPP-A expression is highest in visceral fat in murine models. The PAPP-A KO mice, when fed a high fat diet, showed restrained visceral adiposity and decreased visceral adipocyte size, suggesting that PAPP-A could regulate adipogenesis locally in tissues that express high PAPP-A.

Hypothesis: PAPP-A inhibition is a novel anti-obesity treatment strategy. **Methods/Results:** We fed 20 male and 20 female wild type mice 42% high fat diet (HFD) starting at 10 weeks of age. Concomitantly, we treated 10 mice in each group with either mAb-PA1/41 (a PAPP-A neutralizing monoclonal antibody) or IgG2a (control isotope), intraperitoneally at a dose of 30 mg/kg weekly for the duration of the HFD. At the end of 15 weeks, the mice were sacrificed and the adipose tissue, serum and solid organs were harvested.

Compared to the control (IgG2a) mice, the mAb-PA1/41 treated male and female mice gained 40% less weight ($P = 0.03$) and had smaller visceral fat depots (mesenteric and pericardial). Also, when we looked at individual adipocyte size, the drug treated mice had 45% smaller mesenteric adipocytes ($P = 0.002$) and 44% smaller pericardial adipocytes ($P= 0.003$). Also, the visceral depots in the drug treated mice had 30% more cells ($P = 0.006$). In both groups, there was decreased liver lipid content ($P=0.005$). The mAb-PA1/41 treatment had no significant effect on subcutaneous fat depots.

Conclusion: Pharmacologic inhibition of PAPP-A decreased weight gain, visceral fat depot weight, visceral adipocyte size, hepatic lipid deposition and increased visceral adipocyte cell number in both male and female mice that were fed a high fat diet.

Thyroid

THYROID NEOPLASIA AND CANCER

In Silico Analysis of rs1042522 and rs1042522 Polymorphic Variants of TP53 Gene

Izabela Dal Bó, Bsc, Larissa Teodoro, Msc,
Karina Colombera Peres, Msc, Elisangela Souza Teixeira, Bsc,
Natassia Elena Bufalo, PhD, Laura Sterian Ward, MD, PhD.
Laboratory of Cancer Molecular Genetics, Faculty of Medical Sciences, University of Campinas (Unicamp), Campinas/SP, Brazil.

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The TP53 gene encodes the p53 protein which is a nuclear phosphoprotein that plays a key role in cell cycle regulation, especially in the transition from G0 to G1. It is located on chromosome 17 at position p13.1 and found at very low levels in normal cells, but it is expressed in large quantities in damaged cells. The most frequent alterations in the TP53 gene are point mutations that cause alteration in the base sequence, resulting in a defective protein. The most frequent alteration occurs in codon 72 (rs1042522). P72R shows an exon 4 polymorphism of the *TP53* gene where it there is a substitution of an arginine (Arg) by a proline (Pro). This variant is associated with sporadic thyroid cancer. In addition, codon 72 variants decrease p53's ability to activate apoptosis and are associated with some autoimmune diseases like Graves' disease. The codon variant 47 (rs1800371) P47S has a rare polymorphism in the p53 N-terminal transactivation domain that replaces the serine-like wild-type proline (Ser). This variant is associated with impaired pro-apoptotic p53 activity therefore also increasing the risk of cancer. In order to better understand the role of SNPs (rs1042522) and (rs1800371), based on data obtained from the NCBI dbSNP database and UniProt, we evaluated the effect of amino acid alteration on protein structure. We used bioinformatics tools such as SIFT (Sorting Intolerant from Tolerant), Align GVGD, PolyPhen-2, SNAP (Screening for nonacceptable polymorphisms), PANTHER (Protein Analysis Through Evalutionary Relationships), PredictSNP, nsSNPAnalyzer, PROVEAN, SNP & GO, PMut and MuPRO. Rs1042522 and rs1800371 bioinformatic analysis suggested that the amino acid change alters protein structure (Align GVGD tool), decreases the stability (MuPro tool) and function (SNAP) of the protein. SNPs & GO confirmed an association of these polymorphisms with different diseases. We conclude that SNPs rs1042522 and rs1800371 are important in the process of tumorigenesis, corroborating findings from our group and others that suggest that they difficult the action of p53 protein.