2796-PO

The Association of TNF-a-308G>A Polymorphism in Thai Patients with Type 2 Diabetes and Prediabetes

SOMLAK CHUENGSAMARN, SUTHEE RATTANAMONGKOLGUL, SIVAPORN WANNAIAMPIKUL, THAVATCHAI PEERAPATDIT, CHAICHARN DEEROCHANAWONG, VIPAVEE ANUPUNPISIT, *Nakhon Nayok, Thailand, Bangkok, Thailand*

The tumor necrosis factor (TNF)-alpha-308 G>A polymorphism has been shown the associated gene variant with type 2 diabetes (T2DM) in the largest meta-analysis from Han Chinese population whereas the other Asian ethnicities (Taiwanese, Korean, and Japanese) have not yet been shown in this relationship. Particularly, Caucasian population, it almost showed that no statistical significant data of the association between this polymorphism and T2DM but exception of Moroccan. However, the association between this polymorphism and T2DM remains controversial by a role of ethnic differences or may be affected by insulin function Furthermore, in our literature review, it is still not found the association among this polymorphism to T2DM and pre-diabetes in Southeast Asia especially Thai population. Our study aimed to prove that this polymorphism may be related to Thai ethnic in Southeast Asia in developing or increased risk of T2DM. We enrolled the subjects with T2DM (N=320) and Pre-diabetes (N=170) by American Diabetes Association (ADA) criteria. The control group (N=290) was defined as non-diagnosis of T2DM and/or pre-diabetes by ADA criteria. In this study, we analyzed this polymorphism by polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP). The odds ratio (ORs), 95% confidence intervals (CI), and p-value for GA versus GG genotype of TNF-alpha-308 G>A polymorphism were 1.91 (1.14-3.20) at p=0.01, 2.37 (1.35-4.17) at p<0.00001, 2.08 (1.30-3.34) at p<0.001 in T2DM, pre-diabetes, and overall (T2DM plus Pre-diabetes), respectively. Our result indicated that TNF-alpha-308 G>A (GA) variant was strongly associated with risk factor for development of pre-diabetes over than T2DM in Thai population. Beside of Thai population, more specified other ethnic studies in Southeast Asia related to mechanism of insulin action are required to reveal the detailed physiological characteristics of the TNF-alpha-308 G>A polymorphism.

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2797-PO

The Effect of Genetic Risk of Type 2 Diabetes on Connections of Bone and Carbohydrate Metabolism

BARBARA BUDAY, ATTILA FEK, MARTA VITAI, GYORGYI KOVACS, JOZSEF PAURER, BOTOND LITERATI-NAGY, LASZLO KORANYI, *Balatonfüred, Hungary, Schwabach, Germany*

Type 2 diabetes is associated with increased risk of bone fractures, and the connection between the bone remodeling and carbohydrate homeostasis is decoupled It is not known whether this is a consequence of deteriorating glucose metabolism, and increasing insulin resistance or they belong to the genetic risk of type 2 diabetes. To answer these questions 17 healthy, age and BMI matched metabolically healthy females with first degree type 2 diabetic relatives (GD) and 27 without diabetic relatives (GND) were investigated. Selections were done by hyperinsulinemic-normoglycemic clamps, oral and iv glucose loads.

The correlation between total body glucose utilization (M value: mg/kg/min) and bone mineral density were missing in these healthy females with the genetic risk of type 2 diabetes, same as in manifest diabetes (M-BMD L 1-4: GNDr=-0.4086, p<0.05M; GD: ns; M-BMD total femur: GND: r-0,3768, p<0.05; GD: ns). In the GD risk group the level of low-density-large molecular sized LDL-1 lipids were decreased (GND: 0,93 ± 0,40mmol/l vs. GD:0,61± 0,4mmol/l, P<0.01) and the high-density with low molecular size LDL-3) (GND: 0,05± 0,1 vs. GD: 0,21 ± 0,2mmol/l, p<0.01) and VLDL (GND: 0,96 ± 0,3 vs. GD: 1,52 ±0,8mmol/l, p<0,01) was increased. The decrease of LDL-1 and increases of VLDL and LDL-3 in GD group were significantly correlated to IL-6 cytokine levels (VLDL: r= +0.5492, p<0,01; LDL-1: r= - 0,5702; p<0,01; LDL-3: r= +0,5639; p<0.01). The positive connection in GND group between glucose utilization (M value) and the activity on bone metabolic unit (ratio of bone resorption markers to the bone forming markers = β-crosslaps x katapszin-K x sRANKL/OPG x P1NP) in GND group (r= +0,6589; p<0.001) was also disrupted.

These data suggest that the missing connection between the glucose and bone metabolism is not the consequence of the developing insulin resistance and the deteriorating diabetic metabolism, but it belongs to the inherited diabetes risk, what is strongly connected to altered lipid metabolism.

2798-PO

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IMMUNOLOGY

2799-PO

Utilizing Oral Combination Therapy with Plant-Expressed Proinsulin, GAD65, and Exendin 4 to Prevent Type 1 Diabetes in NOD Mice

AMANDA POSGAI, CLIVE WASSERFALL, MARK A. ATKINSON, DESMOND SCHATZ, KWANG-CHUL KWON, HENRY DANIELL, *Gainesville, FL, Philadelphia, PA*

Oral or nasal administration of type 1 diabetes (T1D)-related autoantigens (AAg) reportedly delays T1D onset in NOD mice, presumably via AAg-specific tolerance induction. However, published literature conflicts regarding the required dose, frequency of delivery, combination of agents, and extent of therapeutic benefit. In a dose optimization study, we observed a trend towards delayed T1D onset in NOD mice that received weekly oral treatment with transplastomic tobacco expressing 500µg glutamic acid decarboxylase 65 (GAD) or 250µg of a cholera toxin B-proinsulin fusion protein (CTB-PINS). Therefore, we hypothesized that weekly administration of both 250µg CTB-PINS + 500µg GAD tobacco would induce AAg-specific tolerance and that the addition of CTB-Exendin 4 (EX4) tobacco would stimulate insulin secretion to prevent T1D in NOD mice. Though not statistically significant, T1D incidence was reduced by 22% in GAD+CTB-PINS vs. control tobacco-treated mice; however, the addition of CTB-EX4 did not result in therapeutic synergism. In mechanistic studies, insulin-stimulated IFN-γ production was reduced in splenocytes from CTB-PINS-treated mice at 14 weeks of age (P = 0.0153), but there was no evidence for durable immunological tolerance as measured by ELISPOT assay (AAg-specific) or flow cytometry (CD4+CD25+Foxp3+ or LAP+ regulatory T cell populations) in the spleen, pancreatic, and mesenteric lymph nodes. Pancreata collected at 6, 10, and 14 weeks of age revealed no difference in the degree of CD3+ or B220+ insulitic infiltration. Interestingly at 14 weeks of age, CTB-EX4 therapy increased insulin production (P < 0.0001) (beta cell insulin stain intensity), but not secretion (non-fasting serum C-peptide). Overall, these data suggest that in NOD mice, oral AAg therapy alone is insufficient to prevent T1D and will likely require additional immunomodulatory agents (e.g., IL-10, anti-CD3 or ATG) to achieve lasting efficacy.

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2800-PO

Delayed Kinetics in the Interface of Innate and Adaptive Immunity during Diabetes-Tuberculosis Comorbidity

BRENDAN K. PODELL, DAVID F. ACKART, NATALIE LAKEY, RANDALL J. BASARABA, *Fort Collins, CO*

The co-epidemic of type 2 diabetes and tuberculosis (TB) is rapidly emerging as one of the most significant risk factors for the development of active TB disease. We have developed a guinea pig model of type 2 diabetes-TB comorbidity that closely mimics the features of the human comorbidity, including elevated innate and type 1 immune responses, higher bacterial burdens and more severe TB disease. However, the immune mechanisms that lead to more severe TB disease remain poorly understood. Because control of bacterial growth and progression of TB disease is largely influenced by cell-mediated immunity, the early immune response to M. tuberculosis infection at the interface of innate and adaptive immunity was evaluated in type 2 diabetic guinea pigs. In contrast to normal animals, diabetic guinea pigs lacked histologic evidence of pulmonary lymphatic inflammation by day 10 of infection and more frequently, an absence of viable organisms in the draining lymph node, suggesting delayed transport of the organism from the lung. Consistent with these findings, diabetic guinea pigs also had a 9.9-fold reduction in antigen-stimulated expression of IFNγ in isolated leukocytes and 4-fold reduction in IFNγ in the lung at day 19 of infection, a time when the cell-mediated response was detectable in non-diabetic guinea pigs. An altered cellular response to infection in diabetic guinea pigs is further supported by a cytokine expression milieu featuring 30-, 23.5-, and 3.8-fold lower IL-23, IL-17 and TNFα expression, respectively but a 18.2-fold increase in IL-6. Collectively, our data suggest that timing of the initial immune response to infection in diabetic guinea pigs is poorly coordinated, leading to a delay in cell-mediated immunity and an inability to prevent further bacterial growth, which may incite severe inflammation later in the course of disease.

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2801-PO

Potential Role of Palmitate in Periodontitis

YOSUKE SHIKAMA, YASUSEI KUDO, NAOZUMI ISHIMARU, MAKOTO FUNAKI, *Tokushima, Japan*

Type 2 diabetes (T2D) is characterized by decreased insulin sensitivity and higher concentrations of free fatty acids (FFA) in plasma. Among FFA, saturated fatty acids (SFA), such as palmitate, have been proposed to promote inflammatory responses. Although many epidemiological studies have shown a link between periodontitis and T2D, little is known about the clinical significance of SFA in periodontitis. In this study, we showed that gingival fibroblasts have cell-surface expression of CD36, which is also known as FAT/fatty acid translocase. Moreover, CD36 expression was increased in gingival fibroblasts of high-fat diet-induced T2D model mice, compared with gingival fibroblasts of mice fed a normal diet. DNA microarray analysis revealed that palmitate increases mRNA expression of pro-inflammatory cytokines and chemokines in human gingival fibroblasts (HGF). Consistent with these results, we confirmed that palmitate induces interleukin (IL)-6, IL-8, and CXCL1 secretion in HGF, using a cytokine array and ELISA. SFA, but not an unsaturated fatty acid, oleate, induced IL-8 production. Docosahexaenoic acid (DHA), which is one of the omega-3 polyunsaturated fatty acids, significantly suppressed palmitate-induced IL-6 and IL-8 production. Treatment of HGF with a CD36 inhibitor also inhibited palmitate-induced pro-inflammatory responses. Finally, we demonstrated that lipopolysaccharide of Porphyromonas gingivals (P.g), an important periodontopathogen, and heat-killed P.g augmented palmitate-induced chemokine secretion in HGF. These results suggest a potential link between SFA in plasma and the pathogenesis of periodontitis.

2802-PO

WITHDRAWN

2803-PO

WITHDRAWN

2804-PO

Associations between Glycemic Status, Cytokine Expression, and Infections in Autologous Hematopoietic Cell Transplantation Recipients

MARILYN J. HAMMER, GAIL D. MELKUS, *New York, NY*

Patients with hematological malignancies undergoing autologous hematopoietic cell transplantation (HCT) are at risk for hyperglycemia, which can impair an already compromised immune system, increasing the risk for infections. Inflammatory cytokines elicit immune responses when microorganisms invade a host. Understanding how hyperglycemia interferes with immune function on a molecular level in patients with cancer can aid in the development of novel interventions to mitigate infections and improve outcomes. Adults (>18 years) without pre-existing diabetes who had autologous HCTs for hematological malignancies were included. Daily morning fasting blood labs were drawn throughout the HCT hospitalization (mean, 29.76+15.9 days). Extra blood samples were drawn at baseline and days 1, 5, 9, and 14 post-HCT for cytokine expression evaluation (IL-6, IL-8, IL-18, IL-10, and TNF-alpha) measured via Multiplex assays. Analyses included de-

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scriptive statistics and Pearson correlations. Fifty-three patients completed autologous HCT. Older age and higher body mass index (BMI) were associated with hyperglycemia (p<0.001). Infections occurred in 47.2% of patients. Increased overall mean blood glucose was associated with infection occurrences (p=.001). Higher pre-HCT glucose was associated with lower IL-6 (p=.002), IL-8 (p=<.001), and TNF-alpha (p<.001) expression. Older age and higher BMI were associated with hyperglycemia. Increased pre-HCT glucose was associated with diminished expression of key cytokines that elicit leukocyte production to detect and eliminate foreign microorganisms. This preliminary analysis suggests that elevated glucose levels may be further interfering with immune system function in this already immunocompromised population. Closely monitoring patients who may be at increased risk for hyperglycemia (older age and high BMI) and intervening early may help mitigate infections in these patients.

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2805-PO

Hyperglycemia and Impaired Glucose Tolerance Exacerbates Tuberculosis and Diabetes Disease Severity

RANDALL J. BASARABA, DAVID ACKART, NATALIE LAKEY, MIKE RICHARDSON, BRENDAN K. PODELL, *Fort Collins, CO*

The increasing incidence of Mycobacterium tuberculosis (M. tuberculosis) infection in patients with diabetes is complicating tuberculosis treatment and diabetes control strategies in low- and middle-income countries where tuberculosis (TB) is endemic. The purpose of this study was to develop a small animal model of M. tuberculosis infection concurrent with type 2 diabetes to 1) better understand the complex pathogenesis of diabetes, TB comorbidity and 2) to develop a pre-clinical model to test new strategies to treat human diabetic patients with tuberculosis. Type 2 diabetes was induced in guinea pigs with diet-induced hyperglycemia and impaired glucose tolerance using low-dose treatment with streptozotozin (STZ). Guinea pigs were then exposed to the H37Rv strain of M. tuberculosis by low-dose aerosol and diabetes and tuberculosis disease severity was assessed. The chronic inflammatory response to M. tuberculosis infection in normal guinea pigs resulted in hyperglycemia, IGT and elevated serum free fatty acids consistent with non-diabetic insulin resistance. In diabetic guinea pigs, TB disease and diabetes severity was more severe as determined by a shortened survival interval, more advanced and disseminated TB lesions, increased tissue bacterial numbers and exacerbated diabetes. The increased energy requirement by host immune cells responding to M. tuberculosis infection may explain the increase in glucose demand and availability as a consequence of non-diabetic insulin resistance and impaired glucose tolerance in the late stages of infection. These data suggest that M. tuberculosis-mediated, non-diabetic insulin resistance contributes significantly to the pathogenesis of tuberculosis concurrent with diabetes and reveals novel therapeutic targets to improve the treatment of this complex and emerging comorbidity.

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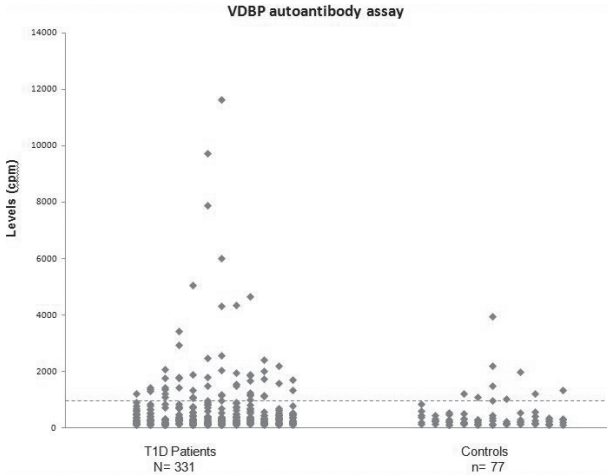
2806-PO

Vitamin D Binding Protein (VDBP) Autoantibodies Were Identified in Patients with Type 1 Diabetes

LIPING YU, ZHIYUAN ZHAO, DONGMEI MIAO, YU LIU, KYOKO TODA TODA, SATORU YAMADA, ATUL BUTTE, KEIICHI KODAMA, *Aurora, CO, Tokyo, Japan, Stanford, CA*

Vitamin D binding protein (VDBP) was identified as a candidate of autoantigen from our meta-analytic approach (eGWAS) using >100 cases and control genome-wide gene expression data. We found a stronger T-cell reactivity to VDBP in NOD mice. In VDBP autoantibody assay experiment, we found excess VDBP is in blood and the autoantibodies, if existed, would be saturated. We designed an assay able to identify VDBP Ab-Ag complex base on electrochemiluminescence technology. In brief, the sera were incubated with biotin labeled anti-human IgG MoAb and catched by Streptavidin coated plate and the VDBP Ab-Ag complexes were detected by sulfo-tag labeled anti-human VDBP MoAb. The Sera from 331 newly diagnosed T1D patients within 6 months and at least one islet Ab present (GADA, IA-2A, and ZnT8A) and 77 age-matched healthy controls were tested and the results were illustrated in the figure. The levels for VDBP Ab-Ag complex were significantly higher in T1D patients (666±1159) than in controls (438±578) (p< 0.0001). Of 331 T1D, 91 (28%) had the signal above 600 cpm vs. 11/77 (14%) in controls (p<0.02); 8 T1D patients had the signal >4,000 cpm while 0 in controls. In conclusion, VDBP Ab were identified with higher levels and frequencies in newly diagnosed T1D patients than in healthy controls. The VDBP autoimmunity including T cell study in human T1D and mechanism of VDBP autoimmunity need to be further studied.



2807-PO

WITHDRAWN

2808-PO

WITHDRAWN

2809-PO

TonEBP Promotes Insulin Resistance by Mediating NFκB Enhanceosome Assembly

HWAN HEE LEE, BYEONG JIN YE, SEUNG MIN AN, JUN HO LEE, WHASEON LEE-KWON, SOO YOUN CHOI, HYUG MOO KWON, *Ulsan, Republic of Korea*

TonEBP is a transcriptional enhancer whose DNA binding domain, Rel-homology domain, is structurally similar to those of NFκB and NFAT. TonEBP plays a central role in hypertonicity stress response and inflammation. When TonEBP haplodeficient mice were fed with high fat diet, these animals displayed improved insulin sensitivity as measured by insulin tolerance test and fasting glucose levels. Since TonEBP haplodeficiency is associated with reduced inflammation in settings of rheumatoid arthritis and atherosclerosis, and inflammation drives insulin resistance, we asked whether TonEBP stimulated NFκB-mediated inflammation. We found that siRNA-mediated knockdown of TonEBP resulted in reduced NFκB activity. Reversely, overexpression of TonEBP stimulated NFκB activity. We discovered that there was an interaction between the Rel-homology domains of TonEBP and the p65 subunit of NFκB. This interaction resulted in the recruitment of the transcriptional cofactor p300 to p65 because TonEBP was constitutively associated with p300. In *TonEBP*$^{\Delta/\Delta}$ MEF cells (mouse embryonic fibroblast (MEF) cell lines established from animals homozygous for the TonEBP$^{\Delta}$ allele in which the Rel-homology domain is deleted in frame), the interaction between the mutant TonEBP and p65 was not observed leading to failure of p300 recruitment and a dramatically reduced NFκB activity. Thus, TonEBP is a key component of the NFκB enhanceosome for the recruitment of p300. Variations in the level of TonEBP expression determines individual variations in inflammation mediated by NFκB and insulin resistance.

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2810-PO

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2811-PO

GIP Suppresses Periodontitis by Inhibition of Inflammatory Cytokine Gene Expressions

YUKI SUZUKI, NOBUHISA NAKAMURA, MEGUMI MIYABE, SHIN-ICHI MIYAJIMA, KEI ADACHI, MAKOTO MIZUTANI, TAKESHI KIKUCHI, KEN MIYAZAWA, SHIGEMI GOTO, KATSUSHI TSUKIYAMA, YUICHIRO YAMADA, NORIKAZU OHNO, AKIO MITANI, TATSUAKI MATSUBARA, KEIKO NARUSE, *Nagoya, Japan, Akita, Japan*

Periodontal disease in diabetic patients which is characterized by the severity and the morbidity is considered one of the diabetic complications. Periodontal disease is a chronic inflammation by the infection of Gram-negative bacteria in the periodontal pocket, following the destruction of periodontal tissue. In this study, we focus on the effects of glucose-dependent insulinotropic polypeptide (GIP) on periodontal disease. We elicited an experimental periodontitis in GIP receptor-knockout mice (GIPRKO) and wild type mice (WT). We also investigated the effects of GIP on monocytes using THP-1 cells. Periodontitis was induced in half of GIPRKO and WT by the placement of ligature wire around the contact point between the left maxillary first molar and second molar. Periodontitis was evaluated by the H-E staining and mRNA expressions of inflammatory cytokines two weeks after the placement of the ligature wire. In cultured THP-1 cells, we analyzed the effects of GIP on LPS- induced mRNA expressions of inflammatory cytokines. Periodontitis increased the mRNA expressions of iNOS and TNF-α in both GIPRKO and WT, however, the increase level was significantly higher in GIPRKO compared with WT. Histopathological evaluation revealed that the inflammatory cell infiltration by periodontitis was the most remarkable in GIPRKO. LPS increased the mRNA expressions of iNOS and TNF-α in THP-1 cells by 3.4-fold and 4.1-fold, respectively, which was inhibited by GIP in a dose-dependent manner. Furthermore, the inhibitory effects of GIP on LPS-induced cytokine expressions was cancelled by the cAMP inhibitor, MDL-12330A, and PKA inhibitor, PKI 14-22. In conclusion, GIP could have an anti-inflammatory effect on periodontitis and cAMP and PKA involve in the anti-inflammatory effects of GIP. These results suggest that GIP may be a novel therapeutic strategy in the treatment of periodontal disease in diabetic patients.

2812-PO

New Insights into the Impaired T-Cell Function in Diabetic Foot Ulcerations

JOÃO MOURA, JOÃO RODRIGUES, MARTA GONÇALVES, CLÁUDIA AMARAL, MARGARIDA LIMA, EUGÉNIA CARVALHO, *Coimbra, Portugal, Porto, Portugal*

Early studies involving murine models have unraveled a dual role of T-cells in the inflammatory and proliferation phases of wound healing, but their impact on diabetic foot ulceration (DFU) has remained elusive. Using a new approach to this problem, we analyzed how diabetes in general and DFU in particular affect T-cell receptor (TCR) diversity, by PCR based studies, and the relative distribution of the most representative T-cell populations (naive, activated/memory and effector), by flow cytometry.

Our results show that diabetes has a profound impact on the circulating T-cell pool of diabetic patients, lowering naïve T-cell numbers to a point where TCR diversity may become an issue to the immune response and some pathogen epitopes may no longer be recognized. We have also shown that this reduced TCR repertoire diversity is mainly due to the accumulation of effector T-cells, which are major TNF-α producers. Moreover, these cells preferentially express inflammatory chemokine receptors (mainly CXCR1 and CXCR2) and thus are better equipped to respond to the inflammatory chemokines produced by the wounded tissues of diabetic patients.

In conclusion, our results may explain the self-sustaining systemic inflammatory environment that is driven by the accumulation of effector cells. TNF-α, one of the cytokines produced by these cells, has been shown to have various harmful effects on diabetic wound healing, from the inhibition of fibroblast and keratinocyte proliferation and migration to the induction of apoptosis in endothelial cells and pericytes, trough the increase in the expression of the FOXO1 transcription factor. Since the accumulation of effector T-cells seems to be in the center of DFU pathology, immunotherapeutic strategies should be devised in order to diminish T-cell activation and tissue accumulation of these cells. Moreover, effector T-cell numbers and the overall TCR-Vβ repertoire diversity may have prognostic value in the treatment of DFU and possibly other diabetes-associated complications.

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INSULIN ACTION—ADIPOCYTE BIOLOGY

2815-PO

WITHDRAWN

TRANSPLANTATION

2814-PO

The Human Pancreas as a Source of Extracellular Matrix Scaffold for a New Generation Bio-artificial Endocrine Pancreas

GIUSEPPE ORLANDO, ANDREA PELOSO, LUCA URBANI, PANAGIOTIS MAGHSOUDLOU, GUOGUANG NIU, SHAY SOKER, EMMANUEL OPARA, JOHN MCQUILLING, ANTONIO CITRO, LORENZO PIEMONTI, MARIO ENRIQUE ALVAREZ FALLAS, VALERIA SORDI, ALAN FARNEY, JEFFREY ROGERS, PAOLO DE COPPI, ROBERT J. STRATTA, *Winston-Salem, NC, Pavia, Italy, Milan, United Kingdom, London, United Kingdom, Milan, Italy*

Our study aims at producing acellular extracellular matrix scaffolds from the human pancreas (hpaECMs), as a first critical step towards the production of a new generation, fully human-derived bio-artificial endocrine pancreas (BAEP). In this BAEP, the hardware will be represented by hpaECMs, while the software will consist in the cellular compartment generated from patient's own cells. To achieve our goal, human pancreata were decellularized with Triton-based solution and thoroughly characterized. Primary endpoints were: complete cell and DNA clearance, preservation of ECM components, growth factors (GFs) and stiffness, ability to induce angiogenesis, and conservation of the framework of the innate vasculature. Secondary endpoint was hpaECMs' ability to sustain growth and function of human islet and human primary pancreatic endothelial cells (hPPEC). Results show that hpaECMs can be successfully and consistently produced from human pancreata, maintain their innate molecular and spatial framework and stiffness, as well as vital GFs. Importantly, hpaECMs are cytocompatible and supportive of representative pancreatic cell types. We therefore conclude that hpaECMs has the potential to become an ideal platform for investigations aiming at the manufacturing of a regenerative medicine-inspired BAEP.

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2816-PO

Erythropoietin Stimulated Erythropoiesis, Metabolic Response and Reduced Body Mass in Mice

HEATHER M. ROGERS, LI WANG, RUIFENG TENG, CONSTANCE T. NOGUCHI, *Bethesda, MD, Macau, China*

Erythropoietin (Epo) is the primary cytokine regulating red blood cell production that acts to promote survival, proliferation and differentiation of erythroid progenitor cells. Increasing evidence in animal models suggest that in addition to increasing erythropoiesis, Epo treatment affects metabolic processes. Epo treatment in wild type (WT) C57Bl/6 mice increases hematocrit and decreases fasting blood glucose levels and fat mass, and improves glucose tolerance. While Epo and leptin share some homology as members of the hematopoietic cytokine super family, leptin is not required for the metabolic effect of Epo that is also observed in ob/ob mice. Epo receptor (EpoR) is highest on erythroid progenitor cells, and primary human erythroid progenitor cells in culture show an Epo dose dependent increase in glucose uptake that peaked at maximal expression of EpoR and Glut1. EpoR is also expressed in white adipose tissue (WAT) and fat specific knockout mice (ΔEpoRWAT) compared with WT mice exhibit increased body weight, blood glucose and serum insulin levels that are more apparent when on a high fat diet (HFD). ΔEpoRWAT mice treated with Epo show only a modest change in body mass, indicating that white adipose tissue contributes significantly to the Epo metabolic response. Fat mass increases with age and older WT mice exhibit greater metabolic Epo responses compared with young mice while the increase in hematocrit appear comparable. These data suggest that Epo metabolic response appears to increase with increasing fat mass/obesity and age, and includes contributions from increased glucose uptake with Epo stimulated erythropoiesis as well as direct Epo response in WAT.