

ABSTRACTS
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Triennial Growth Symposium: Interface Between Growth and Immunology

1 Brain-immune-periphery cross talk: Shared signals that link pathogen sensing and growth biology. J. L. Burton*, *Michigan State University, East Lansing.*

Animal survival depends upon the dual ability to modify metabolism according to environmental cues and mount effective immune reactions against pathogens. Both appear to rely on coordinated cross talk between the brain, immune system, and peripheral tissues such as the liver, skeletal muscle and fat. For example, recent work from our group has shown that stress hormone elaborated during brain-adrenal axis activation modifies the transcriptome of innate immune cells such that they forgo their traditional pathogen fighting behaviors in favor of higher priority metabolic activities such as tissue remodeling and repair. Other researchers have shown that myofibers and adipocytes share striking similarities with immune cells, allowing them to respond to and actively participate in pathogen sensing and local inflammatory responses but modifying their metabolic status to promote protein and fat mobilization in support of the higher priority immune reactions. This coordinated response is possible because the cells of each system express a variety of shared pathogen recognition molecules, receptors, and secreted cytokines/hormones that co-regulate inflammation and metabolism through the ability to influence activities of NF-kappaB and PPAR-gamma, key transcription factors which are also shared by the cells. As such, the brain, immune cells, skeletal muscle, and adipose tissue are both targets of and active participants in inflammation that helps clear pathogens but also modifies protein and fat accretion and thus animal growth.

Key Words: Immunity, Inflammation, Growth

2 Interleukin-15: A cytokine which modulates fat:lean body composition. L. S. Quinn*^{1,2}, ¹*University of Washington, Seattle,* ²*VA Puget Sound Health Care System, Seattle, WA.*

Recent progress in understanding the hormonal control of fat:lean body composition has been made through identification of proinflammatory cytokines and other circulating factors produced by adipose tissue which affect body composition. Adipose-derived factors such as leptin, TNF-alpha, resistin, and adiponectin have been shown to affect muscle protein accretion and insulin sensitivity by direct actions. This talk reviews recent data which demonstrate the existence of a reciprocal muscle-to-fat signaling pathway involving release of the cytokine interleukin-15 (IL-15) from muscle tissue. Data are presented from transgenic mouse models, cell culture studies, short-term in vivo studies, and human genotype association studies which all support the model that muscle-derived IL-15 can decrease fat deposition and insulin sensitivity via a muscle-to-fat endocrine pathway. Fat:lean body composition is an important factor determining the efficiency of meat production, as well as the fat content of meat products. The information presented contributes to an increasing body of literature linking immune and inflammatory factors to growth and control of body composition.

Key Words: Interleukin-15, Muscle, Adipose Tissue

3 Regulation of muscle growth by pathogen associated molecules. R. A. Frost* and C. H. Lang, *The Pennsylvania State University, Hershey.*

Skeletal muscle demonstrates great plasticity in response to environmental and hormonal factors including pathogen-associated molecules, inflammatory cytokines and growth factors. These signals impinge on

muscle by forcing individual muscle fibers to either grow or atrophy. We have recently demonstrated that skeletal muscle cells express multiple Toll-like receptors (TLRs) that recognize bacterial cell wall components such as lipopolysaccharide (LPS). Exposure of muscle cells to LPS and other TLR ligands stimulates an inflammatory response characterized by the autocrine production of cytokines and nitric oxide (NO) by nitric oxide synthase (NOS)-2.

The TLRs signal through protein kinases that phosphorylate and promote the degradation of an inhibitory protein that normally retains the transcription factor nuclear factor kappa B (NFκB) in the cytoplasm. Phosphorylation and degradation of IκB allows for translocation of NFκB to the nucleus and activation of inflammatory genes. Overexpression of a constitutively active IκB kinase in skeletal muscle causes severe wasting and we find that inhibitors of either the phosphorylation of IκB or its proteolytic degradation prevent TLR ligand-induced expression of cytokines and NOS2.

The combination of LPS and IFNγ dramatically enhances the magnitude and duration of LPS-stimulated NOS2 expression and reduces protein translation by 80%. LPS/IFNγ also down regulates signaling from the mammalian target of rapamycin (mTOR) a kinase that directs changes in cell size. NOS inhibitors block the fall in muscle cell protein synthesis and restore translational signaling suggesting that activation of the NOS2-NO pathway is responsible for the observed decrease in muscle protein synthesis.

Our work provides a molecular explanation for reduced muscle growth during infection. Muscle is largely self-sufficient as it expresses receptors, signaling pathways, and effectors to regulate its own size. Prolonged activation of NFκB and NOS2 has emerged as detrimental facets of the immune response in muscle. The interplay between inflammatory components and growth factor signaling clearly places muscle at the interface between growth and immunity.

Key Words: Muscle, Growth, Cytokines

4 Insulin resistance by TNF-alpha in skeletal muscle and fat. M. Lorenzo*, S. Fernandez-Veledo, R. Vila-Bedmar, L. Garcia-Guerra, and I. Nieto-Vazquez, *Biochemistry Department, Pharmacy Faculty, Complutense University, Madrid, Spain.*

Insulin resistance, defined as the diminished ability of a cell to respond to the action of insulin, is an important contributor to the pathogenesis of type 2 diabetes. Obesity is a risk factor for development of type 2 diabetes, due in part to the fact that adipose tissue secretes proteins called adipokines that may influence glucose homeostasis and insulin sensitivity. Among these molecules, tumor necrosis factor (TNF)-alpha has been proposed as a link between obesity and insulin resistance because TNF-alpha is overexpressed in adipose tissues of obese animals and humans, and obese mice lacking either TNF-alpha or its receptors showed protection for developing insulin resistance. We have investigated how the direct exposure to TNF-alpha induces a state of insulin resistance on glucose uptake in myocytes and brown adipocytes by affecting insulin receptor substrate (IRS) proteins through activation of pro-inflammatory pathways. In this regard we identified the residue

Ser 307 in IRS-1 as a site for TNF-alpha-impaired insulin-signaling in myotubes, being p38MAPK and IκB kinase involved in the phosphorylation of this residue. Conversely, serine phosphorylation of IRS-2 mediated by activation of p38- and p42/p44-MAPK by TNF-alpha was the mechanism found in brown adipocytes. Protein-tyrosine phosphatase (PTP)1B acts as a physiological negative regulator of insulin signaling by dephosphorylating the phosphotyrosine residues of the insulin receptor and IRS-1, and PTP1B expression is increased in muscle and adipose tissue of obese and diabetic humans and rodents. We have recently found that TNF-alpha up-regulated PTP1B expression. Accordingly, immortalized myocytes and primary brown adipocytes have been generated from PTP1B-deficient and wild-type neonatal mice. Cells deficient on PTP1B were protected against insulin resistance by this cytokine. In conclusion, the lack of PTP1B in muscle and adipose cells increased insulin sensitivity and glucose uptake and could confer protection against insulin resistance induced by adipokines.

Key Words: TNF-alpha, Insulin Resistance, Muscle and Fat

5 Proinflammatory changes in adipose tissue: Effects of diet-induced obesity. D. K. Brake, H. Wu, C. M. Ballantyne, and C. W. Smith*, *Baylor College of Medicine, Houston, TX.*

Obesity is associated with chronic inflammation, which may contribute to the high risk for type 2 diabetes, cardiovascular disease and metabolic syndrome with elevated markers of systemic inflammation. In obesity, macrophage accumulation in adipose tissue is increased, and monocyte chemoattractant protein 1 (MCP-1, CCL2) and its receptor, CC chemokine receptor-2 (CCR2), are up-regulated. Using a diet-induced mouse obesity model, we examined the expression of adhesion molecules, chemokines, inflammatory cytokines and leukocyte subsets in adipose tissue. Six week old C57BL/6J mice were fed a high fat diet (41% Kcal from milk fat) for 3, 10 and 24 weeks. After 3 weeks, CD54, IL-6 (but not TNF) and CCL2 were expressed in adipose tissue; two populations of CD11b+, CD54+ macrophages significantly increased in the stromal-vascular fraction of adipose, one of which also expressed CD11c and CD14. These changes were seen in male but not female mice. After 10 weeks on the diet, CD54 and IL-6 were further increased in adipose, and TNF expression was detected. The CD11c+ macrophages were still evident and increases in CD3+ cells (T lymphocytes) were evident. In addition to CCL2, CCL5 (RANTES) expression was detected. After 24 weeks, serum levels of soluble CD54 were elevated and positively correlated with fat mass in both male and female mice, though expression was significantly greater in males. CCL5, CCR5 and CD3+ cells were significantly elevated in obese male but not obese female mice. CCL5 mRNA levels were negatively correlated with adiponectin in adipose tissue, but positively correlated with CD3+ and CD11b+ cells. These observations reveal a progressive increase in proinflammatory changes in adipose tissue in dietary obesity that is pronounced in male mice, but minimal in female mice over a 24 week feeding period.

Key Words: Adipose, Inflammation, Mice

6 Critical control points in the impact of proinflammatory immune response on growth and metabolism. T. H. Elsasser*¹, S. Kahl², and J. L. Sartin², ¹USDA-ARS-Growth Bio Lab, Beltsville, MD, ²Auburn University, Auburn, AL.

Growth is dependant on the assimilation of nutrient precursors into the structured components of all tissues. Where in the larger context of species survival, the growth and maturation of young animals into the adult constitutes the processes necessary to reproduce, nurture, and protect following generations. In production situations where we have assumed oversight of many of these life processes for the animals we raise, we have come to define growth largely in terms of production criteria. Intrinsic in the equation for successful animal production is the efficiency of nutrient use for assimilation into useful animal-derived product. However, in many management scenarios there develop time periods during which animals will experience levels of proinflammatory response (PR) as mediated through components of the immune system. The efficiency of nutrient use will proportionally decrease for growth rate at the expense of the redirection of nutrient use to support immune response tissues and processes. These PR events can develop in association with infectious disease and infestation but also are a part of the response to vaccination and the natural and management processes of birth, parturition, and weaning. If growth patterns are tracked during these periods of PR, growth deficits are often apparent, some relatively transient in duration and others quite long lasting, persisten though traditional clinical markers of PR are no longer evident. Recent evidence suggests that the PR cascades initiated by cytokines like tumor necrosis factor- α play a major role in these growth deficits in concert with the functions of Toll-like- and CD14 receptors, NF- κ B proteins, nitric oxide synthase isoforms and superoxide anion generation; where the cascade tends to over-respond, the generation of free radicals and reactive nitrogen intermediates causes the nitration and nitrosylation of select amino acids in many metabolic regulatory and signal transduction proteins altering their functionality. The potential for dietary strategies to moderate PR-affected perturbations in growth are discussed.

Key Words: Proinflammatory Response, Growth, Metabolism

7 Bi-directional communication: Growth and immunity in domestic animals. J. A. Carroll*, USDA-ARS Livestock Issues Research Unit, Lubbock, TX.

Evidence continues to mount supporting the existence of bi-directional communication pathways between the animal's growth axis and immune system. For more than three decades, researchers have sought, and identified, linkages between the somatotrophic axis and health in domestic livestock. Early investigations were particularly interested in the various effects of exogenous growth hormone (GH) on both *in vitro* and *in vivo* aspects of immunity in domestic livestock. During an immunological insult, an uncoupling of the GH/insulin-like growth factor I (IGF-I) axis occurs resulting in elevated concentrations of GH in the presence of low circulating concentrations of IGF-I. Typically, sick animals experience a period of anorexia, thus requiring nutrient repartitioning and nutrient sparing to liberate nutrients for the production of proteins such as the pro-inflammatory cytokines and acute phase proteins that are critical for re-establishing homeostasis. While the energy liberating effects of GH are well-recognized, the significance of elevated GH during times of sickness-induced anorexia may be more profound due to its stimulatory actions on immune cells. In addition to GH, IGF-I and its associated binding proteins (IGFBP) have also generated significant interest with regard to their interactions with various pro-inflammatory cytokines and the overall effect on muscle growth and repair. For example, recent studies have demonstrated that the pro-inflammatory cytokines interleukin 1-beta (IL-1 β) and IL-6 can impair IGF-I stimulated muscle growth, and may alter IGFBP profiles thereby indirectly altering the bioactivity of IGF-I (Broussard et al., 2004). In contrast to the catabolic actions of IL-1 β and IL-6 on muscle tissue, IL-15, a cytokine produced in various tissues including placenta, skeletal muscle, kidney, lung, heart, and macrophages, has been reported to act in an additive fashion with IGF-I on muscle fiber growth (Quinn et al., 1995). Further elucidation of the cross-communication that takes place among the endocrine, neuroendocrine, immune, and nutritional processes within the body will undoubtedly continue to be unveiled as researchers pursue the complexities associated with the regulation of the immune system.

Key Words: Growth, Immune Function, Cytokines