43 Mapping the Hypermetabolic Response in Burn Patients

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Introduction: Hypermetabolism, characterized by drastic increases in whole-body catabolism and resting energy expenditure (REE), is a hallmark response to a severe burn injury. This is believed to be driven in part by alterations in adipose tissue metabolism. We proposed to define the hypermetabolic response in adipose tissue from burn patients and create a roadmap of markers indicative of hypermetabolism to improve prognosis. We hypothesized that catabolic markers, such as uncoupling protein-1 (Ucp1) and growth differentiation factor-15 (Gdf15), would positively correlate with increasing days post-burn and REE.

Methods: Adult burn patients (n=65) admitted to our burn center between 2011—2019 were included in this study. Subcutaneous white adipose tissues (sWAT) from the site of injury (n=85) and plasma were collected from severely burned patients (³20% total body surface area). Gene expression and circulating cytokine levels were measured by RT-qPCR and multiplex assays, respectively.

Results: We found a significant correlation between increasing Ucp1 gene expression and days post-burn ($p< 0.0001$). Moreover, when samples were stratified into acute (1-3 days post-burn), moderate (4-9 days post-burn), and long-term (>10 days post-burn) timepoints, a significant increase in Ucp1 gene expression was detected only in adipose tissues from long-term time points in comparison to non-burned control tissues ($p< 0.01$). However, we found that REE remained stagnant throughout hospital stay after a burn injury in our patient cohort. Thus, we did not detect a significant correlation between Ucp1 gene expression and REE. Further, while Gdf15 expression was most pronounced, albeit statistically insignificant, during the moderate timepoints, we did not detect any significant differences when correlated with days post-burn. Additionally, we determined that circulating levels of IL-6, IL-10, and monocyte chemoattractant protein-1 (MCP-1) were greatly elevated within the first seven days post-burn and gradually decreased over time, while vascular endothelial growth factor (VEGF) concentrations followed a similar pattern to Ucp1 gene expression.

Conclusions: While Gdf15 expression may not accurately reflect catabolism in the adipose tissues of burn patients, Ucp1 gene expression may be used as a marker indicating a peak hypermetabolic period after ten days post-burn. This may also be reflected by circulating concentrations of VEGF. Moreover, IL-6, IL-10 and MCP-1 may be used as early determinants before the onset of hypermetabolism.

44 Endothelial Monolayers Treated with Burn Patient Plasma Exhibit Differential Gene Expression Linked to Cytoskeletal Rearrangement

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Introduction: Burn shock is one of the most serious and complex complications suffered by patients following thermal injury. Endothelial dysfunction may play a role in the pathogenesis of burn shock. However, the mechanisms underlying the contribution to pathophysiology are still largely unknown. Previous studies have shown a connection between the rearrangement of cytoskeletal elements leading to increased vascular permeability. The aim of this study was to examine the differential expression of genes involved in cytoskeletal arrangement in endothelial cell monolayers treated with plasma from burn patients.

Methods: Human umbilical vein endothelial cells (HUVECs) were seeded into transwell plates to form confluent monolayers. Plasma was collected from burn patients 4 hours post-admission. HUVEC cells were exposed to 10% multi-donor pooled healthy human plasma (HHP) or burn patient plasma. Monolayers were subsequently incubated with FIT-C Dextran (40,000 kD) for 2 hours. Monolayer permeability was measured with indices calculated by normalizing values to blank wells (transwell inserts) and HHP-treated monolayer FIT-C diffusion. RNA was isolated from these same cells that had increased monolayer permeability and PCR analysis was carried out using an 84 gene array of human cytoskeletal regulators (Qiagen). A Ct value of 35 was used to indicate expression and a fold change of 1.5 to indicate differential expression in the control vs. injured groups.

Results: Four burn patient plasma samples were utilized to create injuries. Patients were mostly male (75%) with a mean age of 50±20 years and mean %TBSA burn of 37±34%. Differential gene expression in burn vs. HHP was compared. Ten genes showed significant upregulation (ARHGDIB, AURKA, AURKB, CCNB2, CIT, IQGAP2, VASP, SSH2, MYLK and DIAPH1). Four genes showed significant downregulation in (FSCN2, ARHGAP6, CYFIP2, CCNA1). Monolayer permeability indices showed statistically significant increases when compared to controls ranging from 3-13.33% ($p < .05$).

Conclusions: The interplay of burn shock and endothelial dysfunction remains a complex process of which much is unknown. However**,** RNA analyses of burn patient plasma reveals involvement of multiple cytoskeletal regulators. Furthermore, all these samples show a concurrent increase in permeability indices when compared to controls, further strengthening the association between cytoskeletal rearrangement and endotheliopathy. Future research to better understand the specifics of these pathways could help aid in the development of more targeted treatments of endotheliopathy and burn shock. Cytoskeletal rearrangement may be an interesting target for future work to understand this mechanistic interplay.