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Stress Induced Insulin Resistance in Regards to Cellular Organelles, Inflammasome and Inflammation and Lipids

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Insulin resistance post-trauma, -injury and -stress is a common clinical manifestation also referred as critical illness diabetes or stress diabetes [1,2]. Unfortunately, critical illness diabetes is associated with an array of other conditions, such as sepsis and hypermetabolism, which together are predictive of a poor prognosis in these patients [3]. Recent discoveries on type 2 diabetes etiology have opened the path to new possibilities to treat the sequence of events that mediate stress diabetes. Here we will discuss these options with a focus on fat metabolism and cell organelles.

Insulin is the key hormone responsible for maintaining normoglycemia. Initial results have indicated that insulin therapy in critically ill and burn patients aiming at maintaining normoglycemia led to significant improvements in morbidity and mortality. However, following multi-center trials have somewhat contradicted these initial observations [1]. The role of insulin therapy in these patients remains to be determined but it is evident that insulin resistance and hyperglycemia is detrimental and associated with adverse outcomes. Three tissues are of critical importance in the development of insulin resistance and hyperglycemia: the white adipose tissue, the liver and skeletal muscle. The different tissues have different effects but it seems that activation of the ER stress response is commonly observed in these three tissues [1]. ER stress activates stress kinases such as JNK and IKK, which directly inhibit insulin signaling and increase inflammation, further exacerbating insulin resistance [4]. Furthermore, ER stress also leads to the translocation of SREBPs transcription factors, which orchestrate hepatic triglycerides and cholesterol synthesis as well as storage [5]. Consequently, the ER stress response is a likely cause of stress diabetes, and trauma associated hepatomegaly.

While the white adipose tissue seems to play a central role in type 2 diabetes onset, the contribution of this tissue is yet to be better defined in stress diabetes. However, the elevated catecholamines concentrations in combination with the ER stress, most likely explain the increased lipolysis observed in trauma patients. Because the white adipose tissue is also a major endocrine organ secreting hormones with demonstrated influences on insulin signaling and ER stress, future works should also investigate this area and elucidate the role of these so-called adipokines in stress diabetes [6]. Whereas *in vivo* studies indicate that skeletal muscle insulin resistance may manifest at a later stage than in adipose tissue and in liver, the exact role of the skeletal muscle in stress diabetes remains poorly investigated [7].

A general consideration about fat and insulin resistance is the observation that insulin resistance does not develop as long as fat is properly stored where it should be, i.e. in the white adipose tissue. In fact, insulin resistance is typically observed when fat is stored in ectopic depots such as the liver and the skeletal muscle. A second consideration is that the storage of fat under the form of triglycerides seems disconnected with insulin resistance, may these depots be observed in the white adipose tissue or ectopically in liver and skeletal muscle. The rationale explanation for the considerations above is that rather than the storage of fat, it is the free fatty acid flux, which causes

insulin resistance in peripheral tissues [8]. As the function of insulin in the adipose tissue is to prevent triglycerides breakdown, i.e. lipolysis, the most likely explanation for the elevated flux of fatty acids, is that the white adipose tissue has developed insulin resistance in an initial step. A similar scenario is likely to occur in trauma, especially considering the elevated plasma concentrations of catecholamines, cortisol and pro-inflammatory cytokines in these patients, all of which are well known to stimulate lipolysis. We hence hypothesize that similarly to type 2 Diabetes; stress diabetes may initially arise from dysfunctions within the white adipose tissue. On the other hand, liver failure is a major cause of mortality following trauma. The adipocentric view developed above is suggestive that the excess delivery of fatty acids species is responsible for most of the manifestations observed in this tissue. Such hypothesis is in fact supported by the observation that fatty acids, in particular saturated fatty acids are identified ER stress inducers. While the mechanisms involved in the stimulation of ER stress by saturated fatty acids are quite unclear so far, the observation that enzymes producing unsaturated fatty acids species decrease ER stress support the notion that decreased membrane fluidity plays a causative role in this cellular response [9]. In support of this concept, it is of particular interest to note that saturated free fatty acids are known inducers of inflammation and macrophages skewing towards a pro-inflammatory (M1) phenotype [4]. This illustrates that elevated fatty acids flux could amplify insulin resistance in a feed-forward amplification loop via the tissue resident macrophages and contribute to the post-traumatic cytokine storm. Several mechanisms have been proposed for the stimulation of cytokines by free fatty acids however, it is postulated that the production of excessive amount of reactive oxygen species (ROS) following saturated fatty acids oxidation, trigger the activation of the inflammasome [10]. The inflammasome is an interesting multiprotein complex because it leads to the maturation of the key cytokines IL1β and IL18. Furthermore, several publications report that IL1β production by NLRP3 inflammasome is linked with insulin resistance. The exact role of inflammasome in trauma is not well documented so far but its activation would suggest that similarly to other metabolic diseases, critical illness diabetes is a condition involving a sterile type of infection. Sterile infection requires the presence of Danger-Associated Molecular Patterns (DAMPs) and free fatty acids are established TLR4 DAMPs; however other DAMPs for NLRP3 such as ATP released by dead cells may be involved as well

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[11]. Furthermore, the elevated production of ROS by saturated fatty acids result in mitochondrial alterations and, as maximal oxidative capacities are reached, the formation of intermediary, diabetogenic fatty acid species [8]. In this scenario, strategies aiming at protecting mitochondria from oxidative insults should be of particular interest as well as stimulating mitochondrial biosynthesis. One interesting mean to achieve this goal could be by stimulating autophagy/mitophagy. Indeed, mitophagy is a conserved mechanism deployed by the cells in order to rid damaged mitochondria. Interestingly, autophagy is observed in different tissues following trauma. Furthermore, mitophagy is also proposed as an alternative ending to apoptosis following the Unfolded Protein Response and defective autophagy is also associated with hepatic insulin resistance and ER stress in obesity [12,13].

In conclusion, insulin resistance and hyperglycemia are not only major contributors to morbidity in diabetic patients but furthermore in critically ill, trauma, and burn patients. Identification of novel pathways may lead to the development of new perturbations and approaches that may improve outcomes of these patients.

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