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Glucose in endoplasmic reticulum stress and immune system disruption: A possible role in cancer development

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LETTER TO THE EDITOR

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Dear Editor,

This letter suggests that new studies are required into the possible relationship between cancer and the rapid up/down-regulation of glucose levels from long term high sugar dietary behaviour. Where there is no external carcinogenic influence, such as toxic insult or oxidative stress, long-term high glucose intake may play several roles in cancer development and metastasis. Moreover, during endoplasmic reticulum (ER) stress conditions the unfolded protein response (UPR) signalling may become disrupted (under-activated) permitting unchecked misfolded proteins contributing to conditions for cancer initiation. Conversely, UPR signalling may then over-activate hindering immunogenic response to sequester and terminate cancer cells, providing further opportunities in cancer formation.

The endoplasmic reticulum organelle is responsible for folding linear polypeptides into precise 3D protein structures used within cells. ER stress occurs when the supply of unfolded proteins exceeds the capacity of the ER to fold, or when folding errors occur (misfolded proteins). ER stress results in the activation of multiple signalling pathways, called an unfolded protein response, to restore ER organelle homeostasis and hence cell survival. The role of misfolded proteins in cancer development is also studies in order to develop therapeutic models.

Three key ER stress sensors that detect misfolded proteins and initiate UPR are inositol requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6). These sensors are normally held in an inactive state by glucose regulated protein 78 (GRP78). When misfolding occurs, GPR78 has a greater affinity, binding to, the misfolded proteins, thus activating (by detaching from) ER stress sensors to initiate UPR.[1]

High dietary sugar intake provides a direct and rapid upregulation of glucose into the bloodstream. Studies show that chronic hyperglycaemia downregulates UPR response with reduced levels of both GRP78 and UPR signalling pathway sensors (IRE1, ATF6 and PERK).[2] Conversely, GRP78 may be induced through glucose starvation and ad-hoc high sugar diets may contribute to rapid downregulations that may simulate glucose starvation conditions; resulting in GPR overexpression. The precise mechanisms are unclear and require further elucidation however we postulate that GPR78 oversupply may remained attached to stress sensors (IRE1, PERK, ATF6) and thus maintaining an inactive UPR signalling state. Studies show that overexpression of BiP (GPR78) supressed activation of IRE1, ATF6 and to a lesser extent PERK.[3] PERK is involved in pro-apoptotic signalling and increased GPR78 expression correlates to resistance to cell apoptosis.[4] Studies also show that when GRP78 expression is knocked down UPR pathways are activated.[5]

Thus, both the rapid upregulation and downregulation of glucose may play a key role in UPR signalling suppression. Signalling sensor under activation results in a failure to initiate UPR to restore balance thus misfolded proteins may accumulate. Further, continued failure to initiate UPR may finally block the UPR terminate signal that would otherwise induce cell apoptosis. This may ultimately permit some cells under ER stress conditions with excessive misfolded protein errors to progress cell division. The longer terms impacts of such aberrant cell replication may play a role in contributing to conditions for general cell malignancy to develop.

In addition to impacting eukaryotic cells in general, there may also be a more specific effect to immune cell biology. Under high glucose conditions, such as in type 2 diabetes, it is understood that inflammatory conditions prevail with an immune response to high blood glucose levels. This results in further cellular damage as well as general dysfunction of the immune system.[6] When glucose, and GPR78 levels, normalise the UPR sensory network activates. This may now

result in a shift from UPR signalling under activation to a state of over activation. Moreover, there is a state of increased and prolonged expression of UPR sensors (IRE1, PERK, and ATF6) in an effort to process the accumulation of unfolded proteins to reach cellular homeostasis. Such prolonged ER stress conditions now plays an important role in disrupting the regulation of the immune system. Studies highlight the relationship of ER stress on the immune system and its implication for cancer development.[7] In particular, immunosuppression providing an opportunity for cancer formation.

ER stress with prolonged UPR signalling impacts the regulation and apoptosis of various immune cells types including T cells, B cells and immunosuppressive cells (Dendritic, type 2 macrophage, myeloid-derived suppressor cell (MDSC), and TReg). Moreover, MDSC cells are activated which impair the function of CD8+ T Cells, macrophages are suppressed, the antitumor immunity of Dendritic cells are compromised with diminished antigen presentation, and CD4+ T Cell apoptosis, differentiation and dysfunction is induced.[7] Overall, the immune response may be impaired in its ability to infiltrate, sequester and terminate cancer cells.

Long term and ad-hoc high sugar dietary intake results in a rapid up/down-regulation of glucose levels and may influence the under activation and over activation of UPR signalling during ER stress conditions. Consequentially, sustained and long term high sugar dietary behaviour that contributes to ER stress and UPR signalling instability may result in conditions for cancer initiation and development. Hence, it is suggested that these areas require further study.

One final remark, since ER stress has been implicated in the pathogenesis of other diseases, there may also be a more acute relationship during periods of high cellular growth and division. This may influence the ability to conceive, abnormal foetal termination, and neonatal developmental complications.

Sincerely

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