

Sensing Fat in the Diet: Implications for Obesity Outcomes

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Bacteria are associated with diseases; this has been particularly true recently with the discovery that changes in the gut bacteria (microbiome) are associated with energy harvesting and obesity. The increase in firmicutes and decrease in bacteroidetes have sparked massive interest in attempting to understand how diets high in fat cause this change and what implications this has for health [1-3]. For many years bacteria were thought to be autonomous organisms, until the idea of quorum sensing was proposed given rise to the idea that cells (including bacteria) can exchange information using small molecules that bind sensory proteins affecting, directly or indirectly, transcription and translation. This system illustrates that the environment in which the bacteria live will dictate gene expression which underlie various biological pathways. In essence, quorum sensing enables bacterial populations to collectively create an environment that enhances access to nutrients, promote defense mechanisms against invaders and facilitate survival. The research supporting changes in the microbiome in response to high fat feedings suggests that there may be changes in the nutrient gradient which are sensed by the quorum (bacteria) causing activation of pathways associated with obesity. Implications of this notion are unstudied and are of particular interest in our lab.

We are all acutely aware of the impacts of obesity, including increased adiposity and insulin resistance and diabetes. Some of the mechanisms associated with these problems are very well-defined while others are not. The exciting area of the gut microbiome has received a lot of attention and researchers are providing novel insights to implications as a result of these changes. There are however, several questions that still need to be answered. This editorial will briefly summarize what is known about changes in the gut and its microbiome and future directions in this area.

The gastrointestinal (GI) system represents a major route for systemic exposure to both healthy, e.g. carbohydrates, fats, protein, vitamins and minerals, and unhealthy molecules, e.g., toxins and pro-inflammatory particles (lipopolysaccharide (LPS)). The integrity of the GI barrier is critical to restrict unwanted substances from entering systemic circulation. Conversely loss of intestinal barrier integrity leads to increased permeability and diffusion of restricted molecules from the intestinal lumen to the blood. Research has supported that obesity increases intestinal permeability of LPS [4]. LPS is an endotoxin known to activate many transcription factors implicated in enhancing the inflammatory responses. Moreover, it was recently demonstrated that LPS plasma concentrations increase in response to high fat diets, which is likely due to the changes in intestinal integrity [5,6]. Since LPS is fat-soluble it has been concluded that the LPS must come from the gut and is suspected to perpetuate the obesogenic environment within the body [5,7-9].

An area receiving a lot of attention is how LPS exerts its actions, as this may provide clues as to the pathophysiology of the inflammatory response. It has been suggested that toll-like receptor 4 (TLR4) is a key modulator in the cross-talk between inflammatory and metabolic pathways. TLR4 is an essential receptor, along with its adaptor protein CD14, for the recognition of LPS [10]. The activation

of pro-inflammatory response occurs when LPS binds to its receptor resulting in production of interleukin-6 (IL-6) and/or upregulation of downstream inflammatory pathways including I κ B kinase (IKK β)/nuclear factor kappaB (NF κ B) [11]. The upregulation of the IKK β /NF κ B pathway causes additional release of tumor necrosis factor- α (TNF- α) and IL-6 further promoting the inflammatory response. Interventions therefore aimed at reducing LPS in plasma will have a potent impact on the overall systemic inflammatory response. To date it is known that both acute, chronic and resistance exercise can reduce plasma LPS levels [10], reduce TLR4 and CD14 expression [12] as well as some downstream targets including IKK β [10]. Further investigation is needed to examine how exercise may impact the bacterial quorum and if this plays a role in altering intestinal barrier integrity.

LPS in the systemic circulation not only triggers the inflammatory response, but can also cause significant changes to amino acid pools, including lysine, threonine, tryptophan, phenylalanine and valine, a branched chain amino acid (BCAA) (13). While there does seem to be a link between BCAA pools in vivo and increased incidence of obesity and diabetes [14], complete understanding of the mechanisms associated with these changes and how they are precipitated needs to be examined. BCAAs are intimately involved with the intermediates within the Krebs cycle so that energy can be made, disruptions to this cycle may adversely influence energy metabolism, further disrupting an already malfunctioned system.

This editorial highlights the impacts high fat diets have on the intestinal integrity and the consequences which increased LPS permeability to the systemic circulation and subsequent activation of pro-inflammatory cascades. However, it is not known whether LPS production in the gut increases as a result of the gut bacteria being overexposed to high fat diets. Im et al. [15] showed that intentional exposure of the colon to LPS elicited inflammation of the small intestine remotely and this was associated with enhanced inflammatory cytokine production and epithelial damage. However, it is unknown if and how fat in the diet, leads to disruption of epithelial integrity and by which pathways this is occurring through. Using quorum sensing, we possess a tool by which bacterial communications can be analyzed and what changes in transcription and translation occur as a result of this communication. These changes can hopefully provide information about links to diet and gut bacteria that have yet to be explored.

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