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B Cell Activation in Insulin Resistance and Obesity

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Abstract: Our group has demonstrated that inflammatory diseases such as type 2 diabetes (DM), inflammatory bowel disease (IBD), and periodontal disease (PD) are associated with altered B cell function that may contribute to disease pathogenesis. B cells were found to be highly activated with characteristics of inflammatory cells. Obesity is a pre-disease state for cardiovascular disease and type 2 diabetes and is considered a state of chronic inflammation. Therefore, we sought to better characterize B cell function and phenotype in obese patients. We demonstrate that (Toll-like receptor) TLR4, and CD36 expression by B cells is elevated in obese subjects, suggesting increased sensing of lipopolysaccharide (LPS) and other TLR ligands. These ligands may be of microbial, from translocation from a leaky gut, or host origin. To better assess microbial ligand burden and host response in the bloodstream, we measured LPS binding protein (LBP), bacterial/permeability increasing protein (BPI), and high mobility group box 1 (HMGB1). Thus far, our data demonstrate an increase in LBP in DM and obesity indicating increased responses to TLR ligands in the blood. Interestingly, B cells responded to certain types of LPS by phosphorylating extracellular-signal-regulated kinases (ERK) 1/2. A better understanding of the immunological state of obesity and the microbial and endogenous TLR ligands that may be activating B cells will help identify novel therapeutics to reduce the risk of more dangerous conditions, such as cardiovascular disease.

Results:
- TLR4 expressing B cell percentages were higher in DM and obese patients (Figure 1).
- TLR4 expression did not correlate with BMI.
- There was a significant increase in serum LBP levels in obese and DM patients (Figure 2).
- B cells from obese patients have increased CD36 expression, an accessory receptor for TLRs (Figure 3).
- TLR4+ B cells responded to stimulation by hypo-acylated Rhodobacter sphaeroides LPS (RsLPS) by phosphorylating ERK1/2 (Figure 4).

Methods: An obesity related insulin resistant population with a body mass index (BMI) over 30 with varying degrees of insulin resistance but non-diabetic were included. Also included were healthy volunteers with no clinical symptoms of chronic inflammatory disease designated “healthy,” and a subset of healthy volunteers designated “leans” with a BMI of <26. Heparinized whole blood was incubated with fluorescently-labeled antibodies. Assessment of surface expression on B cells was performed with gates generated with anti-CD19 + the appropriate isotype controls for each sample. Serum samples were assayed for protein by standard ELISA. LPS was measured in the serum with Limulus Amebocyte Lysate assay.

Conclusions: We conclude that there is an increased expression of TLR4 on the surface of B cells from obese patients along with an increase in CD36, an accessory receptor for TLRs. An increase in LBP levels in obese patients suggests increased microbial activity in the blood of patients with a non-infectious disease. B cells are responsive to LPS but to unexpected types of LPS suggesting that B cells may have an alternative role in sensing LPS compared to other cells such as macrophages. The clinical relevance of ERK 1/2 phosphorylation following RsLPS stimulation of B cells is under investigation. These data support the hypothesis that altered B cell function and increased microbial ligand load may play a role in the inflammation seen in chronic inflammatory diseases. Because B cells respond to unexpected microbial ligands, understanding the composition of bacteria in blood and which bacteria affect B cells, may allow us to understand the pathogenesis of LPS in insulin resistance and develop targeted interventions.