LAY ABSTRACT

Recent evidence has suggested that obesity is characterized with chronic low grade inflammation and there is a causative link between chronic inflammation and insulin resistance in obesity. However, the fundamental mechanisms for activating inflammatory pathways in obesity are poorly understood. The Toll-like receptor (TLR) 4 has played important roles in initiation of inflammation and immunity, and its expression has been reported in most tissues of the body, including the insulin-sensitive tissues, such as adipose tissue. Because it is activated by lipopolysaccharide and saturated fatty acids, which are inducers of insulin resistance, TLR4 is thought to be a candidate for mediating the cross-talk between inflammatory and metabolic signals. Indeed, recent studies have shown that both TLR4 knockout mice ($TLR4^{-/-}$) and C3H/HeJ mice, which carry a spontaneous mutation inactivating *Tlr4*, are protected against the development of systemic insulin resistance in response to a lipid infusion or a high fat diet, respectively.

Adipose tissue, one of the insulin-sensitive tissues in the body, functions by taking up glucose and store energy in the form of triglycerides, which are subsequently broken down to FFAs and glycerol in times of energy need. In addition to their storage function, adipocytes have recently been shown to be dynamic endocrine cells that produce and secrete various bioactive molecules known as adipokines or adipocytokines, some of which affect the insulin sensitivity of other tissues, including the liver, skeletal muscle, pancreatic islets (β cells), and central nervous system. The insulin resistance that accompanies obesity is attributable, at least in part, to changes in the secretion of adipokines. While the roles of TLR4 in mediating systemic inflammation and insulin resistance is being established, little is known about the relative contributions of local inflammation of adipose tissue to the development of systemic insulin resistance and whether enhanced TLR4-mediated inflammation in adipose tissue is sufficient to induce systemic insulin resistance.

It has been recognized that dietary intervention, such as intakes high in n-3 polyunsaturated fatty acids (PUFA), has been shown to be protective in rodents *in vivo* against a high fat diet that induces insulin resistance. However, the molecular mechanisms underlie the beneficial effects of n-3 PUFA in alleviating insulin resistance are not fully understood. Previously, we have shown that differential modulation of fatty acids on TLR4 activation and preferential inhibition of n-3 PUFA on TLR4 activation *in vitro*. It is not known whether n-3 PUFAs will be beneficial in alleviating TLR4-mediated inflammation in adipose tissue *in vivo* thereby improving insulin sensitivity which is impaired by inflammation.

Therefore, the goals of the proposed study are to determine whether enhanced TLR4-mediated inflammation in adipose tissue promotes the development of insulin resistance and whether dietary n-3 PUFA can suppress adipose tissue inflammation thereby improving insulin sensitivity. To achieve these objectives, we propose to generate a transgenic mouse model, in which adipose inflammation is enhanced by ectopically expressing a constitutive active form of TLR4 that is driven by the promoter of an adipose specific lipid binding protein, aP2. The effects of the dietary fatty acids will be studied in this mouse model. The results from the proposed studies will provide critical translational information for future dietary intervention studies in humans.