

LTRC Concept Sheet # 07-99-0003

Toll-like receptor 2 is an important mediator of airway inflammation in patients with COPD

ABSTRACT

COPD is characterized by chronic inflammation of the airway epithelium. The inflammation is likely modulated by many mediators. One important mediator of inflammation in the airway epithelium is Toll-like receptor 2 (TLR2). TLR2 is bound by peptidoglycan and lipoproteins that are present on the cell wall of gram positive bacteria. Once bound, TLR2 initiates a cascade of signaling through NF- κ B that results in the production of inflammatory cytokines such as IL-6 and IL-8.

Patients with COPD are frequently colonized or infected by gram positive bacteria such as *Streptococcus pneumoniae*, and *Staphylococcus aureus*. Because of this frequent exposure to gram positive organisms, it is likely that TLR2 is upregulated in patients with severe COPD. This would lead to increased inflammatory cytokines and inflammation of the airway epithelium.

Although there has been some study of TLR 2 in peripheral monocytes and alveolar macrophages in COPD, there has been very little study of TLR2 in the airway epithelium. TLR2 has been shown to be upregulated in the peripheral monocytes of COPD patients and downregulated in alveolar macrophages in COPD and smoking. Since the majority of inflammatory damage in COPD is directed at the airway epithelium, it is important to measure TLR2 in the airway epithelium itself.

We propose a pilot study to measure TLR2 in the airway epithelium of patients with very mild COPD (FEV1 > 80% predicted) and those with severe COPD (FEV1<50% predicted). We hypothesize that those with more severe COPD will have an increase in TLR2 receptors. We will quantify this in 2 ways. First, we will perform immunohistochemistry for TLR2 in HOPE and flash frozen specimens. In addition, we will perform real-time PCR to quantify TLR2 mRNA using specimens preserved in RNA Later®. In order to help us understand the inflammatory consequences of elevated TLR2, we will also perform real-time PCR for IL-6, IL-8, on tissue preserved in RNA later. We will also measure IL-6, IL-8 protein using Western blots.

These experiments will increase our understanding how TLR2 helps to modulate inflammation in the airway epithelium in COPD patients. In time, this may lead to novel therapies for COPD using TLR2 antagonists.