Inflammasome Polymorphisms and the Inflammatory Response to Bacterial Infections

av

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Abstract

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NLRP3 inflammasome; a key component of the innate immune system, can be activated by a number of pathogens and other threats of the body. Activation of the NLRP3 inflammasome triggers caspase-1 mediated maturation of IL-1β and IL-18. Polymorphisms Q705K and C10X are two gene variants of the NLRP3 inflammasome that combined or *per se* have been associated with higher risk and severity of chronic inflammation and excessive production of IL-1β. Host genetic factors have been found an important determinants of susceptibility of infectious diseases and disease outcome. The aims of this thesis were to investigate the association between polymorphisms Q705K and C10X with bacterial infections and the inflammatory response, moreover to determine the inflammasome activation state in healthy carriers of these polymorphisms. The data of the thesis show higher levels of IL-1β and IL-33 in healthy carriers of combined polymorphisms of Q705K and C10X as compared to non-carrier controls. This may provide individuals with combined polymorphisms a more robust innate immune response against pathogens, but could also lead to the onset of chronic inflammation, and excessive inflammation during acute infection. In addition, individuals with C10X polymorphism *per se* showed association with the presence of bacteremia as compared with healthy blood donors. No association was found in severely ill patients with negative blood culture bottle. In addition, the results show that LOS of *N. meningitidis* is responsible for the priming and activating steps of the inflammasome. The non-LOS components were found to contribute to the priming step. A higher inflammatory response to *N. meningitidis* was found in individuals who were non-carriers of the polymorphisms than individuals with the Q705K and C10X *per se* or combined regardless of the strain of bacteria. Taken together, the gene variations of the NLRP3 inflammasome are of importance in explaining inter-individual variation in susceptibility to infectious diseases.

Keywords: Bacteremia, Cytokines, Gene variants, Inflammasome, Inflammation, Innate immunity, Neutrophils, Meningitis, *Neisseria meningitidis*.

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