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The Scavenger Receptor, MARCO

with

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What is known about MARCO?

Dawn Bowdish: MARCO (macrophage receptor with collagenous structure) is a receptor expressed on distinct subsets of macrophages. MARCO belongs to a class of receptors called the class A scavenger receptors. These receptors are involved in clearance of bacteria, bacterial products and modified self proteins. Although MARCO is related to some of the better characterised scavenger receptors, it has some unique properties that indicate that it is probably involved in the host's defence against infection. Mouse studies indicate that under steady state conditions (i.e. when the host is healthy) MARCO is expressed in the spleen where it may be involved in maintaining macrophage – B cell interactions. This interaction is probably essential for antigen presentation or linking the innate and adaptive immune response. During *in vivo* experimental infections or upon *in vitro* stimuli with bacterial components, MARCO expression is increased on most macrophages and this increased expression leads to an enhanced ability to phagocytose pathogens, produce cytokines and may have other immunity-enhancing properties.

Why do you believe that *Neisseria meningitidis* is a ligand for MARCO?

Siamon Gordon: *Neisseria meningitidis* is an interesting model organism. Although *in vitro* studies have demonstrated that scavenger receptors can bind a number of bacterial components (e.g. lipopolysaccharide, lipotechoic acid) it was not known how these components contributed to the ability of MARCO to lead to binding and phagocytosis of bacteria. We used a mutant of *N. meningitidis* that does not produce lipopolysaccharide (LPS) and demonstrated that MARCO expressing cells were able to bind and phagocytose the mutant as well as the wild-type bacteria. This demonstrates that MARCO has a ligand on bacteria that is not LPS. We are currently investigating the identity of this bacterial ligand. We believe that MARCO is probably a receptor that recognises, binds and phagocytoses many different kinds of bacteria and we are interested in identifying the ligands that may be involved in this process.

Is MARCO induction dependent from TLR-activation?

Subhankar Mukopadyay: MARCO is an interesting receptor because it may identify a population of macrophages that have undergone "innate activation". It is known that macrophages that are exposed to certain cytokines or a combination of bacterial products and cytokines become "activated". These macrophages undergo a number of phenotypic and functional changes that can result in the macrophages having either an enhanced ability to destroy ingested pathogens, to develop an anti-parasitic response or to resolve infection. The enhanced functional properties of the macrophage depend on the activation stimulus. We have found that MARCO expression increases when the cells are exposed to bacterial stimuli such as LPS and that this occurs through the toll like receptor (TLR) signalling pathway. This is a unique example of a component of the innate immune response whose expression is enhanced by its own ligand (LPS) and of receptor collaboration between a toll-like receptor and a class A scavenger receptor. Once these cells express increased levels of MARCO they have an enhanced ability to bind and phagocytose pathogens, including *Neisseria meningitidis*, indicating that these MARCO expressing cells have enhanced anti-microbial properties. We are currently characterising the properties of these innately activated macrophages.

What evidence is there that MARCO expressing macrophages are involved in human disease?

Dawn Bowdish: Most of our knowledge of the properties and functions of MARCO comes from mouse studies; however, there is intriguing preliminary and indirect evidence that MARCO may be involved in human disease. In experimental mouse models of infection MARCO expression changes from being expressed on a few subpopulations of macrophages to being expressed on virtually all macrophages. In one of the few human studies that have been performed using autopsy samples from patients who had died of meningitis it was demonstrated that MARCO expression occurred on macrophages throughout the tissues. It has also been demonstrated that MARCO expressing macrophages are found in patients suffering from rheumatoid arthritis. Because we know that MARCO expressing cells have enhanced abilities to produce pro-inflammatory cytokines in response to bacterial stimuli and to enhance bacterial clearance we hypothesise that the generation of MARCO-expressing cells may an essential step in host defence against infectious disease. MARCO may become both an important marker for macrophages that have undergone innate activation and may be a potential therapeutic target for drugs which need to be directed to activated macrophages.

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