

CD43 and Mycobacterium tuberculosis with

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What is known about the transmembrane glycoprotein CD43?

Richard W. Stokes: CD43, a member of the family of leukocyte mucins, is a highly abundant sialoglycoprotein expressed on the surface of most lymphohaemopoietic cells (1). CD43 has a relatively simple extracellular domain with a classic mucin structure that is extensively modified by Ser/Thr-linked O-glycans with terminal sialic acid residues (2-4). Defining CD43 function has been the focus of considerable effort and yet its role in leukocyte biology has remained rather obscure.

CD43 is postulated to have a dual function in the control of cell-cell interactions, based on the seemingly conflicting data that (i) there are CD43 specific ligands to which it binds and (ii) CD43 acts as a barrier molecule blocking binding (5). In support of CD43 specific ligands it was shown that transfection of CD43 into a T cell hybridoma

promotes its binding to antigen presenting cells (6) and more recently sialoadhesin (siglec-1) was shown to bind CD43 (7). In support of CD43 function as a barrier molecule, CD43 transfected into HeLa cells resulted in the inhibition of cell adhesion (8).

Using intravital microscopy in CD43^{-/-} mice, a dual function of CD43 in leukocyte rolling and diapedesis was identified (9). Lack of CD43 results in enhanced leukocyte rolling, indicating that CD43 is acting as a barrier molecule. However, CD43^{-ve} leukocytes fail to infiltrate inflamed tissue, indicating that there is also a binding requirement for CD43 in the tissue emigration process.

Interestingly, we were also able to show that CD43 had both adhesive properties (for mycobacteria) and anti-adhesive properties (for zymosan) (10). These observations further support the dual role for CD43.

How important is this molecule in the pathogenesis of Mycobacterium tuberculosis?

Richard W. Stokes: CD43 has been shown to be necessary for the optimal binding of mycobacteria but not other bacteria (10,11). We have also shown (10) that (i) CD43 is responsible for approximately 50% of all binding of *M. tuberculosis* (Mtb) in the absence of serum; (ii) Non-opsonic binding of other mycobacterial species is also reduced in the absence of CD43 but binding of representative gram negative or gram positive bacteria is unaffected; (iii) In the presence of serum, CD43 is

redundant and binding of Mtb is independent of CD43. Of major significance was (iv), our observation that the survival and replication of Mtb was enhanced *in vitro* in CD43 negative macrophages (Mφ) and *in vivo* in CD43 knockout mice. The doubling time for intracellular Mtb in CD43^{-ve} Mφ was significantly shorter than in CD43^{ve} Mφ and the absence of CD43 in mice infected with Mtb resulted in an increased bacterial load within the lungs during both the acute and chronic stages of

infection. In addition, the development of histopathology within the infected lung was affected by the absence of CD43. Why the

presence of CD43 is necessary for optimal control of intracellular Mtb is currently under investigation.

What are the mechanisms macrophages can use for killing M. tuberculosis?

Richard W. Stokes: A number of Mφ killing mechanisms are believed to be involved in controlling intracellular mycobacterial replication. This includes the induction of reactive oxygen and nitrogen species that are toxic to mycobacteria (12), though whether the bacteria are actually exposed to these molecules inside the Mφ is still a subject of debate (13). Other Mφ mycobactericidal mechanisms are the sequestration of iron away from the bacterial phagosome (14), ATP/purinergic P2Z receptor mediated killing (15) and glutathione/ nitrosoglutathione mediated killing (16).

More recently the control of Mtb replication within Mφ has been commonly associated with the host's ability to induce apoptotic death of the infected Mφ. Apoptosis seems to link many of the mechanisms purported to kill Mtb; nitrite, glutathione and H₂O₂ can all be connected to the induction of apoptosis (17-19). In addition, TNF-α is known to trigger apoptosis (20) and the finding that TNF-α production by Mφ interacting with Mtb correlates with the ability of the Mφ to control the replication of the intracellular bacteria (21) supports the idea that TNF-α induced apoptosis is mycobactericidal.

Do you think that your finding in mice is important for humans?

Richard W. Stokes: There is a high degree of conservation of CD43 between human, mouse and other mammals; within the cytosolic and transmembrane regions there is >70% identity at the protein level and within the extracellular domain the mucin structures are conserved and the carbohydrate structures are very similar if not identical (22).

While it is essential to remember that animal models do not duplicate exactly the pathogenesis of tuberculosis in humans, it is also important to recognize that much of our understanding of human biology and disease has come from

the study of model systems. The mouse model of tuberculosis is well established (23) and has been successfully used to advance our understanding of the pathogenesis of TB. Through the use of gene knockout strains, the mouse has been especially useful for studies determining the role of individual host genes in susceptibility, the immune response and the interaction of pathogens with host cells. The close homology of human and murine CD43 supports the idea that our findings in the mouse model will be relevant to human tuberculosis.

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