Epidemiological and immunological studies of environmental mycobacteria - with focus on *Mycobacterium abscessus* -

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen
vid Sahlgrenska akademin, Göteborgs Universitet
kommer att offentligen försvaras i föreläsningssalen (plan 3)
Bakteriologiska laboratoriet, SU/Sahlgrenska, Guldhedsgatan 10A, Göteborg

Torsdagen den 19:e mars 2009, kl. 9.00

av

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Leg. läkare

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Avhandlingen baseras på följande delarbeten:

I. Jönsson B, Gilljam M, Lindblad A, Ridell M, Wold AE, Welinder-Olsson C. Molecular epidemiology of *Mycobacterium abscessus*, with focus on cystic fibrosis.
J Clin Microbiol. 2007; 45(5): 1497-1504.

II. Appelgren P, Farnebo F, Dotevall L, Studahl M, Jönsson B, Petrini B.
Late-onset posttraumatic skin and soft-tissue infections caused by rapid-growing mycobacteria in tsunami survivors. Clin Infect Dis. 2008; Jul 15, 47(2): e11-6.

III. Jönsson B, Ridell M, Wold AE. Environmental mycobacteria are uniquely strong inducers of IL-17 production – role of cell wall lipids. Submitted, 2009.

IV. Jönsson B, Telemo E, Bylund J, Johansson BR, Wold AE. Frustrated phagocytosis of mycobacterial aggregates and formation of monocyte extracellular meshwork. In manuscript.

V. Jönsson B, Ridell M, Wold AE. Frustrated phagocytosis and altered cytokine pattern in response to rough colony variants of *Mycobacterium abscessus*. Submitted, 2009.

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Abstract

Mycobacterium avium, *M. abscessus* and *M. gordonae* are three mycobacterial species that are ubiquitous in the environment. *M. gordonae* is non-pathogenic, while *M. avium* and *M. abscessus* can cause skin abscesses and airway disease, the latter mainly in patients with cystic fibrosis. The aim of this thesis was to examine the molecular epidemiology of *M. abscessus* and interactions of environmental mycobacteria with the human immune system. *M. abscessus* isolates from the airways of cystic fibrosis patients and from skin infections in patients injured during the tsunami catastrophe in Thailand 2004 were analysed by pulsed-field gel electrophoresis (PFGE). Almost all patients had unique strains, indicating that patient-to-patient transmission was rare. *M. abscessus* exhibits two colony variants; smooth and rough, the latter thought to be more virulent. Rough isolates dominated in chronic airway infection, while smooth strains caused wound infection or were transient colonizers of the airways, without associated symptoms. Environmental mycobacteria induced a unique cytokine pattern in human peripheral blood mononuclear cells (PBMC) characterized by very high levels of IL-17, high levels of IL-10, moderate levels of IL-23, relatively little IFN-γ, and no IL-12. The cytokine pattern induced by *M. abscessus*, *M. avium* and *M. gordonae* was identical, despite differences in pathogenic potential. Mycobacterial surface lipids and lipoarabinomannans induced very large amounts of IL-17, but down-regulated production of Th1 cytokines. Morphological analysis of PBMC interacting with *M. abscessus* showed that smooth isolates were readily phagocytosed, while rough strains formed multibacterial cords that escaped phagocytosis. Instead, monocytes appeared to entrap cord-forming bacteria in meshworks containing dsDNA and histones. These meshworks resembled NETs previously described in neutrophils, but to our knowledge, extracellular traps formed by monocytes have not previously been described. Rough isolates of *M. abscessus* induced significantly less IL-10 and IL-23, but more IL-1β than smooth isolates. Our results suggest that cord formation increases mycobacterial virulence and that mycobacterial cell wall lipids efficiently modulate innate responses and possess unique IL-17 inducing properties. The cellular basis for this IL-17 production remains to be determined.

Key words: Mycobacteria, *Mycobacterium abscessus*, colony morphology, mycobacterial lipids, epidemiology, cystic fibrosis, PFGE, human PBMC, cytokine, phagocytosis

ISBN 978-91-628-7708-8 Göteborg 2009