Infectious diseases and fibrotic disorders: Potential novel targets
Duitman, JanWillem

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Preface
PREFACE

Inflammation

Inflammation, in Latin, *īnflammō*, which means “I ignite” or “set alight”, is part of the complex biological response of the body to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of function. Inflammation is required for the induction of innate and adaptive immunity which are essential for the host defense against invading pathogens. An important group of invading pathogens are bacteria. Disease caused by invading pathogens is called an infectious disease.

Infectious diseases

The human body is constantly in contact with all kind of different pathogens, which try to invade thereby causing disease. The skin is in contact with surfaces containing bacteria, the airways are exposed to micro-organisms in a constant fashion and the digestive tract is vulnerable for contact with pathogens via food intake, but there are also other ways how pathogens are able to intrude the body. Under many circumstances our body is successful in its defence because of a physical barrier that is difficult to protrude (e.g. the skin) and no real infection occurs. However, sometimes pathogens do infect our body after which the immune system is activated in order to eliminate the intruders. Despite the discovery of antibiotics in the 1940’s, the mortality rates due to infectious disease (including parasitic disease) are still 21% (see figure 1). Especially respiratory tract infections contribute largely to the number of infectious disease related deaths (28.6%). The reason for these high mortality rates are due to the fact that antibiotics are still not available to many people in the world (mainly third world countries) and the increasing amount of antibiotic resistant bacteria.

The airways are in constant contact with the outside world and are therefore vulnerable to infection by airborne pathogens. The human body has several physical barriers, e.g. nasal hair and mucus production, to keep pathogens out. However, this passive form of protection is not always sufficient and the lungs may get infected by invading pathogens. The gram-positive microorganism *Streptococcus (S.) pneumoniae* is the leading causative pathogen in community-acquired pneumonia (CAP) with a high incidence of morbidity and mortality. *S. pneumoniae* accounts for up to 36% of adult community-acquired pneumonia in the United States. An estimated 570,000 cases of pneumococcal pneumonia occur annually, including 175,000 hospitalized cases and a fatality rate of 5-7%.
GENERAL INTRODUCTION (AND OUTLINE THESIS)

Worldwide *S. pneumoniae* is responsible for an estimated ten million deaths annually and it causes higher mortality rates then caused by any other bacterial pathogen, making pneumococcal pneumonia a major health threat.\(^6\)\(^7\) The gram-negative microorganism *Klebsiella (K.) pneumoniae* is also a common causative pathogen in pneumonia. Although, *K. pneumoniae* is generally perceived as a cause of hospital-acquired pneumonia (HAP), it also contributes to CAP.\(^8\)\(^9\)\(^10\) In this thesis the role of C/EBPδ (extensively introduced in chapter 1) during pneumonia caused by these two pathogens is described.

Next to pulmonary infection, urinary tract infection (UTI) is the second most common infection of humans. In fact, UTI is the most common hospital-acquired infection in the developed world. Estimates suggest that 40-50% of woman and 5% of men will develop a UTI in their life.\(^11\) Over 1 million people need hospitalization because of a UTI leading to an economic burden of $1.6-2.0 billion in medical expenses in the USA alone.\(^11\)\(^12\) UTI typically starts with an infection of the bladder which can develop into acute kidney infection as the bacteria ascent to the kidney via the urinary tract. Although in most patients no permanent damage occurs, especially in specific patient populations like children and renal transplant recipients UTI might lead to renal scarring and eventually renal failure upon persistent infection.\(^13\)\(^14\) The major health and economic burden shows it is of utmost importance to explore novel therapeutic strategies and to obtain basic insight into the factors that contribute to the battle against UTIs or could prevent that UTIs even occur.
More than 70-80% of UTIs are caused by gram-negative bacteria, of which *Escherichia (E.) coli* is the main causative pathogen.\cite{15,16}

The high incidence of infectious disease together with the increasing resistance of common pathogens to antibiotics\cite{17-19} stresses the importance for better understanding the processes underlying infectious disease ultimately leading to additional treatment options. In this thesis we investigated the role of the transcription factor C/EBPδ, generally accepted as a pro-inflammatory factor, during different bacterial infections, e.g. lung and urinary tract, in order to elucidate whether this transcription factor could be a potential novel target in infectious disease.

**Fibrotic disorders**

Tissue fibrosis is the leading cause of morbidity and mortality; approximately 45% of all deaths in the Western world are ascribed to some type of chronic fibroproliferative disorder.\cite{20} Infectious diseases are characterized by acute inflammatory reactions, whereas fibrotic disorders typically result from chronic inflammation. Fibrosis can be defined as a persistent immune response in which inflammation, tissue remodelling and repair processes take place at the same time. Upon different acute or chronic stimuli, including infections, autoimmune reactions, and mechanical injury, tissues are damaged and need repair. Repair of damaged tissues is a fundamental biological process that allows the ordered replacement of dead or damaged cells after injury, a mechanism that is critically important for survival. Two major phases are of importance during the repair process: a regenerative phase, in which injured cells are replaced by cells of the same type; and an excitatory phase, in which the injured cells are replaced by connective tissue. Although initially beneficial, the healing process becomes pathogenic if it continues in an uncontrolled manner, leading to excessive accumulation of extracellular matrix (ECM) proteins (i.e. collagen, fibronectin) and permanent scar tissue.\cite{21} In some cases, this might ultimately result in the loss of function of the affected organs and death.

Because of the high incidence of chronic fibroproliferative disease and the related mortality, better understanding of the underlying mechanisms is needed in order to pursue for better anti-fibrotic drugs that are both safe and effective in limiting or eliminating fibrotic disease without affecting normal healing of the tissue. To get better inside into the underlying mechanism of fibrotic disease we investigated the role of C/EBPδ and the protease activated receptors (PARs; reviewed in chapter 8) during fibrotic disease. The
GENERAL INTRODUCTION (AND OUTLINE THESIS)

results of these different studies are described in this thesis.

Outline of the thesis
This thesis consists of two parts. The first part has the title “CCAAT/enhancer binding protein δ in infectious disease and fibrotic disorders” and aims to clarify the role of the transcription factor C/EBPδ during bacterial infection and fibrotic disorders of the lung and kidney. The second part is called “Protease activated receptors in fibroproliferative disease” and tries to clarify the role of protease-activated receptors (PARs) in fibrotic disorders of the lung and skin.

Chapter 1 reviews the functions of C/EBPδ that are currently known, focusing on the role of C/EBPδ in the inflammatory response and during cell proliferation and apoptosis. In chapter 2 the role of C/EBPδ during experimental pneumococcal pneumonia is described. Subsequently, in chapter 3 we investigated the role of C/EBPδ during K. pneumoniae-induced pneumonia to elucidate whether (part of) the mechanisms described in chapter 2 also play a role during Gram-negative pulmonary infection. Shortly after publication of chapter 3 another study about C/EBPδ was published with seemingly contradictory results. Chapter 4 discusses the different results on C/EBPδ of chapter 2 and 3 in the perspective of the publication of this recent paper and deliberates about the possible role of C/EBPδ during lung infection and inflammation. Chapter 5 aims to elucidate whether C/EBPδ plays an important role during E. coli-induced urinary tract infection and describes the effect of C/EBPδ deficiency in a murine model for acute urinary tract infection. The last chapter of part I focuses on the role of C/EBPδ in fibrotic disease in the kidney. In chapter 6 the effect of C/EBPδ deficiency in a murine model for renal interstitial fibrosis was investigated.

The second part of this thesis concerns the role of different PARs during fibrotic disease. Chapter 7 reviews the PARs focusing on the currently known data of PARs in fibrotic disorders. Subsequently, chapter 8 shows the results of an experiment in which PAR-1 signaling was blocked using a specific PAR-1 antagonist before and after the induction of lung fibrosis. Chapter 9 aims to elucidate whether PAR-4 contributes to pulmonary fibrosis. Chapter 10 aims to assess the contribution of PAR-1 to the development of (burn)wound-induced dermal fibrosis and attempts to elucidate possible underlying mechanisms that might lead to skin fibrosis. Next, in chapter 11, the effect of PAR-2 on the development of (burn)wound-induced skin fibrosis is elucidated by subjecting PAR-2 deficient animals to a murine model of experimental skin fibrosis. Chapter 12 is a general summary and discussion of the preceding chapters.
References

GENERAL INTRODUCTION (AND OUTLINE THESIS)
