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Review

Tuberculosis in the elderly: Why inflammation matters

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ABSTRACT

Growing old is associated with an increase in the basal inflammatory state of an individual and susceptibility to many diseases, including infectious diseases. Evidence is growing to support the concept that inflammation and disease susceptibility in the elderly is linked. Our studies focus on the infectious disease tuberculosis (TB), which is caused by *Mycobacterium tuberculosis* (*M.tb*), a pathogen that infects approximately one fourth of the world's population. Aging is a major risk factor for developing TB, and inflammation has been strongly implicated. In this review we will discuss the relationship between inflammation in the lung and susceptibility to develop and succumb to TB in old age. Further understanding of the relationship between inflammation, age, and *M.tb* will lead to informed decisions about TB prevention and treatment strategies that are uniquely designed for the elderly.

1. Introduction

Increasing age is associated with a multitude of changes throughout the body including the accumulation of DNA damage, loss of tissue function, and reduced cognitive function (Bowen and Atwood, 2004; Carvalho et al., 2014). In addition to increased risk of age-associated diseases such as cancer, cardiac disease, Alzheimer's, and/or an associated loss of mobility/independence (Lin and Woollacott, 2005; Lopez-Otin et al., 2013; Niccoli and Partridge, 2012), the elderly are also more susceptible to developing and succumbing to many infectious diseases (Gardner, 1980; Meyer, 2001). Changes in immune function with increasing age are considered to be a risk factor for susceptibility to infection in old age.

As individuals age, they experience changes in immune function that reflect maturation, dysfunction, and plasticity. The changes that occur in immunity with increasing age are multifactorial and span both the innate and adaptive arms of the cellular and humoral immune system (Weiskopf et al., 2009) and these immune changes are associated with a poor response to and control of infectious agents (Hakim and Gress, 2007). Much research has been previously focused on defining critical changes in innate and adaptive immunity with increasing age at the cellular and molecular level, whereas the influence of inflammation on innate and adaptive mechanisms at the systemic level has only been experimentally recognized more recently. As individuals age they experience an increase in basal inflammation (Franceschi et al., 2000), now recognized as an event called inflammaging. Inflammatory cytokines, including TNF and IL-6, are associated with increased risk for many diseases including sarcopenia, osteoarthritis, and many infectious diseases (Boe et al., 2017; Greene and Loeser, 2015; Lloyd and Marsland, 2017). However, the precise cause and effects of this process are still elusive (Baylis et al., 2013; Franceschi et al., 2000). What we do know is that inflammaging has far reaching effects throughout the body (Franceschi et al., 2000; Franceschi and Campisi, 2014), but the mechanisms of its influence on immune responses and resulting increased susceptibility of aged persons to succumb to infectious diseases is currently still limited (Canan et al., 2014; Goldstein, 2010).

The elderly are more susceptible to many infections, from those that are commonly diagnosed (influenza and pneumococcal pneumonia) (Bahadoran et al., 2016; Krone et al., 2014) to those considered more exotic (anthrax and SARS) (Leung et al., 2004; Lyons et al., 2004). Specific to the focus of this review, the elderly are more likely to develop and succumb to tuberculosis (TB) disease (Mehta and Dutt, 1995; Zevallos and Justman, 2003). The etiologic agent of TB, *Mycobacterium tuberculosis* (*M.tb*) is estimated to infect about one fourth of the world's population (Houben and Dodd, 2016; WHO, 2017). While the global burden of *M.tb* infection is significant, the majority of infected individuals are asymptomatic and harbor very low levels of bacteria in a disease state termed non-replicating persistence or latency (Zumla et al., 2013). It is only when indictors of poor health (HIV coinfection,

Abbreviations: M.tb, *Mycobacterium tuberculosis*; AT, alveolar epithelial cell; ALF, alveolar lining fluid; TB, tuberculosis; P-L, phagosome - lysosome; SP-A, surfactant protein - A; SP-D, surfactant protein - D; IL, interleukin; MHC, major histocompatibility complex; TLR, toll-like receptor

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malnutrition, diabetes, *etc.*) become apparent that approximately 5–15% of these latent individuals go on to develop active infection (reactivation TB) (Getahun et al., 2015). During reactivation, *M.tb* multiplies and the infected individual can become infectious, and may also succumb to symptoms associated with disease (Zumla et al., 2013). Increasing age is a major risk factor for developing and/or succumbing to TB, with over half of TB-related deaths occurring in those 50 years and older (Negin et al., 2015). Although reactivation of latent *M.tb* infection in the elderly contributes to many of the TB cases (Negin et al., 2015), it is also firmly established that the elderly are highly susceptible to developing TB if they become infected with *M.tb* when they are older (primary infection) (Rajagopalan, 2001). Our laboratory seeks to determine the factors that contribute to the increased susceptibility of the elderly to develop or succumb to TB. Our primary research model is the aged mouse, due to its ease of use, availability, and relatively short lifespan. The focus of this review article will be on primary TB in old mice, although our laboratory has more recently initiated studies of age-associated reactivation TB in mice, as well as extended our studies to TB in elderly human subjects.

When adult mice are infected with *M.tb* by the aerosol route, they experience a period of unrestricted *M.tb* growth in the lung for approximately 14–21 days (Turner et al., 2002), after which the adaptive immune system is activated, *M.tb* growth is slightly reduced, and infection is maintained at a stable chronic level for up to one year (Rhoades et al., 1997). This is associated with migration of innate and adaptive immune cells to the lung to control infection, in association with the formation of cellular aggregates called granulomas that prevent *M.tb* dissemination (Gideon et al., 2015; Orme and Basaraba, 2014; Ramakrishnan, 2012). This pattern of events is considered to reflect early *M.tb* infection in humans. Diagnostic tests for *M.tb* infection indicate a lag between predicted exposure and detection of immune responsiveness 4–6 weeks later (Lee et al., 2011; Winslow et al., 2008). Furthermore, many cell and cytokine responses that have been identified as critical for *M.tb* control in mice are also essential in humans (Feng et al., 2006; Flynn and Chan, 2001; Means et al., 1999; Sanchez et al., 2010). In contrast to humans, however, mice do not reduce *M.tb* bacterial loads in the lung to low levels or develop a state of non-replicating persistence (Rhoades et al., 1997). This limitation has the most impact on long term studies where the high *M.tb* bacterial burden in mice substantially shortens their lifespan (Orme, 1988; Rhoades et al., 1997). Similar to humans, TB disease in mice is associated with a loss of immune control and regrowth of *M.tb* to levels that cause tissue damage and impaired lung function. This disease state is accompanied by extensive local and systemic inflammation, characterized by significant weight loss and muscle wasting that has been linked to abundant TNF production (Harris and Keane, 2010; Paton and Ng, 2006; Quesniaux et al., 2010). Because TB is highly associated with a robust systemic inflammatory response, it is likely that age-associated inflammation further contributes to TB pathogenesis in elderly mice, and by extrapolation in elderly humans.

Studies of TB in mice, and specifically studies of aging and TB, have primarily used C57BL/6 or BALB/c mice, the background strains for most genetic knockout mice and strains that are available from commercial vendors at an older age. It has become increasingly recognized that studies of different inbred and outbred mice can more accurately reflect some of the diverse outcomes of *M.tb* infection in humans (Beamer and Turner, 2005; Medina and North, 1998; Smith et al., 2016). While alternates to C57BL/6 and BALB/c mice are still limited for aging studies, it is apparent that differences between C57BL/6 and BALB/c strains can account for some age-associated responses (Boehmer et al., 2005; Renshaw et al., 2002). In the context of *M.tb* infection, our group have used C57BL/6 and BALB/c mice interchangeably without impact on experimental outcomes (Turner et al., 2002).

We and others have previously established that old mice are quicker to succumb to primary *M.tb* infection compared to adult mice (Orme, 1995; Vesosky and Turner, 2005), which is associated with increasing *M.tb* bacterial burden in the lung at late stages of infection (Turner et al., 2002). However, despite this increased susceptibility to develop and succumb to TB sooner than adult mice, old mice can generate potent innate immune responses (Rottinghaus et al., 2009). Indeed, innate immunity is robust enough to restrict the early growth of *M.tb* in the lungs of old mice, which will be the focus of this review. While studies are ongoing in our laboratory to determine how inflammation can alter adaptive immune function in old mice, this aspect will be discussed only briefly in this review. Our focus here will be on how an established state of inflammation in old age can modify the first encounter that *M.tb* has with host cells and molecules within the pulmonary space, the initial site of infection.

2. The lung microenvironment

M.tb is primarily transmitted by aerosol droplets that are inhaled into the lung and either cleared *via* mechanical mechanisms or deposited into the bronchioles and alveolus where infection can be established. It is thought that the status of the lung environment at the time of infection with *M.tb* is an important factor in determining disease severity (Torrelles and Schlesinger, 2017). Although the lung is the primary portal of entry for *M.tb*, the impact of the aging lung has only recently been considered as a factor that may define susceptibility to TB in the elderly.

The physical environment of the lung changes with age (Dyer, 2012; Fragoso and Lee, 2012) and makes the elderly more susceptible to many infections. The elderly experience a decreased lung elasticity and strength of respiratory muscles. Combined with lowered vital capacity (Dyer, 2012), this can impair the expulsion of infectious agents through cough reflex, sneezing or breathing. Furthermore, increased incidence of fluid and/or solid aspiration into the lung with old age, and age-associated inflammatory disease such as chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis (Akgun et al., 2012), make the elderly more likely to have a pulmonary environment that favors the establishment of infection, including *M.tb* infection.

Once *M.tb* has entered the bronchioles and alveolus, the bacterium resides within the lung mucosa that lines the alveolus, and in that mucosa the bacterium is exposed to soluble innate components (*i.e.* surfactant proteins, complement, hydrolases, antimicrobial peptides, antibodies, *etc.*) prior to encounters with resident structural (alveolar epithelium), resident innate (alveolar macrophage) and infiltrating innate (neutrophil, monocyte) cells that can determine the progress of *M.tb* in establishing infection. An inflammatory pulmonary environment in old age has the potential to modify each of these interactions between host cells and *M.tb*. Inflammaging has been historically defined as a change in cytokine levels in the circulation of an aged person, most notable being the increased levels of circulating pro-inflammatory cytokines such as TNF and IL-1β (Franceschi and Campisi, 2014). While we can make assumptions that inflammaging will also be evident in tissues, the presence and source(s) of inflammation in the aged lung has only recently been established by our group (Canan et al., 2014; Moliva et al., 2014).

3. Alveolar epithelial cells (AT) and alveolar lining fluid (ALF)

Lung mucosa or ALF is generated, secreted, and recycled by alveolar epithelial cells (ATs), and is essential for proper lung maintenance (Notter, 2000). In the aged individual, senescent ATs lead to a decrease in lung recycling (Notter, 2000) which in turn can drive a low level of inflammation in the lung (Reynolds, 1987). With systemic inflammaging previously defined in the circulation (Franceschi et al., 2000), it is therefore reasonable to extrapolate that ALF in old age will also have an elevated inflammatory profile. Indeed, studies from our group (Moliva et al., 2014) have shown that ALF isolated from aged mice had significantly increased levels of TNF and IL-6 and a trend for increased IL-