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With mouse age comes wisdom: A review and suggestions of relevant mouse models for age-related conditions

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ABSTRACT

Ageing is a complex multifactorial process that results in many changes in physiological changes processes that ultimately increase susceptibility to a wide range of diseases. As such an ageing population is resulting in a pressing need for more and improved treatments across an assortment of diseases. Such treatments can come from a better understanding of the pathogenic pathways which, in turn, can be derived from models of disease. Therefore the more closely the model resembles the disease situation the more likely relevant the data will be that is generated from them. Here we review the state of knowledge of mouse models of a range of diseases and aspects of an ageing physiology that are all germane to ageing. We also give recommendations on the most common mouse models on their relevance to the clinical situations occurring in aged patients and look forward as to how research in ageing models can be carried out. As we continue to elucidate the pathophysiology of disease, often through mouse models, we also learn what is needed to refine these models. Such factors can include better models, reflecting the ageing patient population, or a better phenotypic understanding of existing models.

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1. Introduction

The utility of the mouse in aiding our understanding of disease is clear; the ability to manipulate its genome, a short breeding cycle, defined genetic backgrounds, and the array of phenotypic interrogations available for the mammalian physiology have all helped elucidate the pathogenesis of disease. Whilst ageing is a risk factor for a range of diseases (Niccoli and Partridge, 2012) and there are many efforts to understand the effect of ageing through the modulation of ageing itself (Fontana et al., 2010; Guarente, 2014) it is also clear many diseases have a significant genetic component. This genetic susceptibility may be exacerbated in the context of an ageing physiology, thereby resulting in the observed increased disease risk with age. Thus, the study of individual disease pathways through specific mouse models could aid our understanding of not only disease but also the increased risk associated with ageing. Studies in young mice are often fruitful, but to understand disease, model it accurately, and subsequently test interventions it is only logical that if one is studying a chronic or age-related disease the best models will be chronic or have an ageing component. The disease burden faced by the aged is wide-ranging and varies from individual to individual but there are diseases that are common among aged patients. It is therefore a challenge in many disease areas to include the role of ageing, which may add additional complications or comorbidities that compound the underlying condition (Fabbri et al., 2015). Here we highlight a subset of relevant illnesses and how mice, young, old, and indeed with accelerated ageing, have been used to study them. In this review we highlight the potential impacts of ageing on disease susceptibility in a range of disease areas to emphasise the relevance of current models, and make suggestions for refinements and new developments.

2. Acute trauma and sepsis

Although traumatic injuries are not the main cause of death in people aged ≥60 years, traumas like falls or motor vehicle collisions are associated with an increased mortality risk in elderly patients (Sampalis et al., 2009; Schoeneberg et al., 2014). Often, the trauma itself is not the actual killer; most frequently, the main cause of the ensuing morbidity/mortality in those patients are secondary infections rapidly progressing to sepsis and/or multiple organ dysfunction syndrome (MODS) (Angus, 2001; Frohlich et al., 2014). Susceptibility and mortality from systemic infections increase with patient's age, and sepsis is among the leading causes of death in ageing patients worldwide (Angus, 2001; Wafaisade et al., 2011). To study the above mentioned critical care conditions, the availability of effective age modeling approaches is essential.

Regardless whether trauma or infection occurs, similar immuno-inflammatory reactions are triggered via either DAMPS (danger associated molecular patterns) or PAMPS (pathogen associated molecular patterns) (Lord et al., 2014; Boomer et al., 2014). With advanced age, the host's capability to mount an adequate immune response against inflammatory stimuli declines. This phenomenon is apparent in humans and laboratory animals, including mice (Frasca and Blomberg, 2015). For example, while the number of B-cells and naïve T-lymphocytes decreases, T_2-helper cells (producing the anti-inflammatory interleukins (IL) 4 and 10) accumulate (Linton et al., 1996; Miller, 1996; Weksler et al., 2002). Simultaneously, ageing is associated with a persistent low-grade increase of various pro-inflammatory and acute phase proteins, many of which are independent predictors of mortality/morbidity in patients (Bruunsgaard et al., 2003; Giovannini et al., 2011; Harris, 1999). All those immunologic changes are part of an age-related decline of physiologic functions termed frailty, which occurs in both humans and mice (Mohler et al., 2014). Thus, those similar immuno-inflammatory characteristics justify the age-oriented investigative utility of the mouse in critical care conditions.

Despite the critical need for such translational studies, preclinical research addressing the mechanisms and impact of age on immuno-inflammatory endpoints is infrequent. The main reason is undoubtedly the financial burden: aged mice must be either purchased (e.g. €156 for an 18-month old female CD-1 mouse) or "matured" from a young age for 18–24 months. The latter option, although seemingly attractive, poses many underappreciated risks that may eventually surpass the costs of "ready-to-use" mice (Miller and Nadon, 2000). Despite those hurdles and recently voiced translational doubts (Seok et al., 2013), many important and findings stem from mouse studies in critical care (Osuchowski et al., 2014). In trauma, the majority of existing studies concentrate not on the age itself but rather on the interplay between the age and gender (Kahlke et al., 2000; Mees et al., 2007, 2008), given that sex hormones influence the immune response and their production is age-dependent. For example, estrogens have demonstrated strong protective effects in sexually mature mice when subjected to sepsis after traumatic insults (Choudhry, 2005) and to burn injuries alone (Kovacs, 2005). A frequently used model combining laparotomy and hemorrhagic shock (Kahlke et al., 2000; Schneider et al., 2007) showed that, similarly to human patients (Livingston et al., 2003), trauma affects the amount of circulating bone marrow-associated cells in mice (Schneider et al., 2007). Moreover, the same model demonstrated the (clinically valid) phenomenon of compartmentalisation of immune responses in aged mice, resulting in different responses in distinct tissues. For example an enhanced inflammation in the spleen and inflammatory depression in peripheral blood mononuclear cells (PBMC) can occur conincidently (Kahlke, 2000; Schneider et al., 2006).

Recently, more sophisticated polytrauma models combining hemorrhage with bone fractures (Kleber et al., 2015; Wichmann et al., 1998; Wichmann, 1996), chest trauma (Seitz et al., 2011) or cecotomy (Gentile et al., 2013) have been introduced. Their main strength is that they more closely recapitulate the immuno-inflammatory deregulations occurring in trauma patients. These include a reduced cytokine release capacity by splenocytes, peritoneal macrophages (Wichmann et al., 1998; Wichmann, 1996) and PBMCs (Seitz et al., 2011) and a loss of major histocompatibility complex class II and CD4+ cells (Gentile et al., 2013). Similar immuno-inflammatory deficits were shown to be induced in aged mouse burn models (Kovacs et al., 2002, 2004; Plackett et al., 2003; Nomellini et al., 2008; Plotnikov et al., 2013). Although traumatic brain injuries (TBI) typically occurs in very young or old humans (Langlois et al., 2006), experimental mouse studies are primarily performed in young subjects. The only three existing TBI studies comparing young and aged mice demonstrated higher mortality, stronger neurological function deficits and increased inflammatory markers (Kumar et al., 2013; Onyszchuk et al., 2008; Timaru-Kast et al., 2012) in the latter. The most sophisticated, and clinically relevant, approach are so called two-hit models combining these trauma-induced immuno-inflammatory deregulations (e.g. after first-hit hemorrhage, laparotomy, and/or bone fracture insult) and infections/sepsis as a delayed second hit (see below) (Seitz et al., 2011; Gentile et al., 2013; Kovacs et al., 2002, 2004). The most commonly used trauma models and their application in aged animals are listed in Table 1.

Sepsis can originate from many sites in the body, most frequently the lungs, abdomen, urogenital tract and iatrogenic sources (e.g. indwelling catheters) (Angus, 2001; Vincent, 2006) and the elderly (and neonates) are most at risk. As our understanding of sepsis pathophysiology and epidemiology has grown, the murine modeling has been gradually evolving in an attempt to match the complex clinical reality but this evolution is too slow regarding the age component. Currently, the live bacteria pneumonias and