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Review

Inflammation and neutrophil immunosenescence in health and disease: Targeted treatments to improve clinical outcomes in the elderly

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ABSTRACT

Despite increasing longevity, many old people are not in good health. There has been an increase in the prevalence of age-associated multi-morbidity (two or more chronic conditions in the same person). Also, severe infections, such as pneumonia, remain significant causes of mortality and morbidity in this aging group. Many chronic health conditions share risk factors such as increasing age, smoking, a sedentary life style and being part of a lower socioeconomic group. However, despite this, multi-morbidities often co-occur more commonly than would be predicted. This has led to the hypothesis that they share common underlying mechanisms. This is an important concept, for if it were true, treatments could be devised which target these common pathways and improve a number of age-associated health conditions.

Many chronic illnesses associated with multi-morbidity and severe infections are characterized by an abnormal and sustained inflammatory response, with neutrophils being key effector cells in the pathological process. Studies have described aberrant neutrophil functions across these conditions, and some have highlighted potential mechanisms for altered cell behaviours which appear shared across disease states. It has been suggested that altered functions may represent neutrophil "senescence". This review considers how and why neutrophil functions change as the cell ages, and how and why neutrophil functions change as the host ages in health and disease and discusses whether neutrophil functions could be targeted to improve health outcomes in older adults.

1. Introduction

Our population is aging, but longevity is not always associated with good health and an increasing number of our older population are burdened with frailty, ill-health and functional limitation (Parker and Thorslund, 2007). There has been a substantial rise in the prevalence of chronic, non-communicable diseases associated with age (World Health Organisation, 2017). For example, the prevalence of cardiovascular disease (including hypertension, coronary heart disease and heart failure) increases from 40% in people aged 40–59 years of age (Mannino et al., 2008) to 70% in people aged 70 years of age (Lloyd-Jones et al., 2009); Chronic Obstructive Pulmonary Disease (COPD) increases from 8% in adults aged 50 to 20% of adults aged 70 (Hanania and Sharma, 2010). Furthermore, it is increasingly common for an older person to suffer with a number of medical conditions. Multi-morbidity (defined as two or more chronic diseases in one person (Barnett et al., 2012)) affects approximately 65% of over 60 year olds, of which 80% live with disabilities (Barnett et al., 2012) and multi-morbidity accounts for 60% of global deaths (Rizzuto et al., 2017). The World Health Organisation has recognized this burden of ill-health (increased lifespan with multi-morbidity) as a major challenge to be faced by global health care systems (World Health Organization, 2016), and in 2016, the first multi-morbidity care guidelines were published (NIfHaC Excellence, 2016), although the evidence base for multi-morbid health care pathways is limited.

The most common chronic non-communicable diseases are associated with inflammation, for example, COPD (Stone et al., 2012), type 2 diabetes (Ayilavarapu et al., 2010), osteoporosis (Ginaldi et al., 2005) and dementia (Bruunsgaard et al., 1999) and these conditions often co-occur. Recent studies have demonstrated patterns of disease clustering (Jackson et al., 2015), with links seen between cardiovascular disease risk factors and conditions, metabolic conditions, and pain, musculoskeletal and psychological conditions (Déruaz-Luyet et al., 2017). Many of these conditions share risk factors of age, cigarette smoking, lower socioeconomic group, and sedentary lifestyle but the odds ratio of them occurring together are greater than would be predicted once these common shared risk factors are taken into account (Mannino et al., 2008; Sevenoaks and Stockley, 2006).

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As well as chronic illness, there is a significant burden of infection related mortality and morbidity in our aging population. Pneumonia (a severe lung infection defined by symptoms of a lower respiratory tract infection and new consolidative changes on a chest radiograph (Lim et al., 2003)) remains the commonest form of infectious death in the developed world, the fifth leading cause of death worldwide. Pneumonia is diagnosed in approximately 10.6 per 1000 person years (Broulette et al., 2013) but 75 per 1000 person years in adults aged over 70 (Fein, 1999). Deaths are highest in old patients, with mortality rates not improved over the last decade (Lindenauer et al., 2012; Klevens et al., 2008). Far from being an acute infection, many who survive the initial episode are frailer and require more social support than they did prior to admission (Restrepo et al., 2013; Dick et al., 2012). Recovery from the primary infection is also associated with an increased risk of secondary infections, and the outcomes from these events is even less certain (van Vught et al., 2016).

Acute bacterial infections such as pneumonia require a functional immune system, and in particular, a coordinated and controlled innate immune response to clear infection without causing excessive host tissue damage; with the neutrophil being a key effector cell. These cells have been implicated also in the pathogenesis of many of the co-morbidities present in old age. For example, neutrophils are associated with lung tissue destruction in COPD (as reviewed in (Stockley et al., 2013)) but are also implicated in myocardial infarction (de Boer et al., 2013), and type 2 diabetes (Alba-Loureiro et al., 2007) and in more general features of ill health in old age, including frailty (Wilson et al., 2017).

2. Classical neutrophil functions

Neutrophils comprise 70% of circulating white blood cells, but have a short lifespan (approximately a half-life of 8 h) necessitating a high daily production rate of 1–2 $\times$ 10^{11} cells/day in health (Amulic et al., 2012; Galli et al., 2011; Borregaard, 2010). Defined as granulocytes and phagocytes, neutrophils contain a specialized antimicrobial granule system and ingest target particles such as bacteria (Amulic et al., 2012; Faurschou and Borregaard, 2003). During maturation, neutrophils develop their characteristic granules, which are traditionally divided into three sub-types; azurophilic (primary), specific (secondary) and gelatinase (tertiary). Azurophilic granules contain the neutral serine proteinases, (neutrophil elastase, proteinase 3, and cathepsin G) myeloperoxidase (MPO) and other antimicrobial proteins (e.g. α-defensins) (Faurschou and Borregaard, 2003; Klebanoff, 1999). Specific (secondary) granules are also predominantly bactericidal and contain products such as lactoferrin (Faurschou and Borregaard, 2003; Cramer et al., 1985; Oram and Reiter, 1968). Gelatinase (tertiary) granules contain metalloproteases (MMPs) such as gelatinase which digest extracellular matrix and aid neutrophil migration (Amulic et al., 2012; Borregaard and Cowland, 1997). Neutrophils are also able to generate reactive oxygen species (ROS) by NADPH oxidase, an enzyme which is only activated when its cytosol-based and membrane-based component parts bind, a process stimulated by pathogenic and host-derived inflammatory signals (Segal, 2005). Degranulation describes mobilization of granules and fusion with the neutrophil membrane, causing release of contents outside the cell or into a phagosomal vacuole (Faurschou and Borregaard, 2003). When released, granules are both anti-microbial and cytotoxic, and have the potential for significant tissue damage, particularly when they are first released from the neutrophil, as here inhibitors of granule contents (such as Alpha 1 Antitrypsin which inhibits neutrophil elastase) are insufficient in concentration to prevent local protein degradation (Liou and Campbell, 1996).

After release from the bone marrow, neutrophils circulate in systemic blood, displaying high levels of physical plasticity, allowing them to move through capillary networks with diameters half that of the quiescent neurophil by elongating their cell shape, without significant delay in transit times (Summers et al., 2010; Summers et al., 2014). Towards the end of their short half-life, neutrophils develop an aging phenotype with increased surface expression of CXCR4 (Furze and Rankin, 2008) which is thought to facilitate clearance by apoptosis and subsequent efferocytosis (clearance of neutrophils by phagocytosis) by stromal macrophages.

During an inflammatory or infectious challenge, neutrophils migrate with great accuracy through tissue to sites of infection and inflammation, where they phagocytose bacteria and cell debris. Direction sensing is achieved via occupancy of G-protein coupled receptors (GPCRs) on the surface of the neutrophil, as soluble chemo-attractants (such as Interleukin-8 (CXCL8) or bacterial N-formyl-methionyl-leucylphenylalanine (fMLP)) form gradients, which neutrophils sense by the binding of ligands to receptors at the leading edge of the cell (Raman et al., 2010). When chemokine's bind their cognate receptors, dissociation of heterotrimeric G proteins activate phosphatidylinositol-3 kinase (PI3K), an enzyme which has been implicated in the regulation of migration (Hannigan and Huang, 2003), phagocytosis (Botelho et al., 2000) and azurophil degranulation (Ito et al., 2002). PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3). In health, fluctuations in PIP_3 are associated with the localized formation of pseudopodia (temporary cytoplasm-filled projections from the neutrophil cell membrane), which steer the cytoskeletal rearrangement required to orient the neutrophil to chemo-attractant cues (Yoo et al., 2010) and are required for migration and opsonophagocytosis. There are a number of PI3K classes and isoforms, but Class 1 delta and gamma isoforms are highly expressed in neutrophils, and thought central to accurate migration. Downstream of PI3K, the small GTPases (RhoA, Rac and CDC42) organize cell polarity, motility and phagocytosis with Rac and CDC42 localizing at the leading edge of the cell (Burridge and Doughman, 2006) and RhoA and ROCK driving propulsion at the rear of the cell (Charest and Firtel, 2007). Migration through the dense extracellular matrix is facilitated by the sequential release of proteinases and reactive oxygen species around the neutrophil (Cepinskas et al., 1999), degrading a path to assist passage. Thus, the process of migration can be associated with tissue damage.

Phagocytosis is an active, receptor mediated process (Amulic et al., 2012). In unopsonized phagocytosis, interactions between neutrophilic pattern recognition receptors (PRRs) (such as Toll Like Receptors (Hayashi et al., 2003)) and surface-expressed pathogen-associated molecular patterns (PAMPs) support slow bacteria envelopment (Amulic et al., 2012). Opsonized phagocytosis is a much more dynamic process, where neutrophils internalize bacteria through their opsonin receptors, Fc receptors and a sub-group of β2-integrins, which bind complement (Lee et al., 2003). In the presence of overwhelming infection or during ingestion of large particles, neutrophils display “frustrated phagocytosis” where they degranulate and release proteinases and reactive oxygen species around the semi-internalized particle into the extracellular matrix (Kovari et al., 2016), causing localized tissue damage. More recently, Neutrophil Extracellular Traps (NETs) have been described, which are large, complex, fibrous structures formed from nuclear chromatin and granular proteins (Brinkmann et al., 2004) which are extruded from neutrophils to ensnare bacteria, bringing them into close association with antimicrobial proteins. These appear to represent a neutrophil's final response to overwhelming infection and inflammation but are also associated with significant local tissue damage (Liu et al., 2016), caused in part by the effects of proteinases which are more resistant to anti-proteinase inhibition when membrane bound (Owen et al., 1995). Fig. 1 provides an overview of these functions.

Neutrophils are thought to exist in three states; quiescent, activated or primed (Sapey and Stockley, 2014). An activated cell is able to degranulate, produce significant quantities of ROS and release NETs, all of which could harm host tissue. Priming appears to be an intermediate and protective step prior to full activation, from which a cell can step up, and become activated, or step down, and become quiescent, providing a natural break before bactericidal and cytotoxic products are released (Sapey and Stockley, 2014).