Ageing Research Reviews 12 (2013) 1069–1078

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

The impact of ageing on natural killer cell function and potential consequences for health in older adults

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ARTICLE INFO

Article history:
Received 6 March 2013
Received in revised form 20 April 2013
Accepted 25 April 2013
Available online 6 May 2013

Keywords:
Natural killer (NK) cells
Ageing
Immunesenescence

ABSTRACT

Forming the first line of defence against virally infected and malignant cells, natural killer (NK) cells are critical effector cells of the innate immune system. With age, significant impairments have been reported in the two main mechanisms by which NK cells confer host protection: direct cytotoxicity and the secretion of immunoregulatory cytokines and chemokines. In elderly subjects, decreased NK cell activity has been shown to be associated with an increased incidence and severity of viral infection, highlighting the clinical implications that age-associated changes in NK cell biology have on the health of older adults. However, is an increased susceptibility to viral infection the only consequence of these age-related changes in NK cell function? Recently, evidence has emerged that has shown that in addition to eliminating transformed cells, NK cells are involved in many other biological processes such as immune regulation, anti-microbial immune responses and the recognition and elimination of senescent cells, novel functions that involve NK-mediated cytotoxicity and/or cytokine production. Thus, the decrease in NK cell function that accompanies physiological ageing is likely to have wider implications for the health of older adults than originally thought. Here, we give a detailed description of the changes in NK cell biology that accompany human ageing and propose that certain features of the ageing process such as: (i) the increased reactivation rates of latent *Mycobacterium tuberculosis*, (ii) the slower resolution of inflammatory responses and (iii) the increased incidence of bacterial and fungal infection are attributable in part to an age-associated decline in NK cell function.

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Abbreviations: ADCC, antibody dependent cell cytotoxicity; Apaf-1, apoptosis-activating factor 1; BID, BH3-interacting domain; CAD, caspase-activated DNase; CMV, cytomegalovirus; DC, dendritic cell; DLN, draining lymph node; FasL, Fas ligand; FADD, Fas-associated protein with death domain; iCAD, inhibitor of caspase-activated DNase; IFN-γ, interferon gamma; IL-8, interleukin 8; KIR, killer cell immunoglobulin like receptor; MHC, major histocompatibility complex; MIC, MHC class I-chain-related protein; MIP-1α, macrophage inflammatory protein-1-alpha; NCR, natural cytotoxicity receptor; NK cell, natural killer cell; NKCC, natural killer cell cytotoxicity; PARP, poly ADPribose polymerase; PBLs, peripheral blood lymphocytes; PMA, phorbol 12-myristate 13-acetate; TB, *Mycobacterium tuberculosis*; tBID, truncated BH3-interacting domain; TNF-α, tumour necrosis factor alpha; Th-1, T helper 1 cell; TRAIL, tumor necrosis factor related apoptotic-inducing ligand.

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http://dx.doi.org/10.1016/j.arr.2013.04.003

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1. Introduction

Comprising 10–15% of the circulating lymphocyte pool, natural killer (NK) cells are large granular lymphocytes of the innate immune system renowned for their ability to recognise and eliminate virally infected, stressed and malignant cells. In humans, NK cells, whose defensive strategies include direct cytotoxicity and the secretion of immunoregulatory cytokines and chemokines, are defined by a $CD3^-$ $CD56^+$ surface phenotype. However, they are not a homogenous population, as based on the differential surface expression of CD56, NK cells are categorised into two major subsets: $CD56^{DIM}$ and $CD56^{BRIGHT}$, which differ both in their receptor profile and function (Cooper et al., 2001a).

Physiological ageing is associated with changes in the composition, phenotype and function of the circulating NK cell pool, a phenomenon referred to as NK cell immunesenescence (Solana et al., 1999; Solana and Mariani, 2000; Tarazona et al., 2012). As NK cells represent the first line of defence against virally infected cells, immunogerontological studies often introduce or conclude their work by proposing that NK cell immunesenescence contributes to the higher incidence of viral infection that is reported by older adults (Mariani et al., 1996; Rukavina et al., 1998; Mariani et al., 2002a; Hayhoe et al., 2010). However, over the past decade, data has emerged demonstrating that NK cell function extends beyond merely the recognition and elimination of transformed cells, with studies being published implicating a role for NK cells in: (i) anti-microbial defence (Small et al., 2008; Schmidt et al., 2011), (ii) the clearance of senescent cells (Sagiv et al., 2012), (iii) the resolution of inflammation (Thoren et al., 2012; Waggoner et al., 2012) and (iv) modulating adaptive immunity (Martin-Fontecha et al., 2004; Vitale et al., 2005). Thus, NK cell immunesenescence may have more far reaching effects upon the health of older adults than simply increasing their susceptibility to viral infection.

Here, after discussing NK cell function and the changes in NK cell biology that occur with age, we review data which suggest that in addition to the previously described association between reduced NKCC in older adults and an increased incidence of viral infection (Levy et al., 1991; Ogata et al., 1997, 2001) that other features of the ageing process may be attributable in part to age-related alterations in NK function and phenotype. These include: (i) the increased reactivation rates of latent *Mycobacterium tuberculosis* (TB), (ii) reduced vaccination efficacy, (iii) slower resolution of inflammatory responses and (iv) the accumulation of senescent cells.

1.1. NK cell function

NK cell cytotoxicity (NKCC) and the secretion of cytokines and chemokines are the two main mechanisms NK cells use to eliminate transformed and virus-infected cells. Induction of these defensive strategies is governed by signals transmitted through germline-encoded activatory and inhibitory receptors (Lanier, 1998). Inhibitory receptors, which include members of the killer-cell immunoglobulin-like receptor (KIR) superfamily and the C-type lectin family member CD94/NKG2A, recognise self major histocompatibility complex (MHC) class I molecules and transmit inhibitory signals through an immunoreceptor tyrosine-based inhibitory motif within their cytoplasmic domain (Lanier, 1998; Pegram et al., 2011). Examples of activatory receptors are the natural cytotoxicity receptors (NCR) NKp30, NKp44 and NKp46, which recognise viral haemagglutinin (Arnon et al., 2001; Mandelboim et al., 2001) and bacterial surface proteins (Esin et al., 2008), the Fc receptor CD16, which allows NK cells to perform antibody dependent cell cytotoxicity (ADCC) and the C-type lectin family member NKG2D, whose ligands include the stress-inducible glycoproteins MHC class I-chain-related protein A (MICA) and MICB (Bauer et al., 1999).

1.1.1. NKCC

NK cells directly eliminate transformed cells through two contact-dependent mechanisms: granule exocytosis and death receptor ligation (Fig. 1; Smyth et al., 2005). Of these, granule exocytosis, which is performed predominantly by $CD56^{DIM}$ NK cells, is the main pathway by which NK cells confer host protection (Sayers et al., 1998; Smyth et al., 1999), and is characterised by the secretion of cytotoxic proteins into the immunological synapse that forms between an NK cell and its target (Fig. 1A; Smyth et al., 2005). Of the proteins released, it is the membrane-disrupting protein perforin and a family of serine proteases termed granzymes that are the critical effector molecules.

Current work suggests that after binding to phospholipid components of the target cell membrane, perforin undergoes polymerisation, triggering a membrane-repair response within the target cell that results in the co-endocytosis of membrane-bound perforin and granzymes (Thiery et al., 2010, 2011). Once inside the target cell, perforin has been shown to induce endosomal lysis, leading to the release of granzymes into the cytosol (Thiery et al., 2010, 2011). Human NK cells express five granzymes, namely A, B, H, K and M (Smyth et al., 2005). Of these, granzyme B has been the subject of considerable interest. As an aspartase, granzyme B cleaves proteins after aspartic acid residues. Consequently, several members of the caspase family are directly activated by granzyme B, including caspase 3 (Goping et al., 2003). This effector caspase induces apoptosis by several mechanisms, which include: (1) activating the endonuclease caspase-activated DNase (CAD) by degrading its inhibitory binding partner, inhibitor of caspase-activated DNase (iCAD) and (2) degrading proteins involved in DNA repair (e.g. poly ADPribose polymerase (PARP)) (Fig. 1A; Heusel et al., 1994; Darmon et al., 1995; Chinnaiyan et al., 1996; Taylor et al., 2008). As well as direct activation, granzyme B activates caspases 3 and 7 indirectly by driving mitochondrial permeabilisation (Fig. 1A). This occurs via granzyme B-mediated cleavage of the BH-3 family protein BH3-interacting domain (BID) death agonist into its truncated form (tBID). Once formed, tBID translocates to the mitochondria where it induces permeabilisation, leading to the release of the pro-apoptotic protein cytochrome c into the cytosol (Fig. 1A; Alimonti et al., 2001). Here, cytochrome c associates with ATP, apoptosis-activating factor 1 (Apaf-1) and pro-caspase 9, forming a structure referred to as the apoptosome (Bao and Kumar, 2007). Formation of this complex results in the activation of caspase 9, which subsequently mediates cell death by cleaving and activating caspases 3 and 7 (Fig. 1A; Bao and Kumar, 2007). In addition to mediating caspase-dependent apoptosis, granzyme B can trigger target cell death in a caspase-independent manner. This is