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Senescent B cells in aging and age-related diseases: their role in the regulation of antibody responses

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Abstract

Immune cells with a senescence-associated secretory phenotype increase in the blood of elderly individuals or individuals with age-associated diseases or with infections. Although senescent immune cells do not proliferate, they are transcriptionally and metabolically active and affect the microenvironment through the secretion of pro-inflammatory mediators. An age-driven increase in senescent B, T and NK cells has been reported and the function of these cells has been characterized. Results published by different groups have demonstrated that cell senescence induces the accumulation of terminally-differentiated cells characterized by the arrest of cell proliferation but with an active secretory profile which regulates their function through the activation of pathways integrating senescence and energy-sensing signals. This review will focus on senescent B cells, their increase in aging, age-associated conditions and infections. Similarities with other senescent immune cells will be presented and discussed.

Keywords

Antibody responses; B cells; Inflammation; Cell senescence

1. Introduction

Aging is characterized by increased low-grade chronic inflammation, called “inflammaging” (Franceschi and others 2000), which represents a significant risk factor for morbidity and mortality of elderly individuals as it is implicated in the pathogenesis of several disabling diseases of the elderly, including Type-2 Diabetes, osteoporosis, Alzheimer’s disease, Rheumatoid Arthritis, atherosclerosis (Alexopoulos and others 2014; Libby 2012) and coronary heart disease (Holmes and others 2009; Isaacs 2009; Lindholm and others 2008; Mundy 2007; Sarzi-Puttini and others 2005). Circulating inflammatory mediators such as cytokines and acute phase proteins, are markers of inflammaging. Among these, elevated

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serum levels of IL-6 and C-Reactive Protein, have been shown to predict 3-year mortality in the elderly by the Invecchiare in Chianti study (Alley and others 2007).

The ways in which inflammaging contributes to adverse health outcomes is not completely understood, and therefore the identification of pathways controlling inflammaging across multiple systems is important, in order to design protocols of intervention to reduce inflammaging and potentially improve the health of elderly individuals.

Several factors contribute to inflammaging, including polymorphisms in the promoter regions of pro-inflammatory genes, chronic stimulation of immune cells with viruses such as cytomegalovirus (CMV), obesity, changes in the gut microbiome, increased permeability from the intestine [reviewed in (Frasca and Blomberg 2016)]. Cellular senescence has also been proposed to be a significant contributor to inflammaging, due to the acquisition of the senescence-associated secretory phenotype (SASP) by fibroblasts (Freund and others 2010), endothelial cells (Olivieri and others 2013) and immune cells (Sikora and others 2011). A large-scale characterization of the SASP has been performed in fibroblasts and endothelial cells using antibody arrays to quantitatively measure pro-inflammatory mediators, such as cytokines, chemokines, micro-RNAs, growth factors and proteases (Campisi 2011). Work under way is aiming at thoroughly characterize the senescent secretome of immune cells.

Senescent cells are characterized by the arrest of cell proliferation and have short telomeres, but they are transcriptionally and metabolically active. This high activity of senescent cells derives from the SASP, which leads to the secretion of multiple factors with potent biological activities on surrounding cells and tissues.

The term “senescence” has recently generated controversy within the aging field, especially because the arrest of cell proliferation has been observed in highly differentiated immune cells which can secrete multiple factors regulating their function. In the case of B cells, these highly differentiated cells represent the terminally-differentiated subset, as they derive from IgM or switched memory B cells (Bagnara and others 2015). This process of differentiation seems to occur through the activation of non canonical pathways integrating senescence (Frasca and others 2017a) and energy-sensing signals (Torigoe and others 2017), similar to what has been shown for T (Henson and others 2014; Henson and others 2015; Lanna and others 2014) and NK (Muller-Durovic and others 2016) cells.

Changes in glucose levels in the extracellular milieu occur with age (Spazzafumo and others 2013), and may be responsible for decreased function, as B cells utilize glucose for proliferation and differentiation (Caro-Maldonado and others 2014), as it has also been shown for T cells (Heikamp and Powell 2012; Verbist and others 2012; Xu and others 2012) and macrophages (Recalcati and others 2012). Briefly, T cell activation leads to metabolic reprogramming characterized by a rapid increase in the expression of glucose transporters to support glycolysis over oxidative metabolism and pathways of this metabolic reprogramming have been characterized (Frauwirth and others 2002; Rathmell 2012). Similar to T cells, B cells also increase the expression of glucose transporters and mitochondrial mass upon mitogen or antigen stimulation, and deletion of glucose transporters reduces B cell numbers and antibody production (Caro-Maldonado and others

2014). Experiments in our laboratory are currently evaluating the energy metabolism of the different B cell subsets, by performing gene expression analysis of pathways related to the glucose metabolism, measuring glucose uptake upon cell stimulation, and determining mitochondrial morphology, abundance and function.

2. Senescent B cell subsets are increased in the blood of healthy elderly individuals

Inflammaging is associated with changes in the distribution of B cell subsets in the peripheral blood. Four major peripheral B cell subsets can be measured by flow cytometry in the human blood: naive (IgD+/CD27−), IgM memory (IgD+/CD27+), switched memory (IgD−/CD27+), late memory (LM, IgD−/CD27−). We have shown that LM B cells are increased in percentages (and numbers) in the blood of healthy elderly *versus* young individuals (Frasca and others 2017a; Frasca and others 2017b; Frasca and others 2016), similar to what has also been reported by other groups (Martorana and others 2014; Rinaldi and others 2017). Phenotypic and functional characteristics of LM B cells are summarized in Table 1.

The frequency of LM B cells in blood has been found to be negatively associated with a protective response against the influenza vaccine, measured by hemagglutination inhibition assay at t28 (one month after influenza vaccination) (Frasca and others 2017a), or by the frequency of plasmablasts in blood at t7 (one week after influenza vaccination) (Rinaldi and others 2017). Both measures represent good correlates of vaccine protection. This negative association was expected, based on the fact that this B cell subset is highly inflammatory and has been reported to show characteristics of cell senescence, such as poor ability to proliferate *in vitro* in response to mitogenic stimulation and reduced telomerase activity (Colonna-Romano and others 2009; Martorana and others 2014).

Although LM B cells do not proliferate *in vitro* in response to mitogenic stimulation, they are transcriptionally active. In our recently published work (Frasca and others 2017a), we have evaluated the functional quality of the B cell pool, as this influences the individual's response. We have shown that unstimulated memory but not naïve B cells from both young and elderly individuals, evaluated at t0 (before vaccination), express RNA for multiple SASP markers, such as the pro-inflammatory cytokines TNF-α/IL-6/IL-8 and for the pro-inflammatory micro-RNAs (miRs)-155/16/93. Levels are higher in B cells from elderly *versus* young individuals. Among memory B cell subsets, the LM subset expresses the highest level of SASP markers.

Unstimulated memory but not naïve B cells from both young and elderly individuals also express RNA for $p16^{INK4}$ with the LM subset showing the highest levels of this SASP marker. The fact that switched memory and IgM memory B cells from elderly individuals show higher levels of expression of SASP markers as compared to younger individuals may help to explain their decreased function in the elderly. Through secretion of these pro-inflammatory mediators, LM B cells affect the microenvironment and in turn sustain and propagate the inflammatory response and negatively regulate the function of other immune cells. We have indeed previously shown that the levels of endogenous TNF-α in B cells

negatively impact their ability to proliferate, differentiate and generate optimal antibody responses (Frasca and others 2014). These results demonstrate that basal (pre-stimulation) levels of TNF-α in B cells negatively impact the ability of the same B cells to generate optimal function. Moreover, pre-incubation of B cells with an anti-TNF-α antibody, before in vitro stimulation, significantly increase B cell function, indicating that it is possible to improve B cell function and antibody production by counteracting intrinsic levels of TNF-α (Frasca and others 2014). Recent evidence from our laboratory has shown that if LM cells are sorted out from the total B cell pool, class switch increases, and more in individuals with high endogenous levels of TNF-α (manuscript in preparation).

LM B cells are also characterized by $CD95^{high}$, $CD21^{low}$, T-bet and CD11c expression as compared to the B cell subsets (Frasca and others 2017b). Up-regulation of CD95 (Fas ligand) (Jacobi and others 2008) and down-regulation of CD21 (complement receptor type 2, complement C3d receptor, or Epstein-Barr virus receptor) (Moir and others 2008) have been shown to be independently associated with B cell activation. Moreover, experiments in mice have shown that T-bet+CD11c+ B cells are potent antigen-presenting cells in viral immunity and autoimmunity (Rubtsov and others 2015). It is likely that the *in vivo* accumulation of LM B cells with age is due to the terminal differentiation of subsets that have undergone class switch after (chronic) exposure to antigens such as CMV and we have evidence (unpublished) that LM B cells increase 3–4 fold in the blood of CMV-seropositive individuals as compared to CMV-seronegative controls. We believe that these cells control latent infections through the secretion of specific IgG antibodies. Similarly, these cells may accumulate in response to autoantigen stimulation, and they may secrete IgG antibodies, such as anti-nuclear and anti-cardiolipin, which are frequently found in the blood of healthy elderly individuals. Both hypotheses still need to be validated.

LM B cells express markers associated with homing to sites of inflammation, including the chemokine receptor CXCR3 (Bulati and others 2014) and CD11c (Frasca and others 2017b), the expression being higher in LM from the elderly than in those from the young, suggesting that these cells may migrate to inflamed tissues and contribute to local inflammation by secretion of pro-inflammatory mediators. The ligands of CXCR3, CXCL9 and IP10 (CXCL10), are indeed expressed by endothelial and epithelial cells in inflamed tissues and B cells expressing CXCR3 can directly enter these tissues from the blood.

The expression of SASP markers in LM B cells (but not in IgM memory B cells) is associated with activation of NF-kB, due to spontaneous activation of AMP-activated protein kinase (AMPK), the energy-sensing enzyme and key metabolic regulator ubiquitously expressed in mammalian cells (Ruderman and Prentki 2004). This leads to spontaneous p38MAPK and NF-kB activation, suggesting that senescence and energy-sensing signaling pathways converge to regulate functional responses in these cells (Frasca and others 2017a).

Similar to LM B cells, terminally-differentiated CD4+ T cells (Henson and others 2014; Henson and others 2015; Lanna and others 2014) show spontaneous activation of AMPK which leads to the recruitment of p38MAPK to the scaffold protein TAB1 and consequent p38MAPK phosphorylation, resulting in inhibition of telomerase activity, T cell proliferation and TCR signaling.

NK cells showing high expression of the inhibitory killer cell lectin-like receptor (KLRG1) increase with aging, are considered terminally-differentiated and are less functional as compared to those that are KLRG1^{low}. This has been associated with spontaneous phosphorylation of AMPK which is further amplified by ligation of KLRG1 on the surface of these cells, leading to impaired cytotoxicity, IFN-γ production, telomerase activity and proliferation (Muller-Durovic and others 2016).

We believe that the signaling pathways leading to the spontaneous activation of AMPK in terminally-differentiated B, T and NK cell subsets should be interrogated as the detrimental effects of chronic AMPK activation may overshadow the beneficial systemic effects of treatments like Metformin, now used in clinical trials to target aging and age-related diseases (i.e. “Targeting Aging with Metformin”, TAME clinical trial).

3. Senescent B cell subsets in age-associated diseases and infections

The senescent LM B cell subset is significantly increased in the blood of patients with Rheumatoid Arthritis (Adlowitz and others 2015), SLE (Wehr and others 2004), Multiple Sclerosis (Claes and others 2016), Sjogren (Saadoun and others 2013) or Alzheimer’s disease (Bulati and others 2014; Martorana and others 2014); in the blood of individuals infected with HIV (Meffre and others 2016; Moir and others 2008), Hepatitis C (Chang and others 2016) or malaria (Illingworth and others 2013; Portugal and others 2015); in the blood of individuals with obesity (Frasca and others 2016). In all the conditions above, senescent LM B cells have been called with different names, such as tissuelike, double negative, or atypical memory B cells. Nevertheless, they represent the most pro-inflammatory B cell subset, with low proliferative capacity and an immune activated phenotype characterized by the expression of CD95^{high}, CD21^{low}, CD11c, T-bet. These cells also express inhibitory receptors (FcR-like family), leading to decreased B cell receptor signaling, impaired proliferation and antibody production.

The fact that LM B cells are increased in the blood of patients with autoimmune and infectious diseases suggests that these cells may expand *in vivo* in the presence of autoantigens or pathogen-derived antigens, in the context of a favorable inflammatory microenvironment, leading to the production of pathogenic (autoimmune) or virus-specific antibodies, respectively. In HIV-infected individuals it has indeed been reported an enrichment of HIV-specific (HIV envelope gp120) antibody responses within the subset of LM B cells (called tissuelike in HIV-infected individuals), whereas influenza-specific antibody responses have only been observed in classical memory B cells (Moir and others 2008).

4. Conclusions

Lymphocyte metabolism has been shown to regulate the function of immune cells. Specific signaling pathways provide energy to support cell function. However, if energy sources or metabolic pathways of lymphocytes are dysregulated, as it has been shown to occur during aging, metabolic checkpoints can become activated and cell function becomes impaired.

Results reported in this review clearly indicate that during aging not only senescence-associated signaling but also “non canonical” energy-sensing signaling pathways become activated and these may be responsible for the accumulation of dysfunctional terminally-differentiated immune cells. The observation that in elderly individuals B, T and NK cells (and maybe also other immune cells) share these signaling pathways suggests the possibility to use a single therapeutic intervention (for example diet) to target different cell types and improve the health of the elderly population.

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HIGHLIGHTS

1. Senescent B cells increase with age
2. Their frequency in blood is negatively associated with a protective response against the influenza vaccine
3. Senescent B cells do not proliferate
4. They are transcriptionally active and express multiple SASP markers
5. Senescent B cells preferentially activate energy-sensing signaling pathways

Table 1

Phenotypic and functional characteristics of LM B cells from healthy individuals

MEASURE	REFERENCES
Membrane markers of immune activation	
$CD95^{high}$	Adlowitz (2015), Frasca (2017b)
$CD21^{low}$	Adlowitz (2015), Claes (2016), Frasca (2017b)
CD11c	Claes (2016), Frasca (2017b)
Chemokine receptors	
CXCR3	Bulati (2014)
Inflammatory cytokines/chemokines	
TNF-α/IL-6/IL-8	Frasca (2017a)
Inflammatory micro-RNAs (miRs)	
miR-155, miR-16, miR-93	Frasca (2017a)
Cell cycle regulators	
$p16^{INK4}$	Frasca (2017a)
Telomere length	
Short	Colonna-Romano (2009), Martorana (2014)
Cell proliferation	
Reduced	Colonna-Romano (2009)
Spontaneous AMPK/p38MAPK/NF-kB activation	
High	Frasca (2017a)
T-bet expression	
High	Chang (2016), Frasca (2017b)
Class switch and antibody secretion	Frasca (2017a), Frasca (manuscript in preparation)
Reduced	

Results indicate changes in expression/function as compared to the other B cell subsets (naïve, IgM memory, switched memory) from both young and elderly individuals