Title: The emerging role of ECM crosslinking in T cell mobility as a hallmark of immunosenescence in humans

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Abstract

Immunosenescence is thought to result from cellular aging and to reflect exposure to environmental stressors and antigens, including cytomegalovirus (CMV). However, not all of the features of immunosenescence are consistent with this view, and this has led to the emergence of the sister theory of “inflammaging”. The recently discovered diffuse tissue distribution of resident memory T cells (T_{RM}) which don't recirculate, calls these theories into question. These cells account for most T cells residing in barrier epithelia which sit in and travel through the extracellular matrix (ECM). With almost all studies to date carried out on peripheral blood, the age-related changes of the ECM and their consequences for T cell mobility, which is crucial for the function of these cells, have been largely ignored. We propose an update of the theoretical framework of immunosenescence, based on a novel hypothesis: the increasing stiffness and cross-linking of the senescent ECM lead to a progressive immunodeficiency due to an age-related decrease in T cell mobility and eventually the death of these cells. A key element of this mechanism is the mechanical stress to which the cell cytoplasm and nucleus are subjected during passage through the ECM. This hypothesis is based on an “evo-devo” perspective bringing together some major characteristics of aging, to create a single interpretive framework for immunosenescence.

Keywords: aging, immunosenescence, extracellular matrix, mobility, immune cells.

Contents

1. Introduction

Immunosenescence is defined as age-related changes in the immune system. It is associated with a progressive deterioration of the ability to mount immune responses and with a higher mortality rate in the elderly. Immunosenescence is currently thought to depend on lifelong antigen load, leading to the senescence of cells in the immune compartment, with a prominent role attributed to the chronic anti-cytomegalovirus (anti-CMV) response. There seems to be an increasing use of immune resources allocated to the anti-CMV response with aging, a process that ultimately leads to exhaustion. The cause remains unclear and in humans the few studies examining the presence of viral reactivation in the blood, found it negative. More data are therefore needed in the field of human aging in order to conclude on this point (McVoy and Adler, 1989) (Stowe et al., 2007) (Pawelec and Derhovanessian, 2011) (Parry et al., 2016). The role of CMV in immunosenescence is clearly important, but, rather than being directly causal, can also be interpreted as a consequence of more general age-related changes in the three-dimensional microenvironment in which most immune cells are mobile and operate, the ECM. Immunologists have neglected the implications of such changes, partly because most of the studies carried out on immunosenescence, at least until very recently, focused on blood because it is the most accessible source of cells and biological fluid in humans. Although of value, these data, lead to an overestimated qualitative and quantitative importance of this compartment in the understanding of the immune system physiology. The recent discovery of resident memory T cells, or $T_{RM,}$ showed immune surveillance to be largely local and, therefore, not readily accessible through studies on blood [see for review (Carbone, 2015)].

Here, we argue that efforts to decipher immunosenescence must consider both blood and the ECM. The T_{RM} are located in the ECM, and the known biochemical and biophysical modifications to this medium associated with aging consequently hampers local immune surveillance by these cells. ECM proteins and proteoglycans have well-documented roles in scaffolding, but they also have a profound effect on cell behavior, through interactions with secreted ligands or cell-transmembrane receptors, in particular integrins. We suggest that the progressive and irreversible age-related changes in the extracellular matrix may actually provide a unifying framework explaining all the molecular and cellular features of immunosenescence. The key point is that for the immune cells to be functional, they must be free to recirculate, navigate and rest within the extracellular matrix, in tissues and organs. This point is instrumental in tissue surveillance and protection (Ariotti et al., 2012) even in the absence of peripheral lymphocytes (Steinbach et al., 2016). We will consider immunosenescence within this framework, focusing on the adaptive immune system and T cells in particular, even though these cells are neither the only ones to be affected during aging nor the only ones concerned with mobility.

We argue that the mobility of immune cells in non-lymphoid tissues is a necessary element for effective immunity. A lack of immune cell mobility, either *intrinsic*, as in hereditary defects affecting actin remodeling for example as we will see later, or *extrinsic*, as in aging, results in an impairment of immune responses. No three-dimensional (3D) model of deregulated cell mobility has ever been proposed or explored in the context of immunosenescence. We show here that our hypothesis is more consistent with the available data than current alternative theories. We hope that this hypothesis which is based on reviews of fields that have not hitherto be connected together will promote future studies, *in silico* and *in vitro*, to validate this theory experimentally. The 3D model can reconcile many features of aging, such as the altered responses to vaccination, which is in essence both a memory and a local process, and dysfunctions of peripheral tolerance (autoimmunity). The chronic process of T cell death due to mechanical stress within the cross-linked mesh of the aged ECM may also account for activation of the inflammasome (IL1, IL18, NFκB), leading to inflammaging, and to a state of immune deficiency typical of aged subjects. These two elements together underlie the phenomenon of viral reactivation (at the beginning local and ultimately systemic) leading to the clonal amplification of $CD8^+$ T cells and an increase in the proportion of memory T cells found in the blood (Sylwester et al., 2005) (Nikolich-Zugich, 2008) (Fulop et al., 2013) (Fulop et al., 2015).

A large amount of T cells in the body are tissue-resident memory T cells that don't recirculate, as demonstrated by the most recent studies (Thome and Farber, 2015) (Park and Kupper, 2015) (Carbone, 2015) (Steinert et al., 2015) (Fan and Rudensky, 2016). Physiological mobility in ECM and its impact on T cell survival and differentiation are therefore of the utmost importance, including for local anti-CMV defense (Thom and Oxenius, 2016). T cell survival is impaired in very constrained environments, as the forced passage of the cells in such constrained

conditions leads to multiple damage to the plasma membrane and nucleus, potentially culminating in cell death (Denais et al., 2016) (Raab et al., 2016). Inflammasomes are activated in response to incremental production of danger signals coming either from inside or outside the cells (Ostan et al., 2015) and leading to production of IL1, IL18 as well as the activation of the NFκB pathway typical of inflammaging (Franceschi and Campisi, 2014). Furthermore, limited mobility decreases the numbers of the most needed T cells locally present in tissues, leading to: (i) viral reactivation not necessarily detected in blood, due to a lack of proper local immunosurveillance as shown in hereditary immune deficiencies resulting in severely impaired lymphocyte mobility; (ii) clonal expansion of a very limited range of T cells following antiviral responses; (iii) repertoire reduction due to homeostatic forces in the absence of the thymus, as homeostasis is purely about maintaining cell numbers, not their diversity. All these factors are additional features typical of aging, mutually enhanced in a vicious circle that, we suggest, is mediated by age-related ECM degradation and a direct consequence of impaired lymphocyte mobility.

We will develop this idea and its consequences through a series of steps. We will first (Section 2) discuss aging by focusing, in particular, on the aging of the immune system (immunosenescence). We will relate the importance of immune cell mobility to the mechanisms underlying ECM aging and cross-linking, which increase the constraints on cell mobility.

We will highlight the functional consequences of lower T cell mobility and T cell death, through well-known hereditary immune deficiencies resulting in impaired T cell mobility, such as DOCK8, Coronin-1, CDC42 or PGM3 deficiencies.

We will then (Section 4) associate the impaired mobility of T cells with ECM aging. Finally (Section 5), we will discuss the likely specific consequences of this lack of motility and induced cell death for establishment of the immunosenescence phenotype.

2. Aging and immunosenescence: current knowledge and the biases of previous studies based on blood

Over the last 30 years, considerable efforts have been made to understand the relationship between aging and the decline of the immune system and the contribution of immunosenescence to the phenotypes observed in aging individuals (Franceschi et al., 2000) (Franceschi et al., 2000a) (Salvioli et al., 2006). These phenotypes include the accumulation of $CD8^{+}CD28^{-}$ cells, CMV seropositivity, and an inversion of the CD4/CD8 ratio, part of the immune risk profile (IRP) that seems to predict mortality in people over the age of 65 (Hadrup et al., 2006).

One key question concerns the extent to which thymic mature lymphocyte output contributes to T cell homeostasis, and therefore, the extent to which age-related changes in this organ can be considered to drive T cell aging. Maintenance of the naive T cell pool is highly

dependent on thymic output in aging mice. In humans it seems to be based mainly on the peripheral division of pre-existing T cells, in a phenomenon known as homeostatic proliferation, as demonstrated in cases of neonatal thymectomy (Johnson et al., 2012) (Sauce et al., 2012) (den Braber et al., 2012) (Thome and Farber, 2015) (van den Broek et al., 2016). The global repertoire of naive $CD4^+$ T cells remains diverse until ninth decade of life, when there seems to be an increase in cell turnover, rapidly followed by repertoire contraction. A loss of thymic T cell output can, therefore, be quantitatively compensated by homeostatic proliferation in ordinary conditions, without further consequences due to the wide diversity of the repertoire. However, homeostatic proliferation cannot compensate for a loss of T cell diversity. In elderly individuals with a continual, progressive, stochastic loss of T lymphocytes due to an external cause, and characterized by a cumulative effect over time, homeostatic proliferation of the remaining cells accelerates the loss of T cell diversity, by diluting out existing minority clones (Goronzy and Weyand, 2005). Regardless of the actual age of the patient, advanced HIV infection, characterized by a massive and continuous loss of T cells, seems to reproduce some features of aging, with underlying immunosenescence and inflammaging (Nixon and Landay, 2010) (Zapata and Shaw, 2014). Therefore, both in aging subjects and in patients with advanced HIV infection, immunosenescence of the adaptive immune system is not a simple deterioration of the immune system. Instead, it results from a dynamic drift under the pressure of continuous exposure to an antigenic load and an increasingly limited capacity to generate new TCR-bearing cells, leading to the accumulation of memory T cells and an age-associated decline in T cell repertoire diversity (Yager et al., 2008). Notably, decrease in naive T cell levels, leading to repertoire shrinkage, has also been reported in aging apes (Cicin-Sain et al., 2007).

The causal mechanisms underlying these adaptations have yet to be identified, but are almost certainly diverse. However, homeostatic proliferation to correct imbalances in the number of T cells involves the recognition of self–determinants by naive T cells (Richards et al., 2016), which may constitute an important link between aging and autoimmunity (Khiong et al., 2007).

The environmental context in which the cells are found must also be considered, in addition to the reported cell-autonomous defects and stem-cell aging [see for review (Montecino-Rodriguez et al., 2013). The importance of cell environment is highlighted by two remarkable examples. Firstly, mouse $CD4^+$ T cells generated from hematopoietic stem cells (HSC) from old donors are functional in young but not in old recipients (Eaton et al., 2008). Secondly, changes in the epithelial component of the thymus, the lymphopoietic organ, have shown to be crucial for the early progressive decrease in thymic output with age (Hamazaki et al., 2016) (Youm et al., 2016).

Immunosenescence is also influenced by the general mechanisms of aging occurring in the body, though these mechanisms remain elusive (Grimm, 2015) (Cohen, 2015). Several hallmarks of aging have been identified, all of which have profound direct or indirect effects on the immune system (Lopez-Otin et al., 2013) (Kennedy et al., 2014). The first mechanism of aging to be

identified was cellular senescence, in which telomere shortening limits the number of replication cycles (Hayflick and Moorhead, 1961) (Campisi, 2013). Senescent cells that have accumulated DNA damage have a *senescence-associated secretory phenotype* (SASP), characterized by the production and secretion of large amounts of proinflammatory cytokines, matrix metalloproteinases (MMP) and other soluble mediators (van Deursen, 2014). Senescent cells accumulate in older individuals, and this is the basis of "inflammaging", a concept put forward by one of us (CF) to stress the close links between aging and chronic inflammation (Franceschi et al., 2000b) (Salvioli et al., 2006) (Franceschi et al., 2007). The state of chronic inflammation that is a hallmark of aging in humans accounts for the comorbidities (Fig.1) and mortality associated with aging among which atherosclerosis, osteoporosis, osteoarthritis, diabetes [see for review (Franceschi and Campisi, 2014) (Kennedy et al., 2014)]. However, cellular senescence alone cannot account for immunosenescence.

The decrease in naive T cells and the increase in memory T cells can both be explained by a sustained loss of cells in a context of chronic immune responses associated with a decrease in thymic output (Nikolich-Zugich, 2008) (Fulop et al., 2013). This immunodeficiency would account for the strong association between CMV seropositivity and mortality due to cardiovascular causes observed in the elderly (Savva et al., 2013). Chronic CMV replication may be seen as an indirect consequence of the slow development of this immunodeficiency, as latent viruses are reactivated once a certain threshold of immunodeficiency is reached as shown also in mouse models (Polic et al., 2001). From this standpoint, CMV should not be seen as the causal agent of immunosenescence, although we acknowledge this virus and the immune response to it, contribute to repertoire shrinkage and inflammation (Fulop et al., 2013).

Crucially, the current overall view of immunosenescence is partial because most, if not all, studies on aging in humans are based on blood samples, for practical reasons. However, T cells in the blood are subjected to strong selection through trafficking regulation [see for review (Thome and Farber, 2015)]. The tissue-resident memory T cells (T_{RM}) (Sathaliyawala et al., 2013), which have yet to be studied in aging research, are of particular importance here (Gebhardt et al., 2011). In tissue, T_{RM} are more numerous than T cells recirculating from the blood (Steinert et al., 2015), and they may remain within tissues for the entire lifetime of the individual. This tissue retention is controlled by CD69 expression and the downregulation of factors promoting tissue egress. It is developmentally regulated through expression of the specific transcriptional regulators Hobit and Blimp1 (Mackay et al., 2016). The lymphocytes resident in tissues include not only T cells, but also NKT, or even NK cells in the liver, reproducing the diversity of the subpopulations known to be present in blood and barrier tissues (Gasteiger et al., 2015) (Fan and Rudensky, 2016). Tissue-resident lymphocytes have been found in the gastrointestinal tract, lungs, skin and reproductive tract (Farber et al., 2013) [see for review (Schenkel and Masopust, 2014) and (Clark, 2015)] but also in the brain (Steinbach et al., 2016). In mouse, they have been shown to be a key element in

immune defenses against all microbes, including CMV (Smith et al., 2015) (Thom et al., 2015). In both mice and humans cytomegalovirus induces T_{RM} particularly in mucosal tissues which are important viral sanctuaries and entry sites (Thom and Oxenius, 2016). They seem to function as an organ-autonomous first line of defense even in the absence of circulating CD8+ memory T cells (Steinbach et al., 2016) showing that recirculation of these cells between the blood and these tissue-compartments are dispensable for efficient organ protection. Known in mouse model of CMV infection, viral latency of CMV, can promotes the continuous, low-level recruitment of circulating CMV-specific T cells to the T_{RM} population of the salivary gland maintaining a pool of T_{RM} at the site of viral replication (Smith et al., 2014), a point which remains to be formally proven in human aging.

Given the crucial importance of T_{RM}, any exploration of immunosenescence should take into account the ECM, the environment in which these cells are found. This placing of immune system physiology into context is of vital importance, but still rarely (if ever), done in studies on immunosenescence.

3. The tight connection between immune cells and the ECM

3.1. Mechanical stress on the nucleus, the largest and most rigid cell component

Cells may be carried along in a mobile medium, such as lymph or blood, but here we will exclude such passive mobility, to focus instead on the requirements for the intrinsic motility of T cells, particularly within the ECM. The trans-endothelial migration of lymphocytes is relevant in this context, because of the biochemical and biophysical nature of the ECM in the vessel wall (Kohn et al., 2015).

We will deal here exclusively with T cells, but many different cell types from both the adaptive and innate arms of the immune system are motile within the ECM. Neutrophils, for example, are probably the most mobile of all immune cells, recirculating frequently and rapidly between the bone marrow, blood and then tissues. These cells display an age-related loss of migratory capacity, with predictable consequences aging (Sapey et al., 2014). Neutrophils are highly deformable and can cross pores only microns in diameter (Rowat et al., 2013), due to the flexibility of their nuclear membrane, which lacks lamin-A, a molecule that restricts nuclear deformability, thereby limiting migration through constrictions and the rate of 3D migration (Harada et al., 2014). There is a delicate balance between the mechanical protection from rupture afforded by the presence of lamin in the lamina, limiting cell motility and nuclear plasticity allowing movements of cells through mesh (Gerlitz and Bustin, 2011). Unsurprisingly, laminopathies, an heterogeneous group of hereditary diseases caused by mutations of the lamin-A gene, are often characterized by both accelerated aging and high levels of inflammation (Burtner and Kennedy,

2010). T lymphocytes display lamin-A expression when activated, but not when resting, possibly reflecting differences in motility before and after activation depending on cell location and function. The few studies focusing on the lymphocyte compartment in laminopathies have reported major changes in T cell behavior, due to altered synapse formation and activation processes, consistent with the hypothesis that lamin-A is required for activation (Rocha-Perugini and González-Granado, 2014). Lymphocyte developmental abnormalities have also been reported in the lamin KO model (Hale et al., 2010), but a relationship between the quality of immune responses and the mobility of immune system cells has yet to be demonstrated in affected patients. Matrix stiffness, lamin-A protein levels in the nucleus and cell mobility are known to be related (Swift et al., 2013), but the potential consequences of these relationships for the immune system during aging have not been explored.

It has recently been shown that migrating mammalian cells are susceptible to rupture of the nuclear membrane when subjected to strong mechanical constraints, such as passage through small pores (3µm in diameter). Such ruptures would result in a mixing of the nuclear and cytoplasm contents. Major events of this type are frequent (90% of the cells *in vitro,* according to a recent study (Denais et al., 2016)), but seem to be rapidly repaired (along with the DNA double-strand breaks they create) by specific mechanisms (Raab et al., 2016) (Denais et al., 2016), and among which autophagy or proteasome roles could be hypothesized. However, the repair mechanisms may not be always completely successful, potentially leading to cell death, or cancerous transformation (Hnisz et al., 2016) (Zhang et al., 2015). The stress to which the nucleus is subjected, in addition to causing DNA strand breaks, also induces major inflammatory pathways (IL6 and NFκB), potentially accounting for the inflammatory status associated with aging and adding to current knowledge of cell senescence (Le Berre et al., 2012) (McGregor et al., 2016). The nucleus appears therefore as the place where genetic information is stored but also as a mechanical sensor [see for review (Bustin and Misteli, 2016). As observed for the nuclear envelope, the stress on the plasma membrane and its maintenance probably play important roles also in aging (Lauritzen et al., 2015). As discussed in Section 4 below, the mobile cells of the immune system have particularly high levels of exposure to these risks.

3.2. Lessons learned from various hereditary immune deficiencies in which cell mobility is altered

DOCK8 is a guanine nucleotide exchange factor (GEF) that activates small GTPases (Coté and Vuori, 2007), and also acts as an adaptor in the TLR9-MYD88 signaling pathway (Jabara *et al.,* 2012). DOCK8 controls cell cytoskeletal functions (secretion, cell interactions) and migration, and is expressed only in cells of the immune system. DOCK8 mutations result in a combined immunodeficiency syndrome. DOCK8-deficient patients have recurrent otitis, sinusitis, and pneumonia, recurrent *S. aureus* skin infections, *H. simplex* or *H. zoster* infections, and persistent human papillomavirus infections. Most patients have severe atopy with anaphylaxis, and

several develop squamous-cell carcinomas. Biologically, some have high serum IgE levels or hypereosinophilia, others present low counts of T cells and B-cells, and low serum IgM levels while their IgG antibody responses are variable (Zhang et al., 2009). T cell activation, survival, proliferation and priming by dendritic cells are affected. Other cells, including dendritic and NK cells, are also crippled, resulting in poor cell cytotoxicity and low levels of antiviral cytokine production. Notably, DOCK8-deficient dendritic cells migrate poorly to the lymph nodes (Lambe et al., 2011) (Randall et al., 2011). Microscopy observations of T cells from patients, migrating within the three dimensions of the dermis microenvironment in human skin biopsy samples, showed that these cells had abnormal elongated shapes and long migration times within the mesh, phenotypes observed in normal cells after DOCK8 silencing with siRNA. Remarkably, DOCK8-deficient cells sense and migrate toward a SDF-1 chemokine (CXCL12) gradient normally in two-dimensional and liquid environments. Moreover, in 3D environments, but not in liquid medium, T cells from normal individuals in which DOCK8 is silenced induce a specific form of death known as “cytothripsis” (Q. Zhang et al., 2014). This type of cell death results from the exertion of mechanical forces on the plasma cell membrane and the more rigid nucleus, leading to tearing of the plasma membrane. The elongated cell phenotype leading to death also occurs when T cells migrate through pores, agarose, ICAM-coated or collagen-coated surfaces to which they adhere, demonstrating a clear relationship between shape and local constraints on mobility. Thus, the abnormal shape and death of cells lacking DOCK8 are associated with movement constraints due to a confined space, observed in the dermis, accounting for the phenotype of patients, with their high frequency of skin diseases (Mouw et al., 2014).

DOCK8 activates CDC42, which regulates lymphocyte shape and cytoskeletal structures during cell movements, including dendritic cell migration (Harada et al., 2012). CDC42 then activates several effectors, including P21-activated kinase (PAK) and the Wiskott-Aldrich Syndrome Protein (WASP). Knockout of the small Rho GTPase CDC42 reproduces some of the features of DOCK8 deficiency, whereas WASP loss from T cells does not (Humblet-Baron et al., 2007). However, WASP deficiency is associated with abnormal immune responses, reflecting the complex interplay between these proteins in the orchestration of cell mobility.

Similarly, Coronin-1 (Coro1) deficiency leads to a pronounced immunodeficiency phenotype resembling that of DOCK8-deficient patients (Föger et al., 2006) (Shiow et al., 2008) (Hogquist, 2008). Coro1 regulates actin polymerization. Mutation of the CORO1A gene causes profound peripheral T cell lymphopenia, thought to be due to an inability of T cells to migrate out of the thymus and to enter and leave lymph nodes. However, these cells were also shown to be generally less mobile in the presence of this mutation.

The immune defect in DOCK8-deficient individuals principally concerns the maintenance of the T_{RM} compartment, but in normal individuals, it could also rely on ECM quality and quantity which are specific to each tissue (Bonnans et al., 2014). Alterations to the ECM would modify the mobility of cells through this matrix, in a similar manner to DOCK8 mutation. In addition, the mobility of immune cells is required for correct activation of T cells and is a preliminary step for contact between T cells or Treg cells and DCs in secondary lymphoid organs (Sixt, 2011) (Kastenmüller et al., 2012) (Honda et al., 2014) (Liu et al., 2015). ECM alterations may also affect diverse processes, including the formation of the thymic epithelium, which plays a key role in T cell production (Shen et al., 1994) (Mouw et al., 2014).

The various degrees of lymphopenia observed at different sites in the body (spleen, skin,

etc.) in DOCK8-deficient patients probably result from a combination of factors differing in magnitude between patients. Lymphopenia in blood and tissues is associated with poorer control over latent viruses, in turn triggering acute antigen-driven clonal amplification and inflation of the T_{EMRA} compartment. In the long term, lymphopenia may be compensated by homeostatic proliferation and/or thymic output, depending on the age of the patient, but with a change in their respective frequencies. Indeed, CD8+ T cells that are $CD57^+$ (Brenchley et al., 2003), $CD57^+/CCR7^-/CD27^-$ (Papagno et al., 2004), or $CD45RA^+/CCR7^-/CD27^-/CD28^-$ (Rufer et al., 2003) (Romero et al., 2007) display the greatest expansion *in vivo*, as demonstrated by TCR excision circle (TREC) quantification or telomere length measurement, but these cells do not proliferate *in vitro* following TCR-mediated stimulation. DOCK8-deficient $CD8^+$ T cell subsets have higher proportions of $CD57^+CD27^-CD28^-$ cells in both the memory and T_{EMRA} cell subsets, with naive cells displaying unusually high levels of CD95 expression (Randall et al., 2011). These features are similar to those observed in young HIV-infected patients (Boasso and Shearer, 2008) (Zapata and Shaw, 2014) and in the elderly (Vescovini et al., 2014).

Actin dynamics and cell longevity are known to be linked in yeast, in aged mice and humans (Föger et al., 2006) (Brock and Chrest, 1993). Yeasts with slow actin dynamics accumulate F-actin, release ROS and have higher rate of cell death. Conversely, increasing actin dynamics in normal cells can increase lifespan by 65% (Gourlay et al., 2004). Actin dynamics and its regulation therefore profoundly affect many aspects of lymphocyte life and survival, as noted some time ago for T lymphocytes (Brock and Chrest, 1993). All these studies concentrated on intrinsic defects of cell dynamic but extrinsic factors should also be considered.

In this view, abnormalities of certain types of glycosylation due to autosomal recessive phosphoglucomutase 3 (PGM3) mutations (Y. Zhang et al., 2014) have also recently been described. Affected patients present a syndrome resembling DOCK8 deficiency, with atopy, immune deficiency, autoimmunity and neurocognitive impairment, suggesting a possible decrease in cell mobility in these patients too, potentially due to changes in the extracellular matrix with effects on cell migration.

4. Immunosenescence, cell mobility and age-related changes in the ECM: the “mesh” connection

The ECM is an acellular 3D structure composed of tissue-specific combinations of a large number of fibrillar proteins such as collagens, proteoglycans, and glycoproteins (Hynes, 2009). Collagen fibers maintain the shape of the tissues, as they are inextensible, but flexible and strong. Collagens are the most abundant proteins in the ECM (Bella, 2016)There are 28 different forms of collagen, belonging to eight classes that differ biochemically in the nature of their aggregated forms

and species composition.

Fibroblast-matrix interactions have long been known to be important in aging (Bailey et al., 1998) (Varani et al., 2006). These interactions are currently the focus of intense research in development and cancer biology. In aging, stiffening of the joints and of the vascular tree in the kidney, retina and heart are observed, together with changes in basal membrane properties due to profound alterations to collagen structure and metabolism, through the cross-linking of fibers, in particular. Moreover, the rate of collagen synthesis is also affected. It gradually slows down during childhood, reaching a plateau in adults and then decrease in most tissues in the elderly.

In cancer, cross-linking and subsequent stiffening of the ECM around the tumor seems to be a prerequisite for transformed cell invasiveness and importantly for the protection of these cells against immune system control (Levental et al., 2009). ECM alterations probably also promote cell transformation (Seo et al., 2015). Cellular integrins, which bind to the ECM, provide cancer cells with the positive signals required for tumor progression (Chen et al., 2015). This situation resembles that described for stem cells, the fate of which is also largely determined by ECM interactions (Guilak et al., 2009).

4.1. ECM changes over time: how, when and why?

The cross-linking theory of aging dates from the late 1950s. According to this theory, proteins, in particular collagens, lose their functions following excessive cross-linking due to reaction with aldehyde metabolites [see (Bailey et al., 1998)]. Two different mechanisms drive the changes in the mechanical properties of collagen with age. The first involves the specific enzymatic cross-linking of lysine or hydroxylysine, and is fundamental to development. With age, a second, non-specific, cross-linking mechanism occurs. This mechanism involves the non-enzymatic chemical reaction of protein, peptides, amino acids, nucleic acids, and lipids with glucose, fructose, ascorbic acid or pentose (Sell and Monnier, 1989), in a process known as glycation (Maillard reaction), to generate advanced glycation end products (AGEs) (Sjöberg and Bulterijs, 2009). Glucosepane is the most abundant type of protein cross-link identified to date *in vivo.* It is found in the extracellular matrix, where it participates in collagen cross-linking. By increasing collagen stiffness and limiting porosity size, glucosepane cross-links may have significant implications for several age-related diseases, including cardiovascular disease, diabetes, and osteoporosis (Monnier et al., 2014) (Boger, 2015) (Draghici et al., 2015). Protein turnover is an important determinant of AGE accumulation in proteins and, therefore, of their degree of cross-linking (Gaggar and Weathington, 2016). Collagens have a very long half-life (117 years for cartilage, 15 years for skin), resulting in high and cumulative rates of glycated product accumulation in the ECM (Verzijl et al., 2000). This accumulation is accelerated by hyperglycemia in diabetic patients, and this is thought to be the major cause of higher morbidity and mortality in these patients. Diabetic patients have impaired tissue repair mechanisms and are known to be prone to skin infections. The

prevalence of diabetes increases with age, potentially worsening aging outcomes overall. Glycation is thought to occur mostly in the extracellular environment, but proteins within cells may also be specifically glycated. This is the case for vimentin, which seems to be a highly sensitive target for chemical glycation, but with a high turnover, likely limiting the relevance of this factor in our discussion (Kueper et al., 2007). This observation is, however, of interest when considered together with those for lamins, as both molecules play key roles in nuclear envelope biology. In addition, glycated collagens can oxidize lipids, generating molecules such as malondialdehyde, which has a long half-life and diffuses away to react with proteins or nucleic acids, thereby modifying their biological properties. Relevant to cell mobility, *in vitro* treatment with methylglyoxal, another oxidizing agent, has been reported to decrease cell adhesion to matrices by 70 to 90% (Bailey, 2001).

Proteoglycans are another abundant component of the connective matrix involved in the age-related changes to the physical properties of tissues. Through their electric charge, these components of the ECM are also important for the binding of growth factors, such as IGF1, to their scaffolds (Parker et al., 1998) and for the release of IL1alpha following ECM modification by granzyme B (McElhaney et al., 2012). Decorin, the main proteoglycan in skin, regulates collagen matrix assembly. This protein is distributed along collagen fibrils and the decorin glycoaminoglycan (GAG) chain controls the distance between these fibrils. Reducing the length of decorin GAG chains reduces the distance between collagen fibrils, decreasing mesh porosity, as observed in aging (Bailey, 2001).

4.2. Consequences of ECM alterations with age

Changes to “mesh” porosity due to cross-linking or alterations in relative collagen species composition would be expected to modify cell mobility profoundly in the ECM. This change in mobility would particularly affect the immune cells, although modifications are expected to be both location-dependent due to variable compositions of ECM in distinct tissues (Groulx et al., 2011) (Soret et al., 2015) (Hallmann et al., 2015) and cell-dependent, due to variability in the adaptation of nucleus stiffness to the environment (Wolf et al., 2013) (Swift et al., 2013).

In mice, low levels of growth hormone production due to an embryonic pituitary gland defect result in the production of mice one third the size of normal mice, but with a 40% higher lifespan (Flurkey et al., 2001). Interestingly, collagen cross-linking levels in the tail were found to be only one third of those in normal mice, which suggests that a complex interplay between pituitary gland and ECM exists. As shown by the naked mole rat model of aging seen below, one link is embodied by CD44 signaling (Tian et al., 2013). In this regard, aged dwarf mice have $CD4^+$ and $CD8^+$ memory T cell levels ($CD44^+$) similar to those seen in young control animals, and much lower than those in aged control mice (Flurkey et al., 2001). Furthermore, very significant differences are observed in five other tests probing the immune status of these animals, supporting the conclusion

that in these mice, the higher life expectancy and the better immune status than wild-type mice, are correlated with differences in the ECM. However, no relationship has yet been experimentally confirmed in this field.

In Ecuador, a group of humans with lifelong IGF-1 deficiency caused by a GH receptor (GHR) mutation (Laron syndrome) have been shown to be much more sensitive to insulin than age- and BMI-matched control relatives, despite having a high percentage of body fat. None of these individuals were diabetic, whereas 6% of their unaffected relatives were diabetic, and only one of the 20 individuals with GHR deficiency died from cancer, whereas 20% of their relatives died from this disease (Guevara-Aguirre and Rosenbloom, 2015). Interestingly, the offspring of one centenarian was found to have low levels of circulating IGF1 bioactivity, inversely correlated with insulin resistance (Vitale et al., 2012).

Taken altogether, these data are consistent with a role for the IGF-1 pathway in aging, but this role may be at least partly indirect, and should consider the possibility of ECM alterations.

4.3. ECM and the C. elegans model of aging

In nematodes, mutations preventing insulin/IGF1 signaling, such as daf-2 mutations, double lifespan. Removal of the germline precursor cells also extends worm lifespan 60%, probably by altering endocrine signaling. These two effects are additive, resulting in a quadrupling of lifespan. By manipulating the expression of a few genes from the insulin/IGF1 axis lifespan can be increased by a factor of six, with no apparent loss of health or activity (Arantes-Oliveira, 2003).

About a dozen pathways are known to be important in aging, but matrix remodeling has been identified as an essential signature of longevity in all species tested, including nematodes, leading to the conclusion that the promotion of ECM conservation is highly beneficial (Ewald et al., 2014) and could serve as an additional target in the control of aging.

The molecular role of ECM in the prevention of aging remains to be understood, but diverse mechanisms appear to be involved. These mechanisms may be related to resistance to oxidative stress or may operate at the interface between several signaling pathways, including those involving CD44 (Tian et al., 2013) (Ponta et al., 2003), TGFbeta, bound IGF1, and integrins. They may also relate to the mechanical relationships between the nucleus and the ECM as pointed out before. The ability of the ECM to bind growth factors is another key aspect that could be modified for research purposes (Martino et al., 2014). In this regards, parabiosis experiments have shown that the transfer of blood from a young mouse to an old mouse increases brain cell growth, promotes brain plasticity, memory formation and the repair of damaged spinal cord, and reverses the age-related thickening of the heart walls. These rejuvenation processes may reflect a reversal of the degradation of ECM function in aged individuals, including the quenching of ROS and AGE, decreases in ECM cross-linking, and the replenishment of the ECM with growth factors, such as IGF1 (Conboy et al., 2005) (Loffredo et al., 2013) (Villeda et al., 2014) (Elabd et al., 2014)

(Scudellari, 2015). The effects probably differ between tissues, reflecting differences in ECM composition and interestingly also linked to the distinct rates of aging noted for different organs (Cevenini et al., 2008).

Such treatment would also reverse the decline in immune status associated with aging, leading to a decrease in inflammaging, the replenishment of naive mature T cells and hematopoietic stem cells, and an abolition of latent virus reactivation, but these effects have yet to be demonstrated experimentally (Conboy and Rando, 2012).

4.4. ECM and the naked mole rat model of aging

The naked mole rat has an exceptionally long lifespan, at over 30 years, much longer than the four years for related mouse species of similar size. Furthermore, no case of cancer has ever been reported in this species, despite many years of observation of naked mole rat colonies. This remarkable resistance to cancer seems to be due to the secretion by fibroblasts of large amounts of an ECM component, the high-molecular mass molecule hyaluronan (HMMH), due to high levels of synthesis and low levels of catabolism. The hyaluronan synthase of the mole rat differs from those of 13 other species tested by two amino acids in the catalytic domain (N178S and N301S). One of these differences concerns an asparagine (N) residue totally conserved in all other species tested. These findings should led to a search for polymorphisms of the hyaluronan synthase gene in humans that might be associated with centenarians (Tian et al., 2013). The skin, heart, brain and kidney of naked mole rats are highly enriched in HMMH. The disruption of signaling pathways, inducing the malignant transformation of mouse fibroblasts (H-RAS and SV40), does not lead to the transformation of naked mole rat fibroblasts. However, the elimination of hyaluronan overproduction, by knocking down expression of a gene required for its synthesis or overexpressing gene required for its catabolism, renders the resistant cells susceptible to malignant transformations and leads to tumor formation in mice. This remarkable phenotype seems to involve signaling through the hyaluronan receptor CD44. The intracytoplasmic part of CD44 interacts with NF2, which participates in a pathway mediating contact inhibition. In addition, the affinity of CD44 to hyaluronan in naked mole rat cells is twice that in mouse or human cells. T_{RM} do express CD44, which is a hallmark of memory T lymphocytes, raising the possibility that the hyaluronan effect may also be mediated partly by immune cells.

However, to the best of our knowledge, no studies have yet been carried out on the naked mole rate immune system, with investigators instead focusing in cell-intrinsic clues to cancer resistance rather than on extrinsic factors, such as the immune system in relation to ECM.

4.5. Hyaluronans can also be inflammatory

Hyaluronan degradation products at injury sites can stimulate the expression of inflammatory genes by various immune cells (Jiang et al., 2007). CD44 seems to be required for

the clearance of hyaluronan degradation products in lung injury and transplantation, in which hyaluronan clearance may be impaired by the absence of draining lymph vessels in the graft, resulting in persistent inflammation and rejection (Jiang and Nicolls, 2014) (Maltzman et al., 2015). In type 1 diabetes, autoimmune insulitis is associated with the islet-specific deposition of hyaluronan, whereas the inhibition of hyaluronan synthesis prevents the disease in mice (Nagy et al., 2015). Hyaluronan fragments use both Toll-like receptor (TLR) 2 and TLR4 to stimulate the expression of inflammatory genes in macrophages (Scheibner et al., 2006). Low-molecular weight hyaluronan fragments and in general degradations products of ECM (matrikines) are therefore candidates for a direct role in inflammaging, mediated directly or indirectly as DAMPs through the immune system (Evanko et al., 2012) (Gaggar and Weathington, 2016).

ECM alterations may have indirect pro-inflammatory effects, by disrupting the interaction with cell integrins responsible for connecting the cell surface to the actin network. Interestingly, in dendritic cells, the absence of beta2-integrin-mediated cytoskeletal organization leads to membrane compartmentalization and an absence of association of the GM-CSF receptor with actin, resulting in higher levels of signaling via this receptor and conferring a migratory maturation phenotype on dendritic cells, leading to the Th1 priming of naive T cells and an higher neutrophil survival (Morrison et al., 2014).

4.6. ECM, mechanotransduction and the mobility of immune cells

(Friedl et al., 2011). The mechanism by which cells sense ECM stiffness is called mechanotransduction (Iskratsch et al., 2014). Mechanotransduction plays a key role in adjusting ECM mechanics to cell behavior or function, mostly through integrins (Humphrey et al., 2014). For this reason, 2D *in vitro* experimental settings are not entirely representative of 3D situations *in vivo*, as reported in previous studies (Harunaga and Yamada, 2011) (Horton et al., 2016). Mechanotransduction is also a potent trigger of epithelial mesenchymal transition (EMT) (Nelson and Bissell, 2006) (Bissell and Hines, 2011) (Arendt and Kuperwasser, 2015). It also plays a widely accepted and studied role in development (EMT type 1) (Dupont et al., 2011) (Halder et al., 2012), (Piccolo, 2012) (Heisenberg and Bellaiche, 2013) (Porazinski et al., 2015). It has been closely linked to the progression of cancers to metastasis (EMT type 3) and implicated in cancer initiation (Seo et al., 2015) (Arendt and Kuperwasser, 2015) (Bissell and Hines, 2011), but rarely associated with wound healing (EMT type 2), and immunology.

Immune cells have a number of specific features of importance in this context, and their intrinsic mobility is closely linked to surveillance, as illustrated by the descriptions of immunodeficiencies provided above. Life on Earth began with single cells, some of which much later, grouped together and evolved into metazoans (Davies and Lineweaver, 2011). In multicellularity, there is a need for cells to anchor themselves together to achieve mechanical coherence. We can still see evidence of the steps leading to the development of complex

multicellular individuals from single cells, in intermediate forms, from *Chlamydomonas* to *Volvox* (Kirk, 2005) (Shelton and Michod, 2014). From this model, experimental data show that ECM plays a striking role in this process (Hallmann and Kirk, 2000). No information about the role of the ECM in immune system biology is available, with the exception of secondary lymphoid organ physiology, which is not considered here (Kastenmüller et al., 2012). Mobile cells might therefore be expected to have evolved specific mechanisms modulating the consequences of anchorage within the ECM. An understanding of these mechanisms would greatly improve the way we see and understand immunity and the pathophysiology of many diseases, including autoimmune (Sofat et al., 2015) and infectious diseases and of course aging.

In summary, the mechanisms of ECM cross-linking in aging are well established, but their effects on immune cell mobility in the body remain largely unknown. Given recent findings for memory resident T cells and the functional importance of cell trafficking between lymph nodes, blood and, above all, within tissues, we suggest that a link between these two aspects could account for the features associated with immunosenescence.

5. Consequences of the lower mobility of T-lymphocytes and their higher death rate

5.1. Necrosis, apoptosis, pyroptosis and inflammasome activation

The preservation or loss of membrane integrity in dying cells determines whether cell death is inflammatory (Wallach et al., 2016). Some of cell components leaking out of cells have been identified as damage-associated molecular patterns (DAMPs). These components, together with pathogen-associated molecular patterns (PAMPs), constitute the generic “danger signals” that, according to the danger theory (Matzinger, 2002), are sensed by dendritic cells, leading to an upregulation of their expression of costimulatory molecules on the antigen-presenting cell surface (Pradeu and Cooper, 2012) (Kono et al., 2014) necessary for naive T cell activation.

Conversely, membrane integrity is maintained for a while during early apoptosis, before caspase-mediated fragmentation. This allows the macrophages to engulf and clear the danger signals, thus preventing inadequate activation of T cells (Green et al., 2009). However, if too many apoptotic cells are produced, overwhelming the clearance capacity of the macrophages, or if this capacity is decreased for some reason, then apoptotic cells might not be cleared rapidly enough, resulting in the leaking of apoptotic bodies. These bodies would release DAMPs, resulting in a highly inflammatory environment. From our hypothesis, we can predict that these two situations would occur in synergy over long periods during aging, as ECM remodeling would severely impair the mobility of lymphocytes and macrophages, ultimately leading to the death of these cells *in situ* in response to mechanical stress. Other triggers may also be important. In particular, High Mobility

Group Box 1 (HMGB1) is a nuclear protein released by necrotic cells that promotes cytokine release by interacting inflammatory cell recruitment via TLR4 and CXCL12 cell migration (Schiraldi et al., 2012). This and other examples (Lim et al., 2015) (Vacchelli et al., 2015) demonstrate that inflammation may be closely connected to impaired mobility, potentially leading to the establishment of a vicious circle in the contexts of aging and ECM modifications.

Furthermore, the release of IL1beta induces a highly inflammatory form of cell death known as pyroptosis, which has recently been shown to account for the massive T cell loss and inflammatory status of HIV patients (Doitsh et al., 2014). The innate molecular part of the immune system senses these otherwise hidden cell components (Davis et al., 2011) (Lamkanfi and Dixit, 2012), whereas cells, such as macrophages, drive a vicious circle by responding to IL1 and further degrading the ECM leading to “macroph-aging” (Franceschi et al., 2000b). IL1beta and IL18 are prototypical inflammatory cytokines secreted following cytoplasmic cleavage of the corresponding proproteins by caspase-1 activated following polymerisation of inflammasome. The transcriptional activation and expression of these proproteins and of inflammasome components follows signaling through TLR and cytokines in diverse cells [for details see (Martinon et al., 2009)]. IL1 is then secreted, activating signaling via its receptor, through the NF-κB pathway, and triggering the inflammatory program in target cells (Mathews et al., 2008). Six types of inflammasomes have been described in humans, each essentially specific for an array of PAMPs or DAMPs, most of which are abundant molecules with important functions, enabling the inflammasome to sense cellular injuries. For example, ATP, RNA, DNA, cholesterol deposition and crystals are known to activate the NLRP3 inflammasome, which plays a major role in atherosclerosis (Zheng et al., 2014). Interestingly, the inflammasome has also been reported to sense actin dynamics, which is essential for the detection of intracellular pathogens (Kim et al., 2015). As described above, the low-molecular weight products of hyaluronan breakdown, a result of ECM injury, bind to TLR2, inducing production of pro-IL1 and pro-IL18 (Scheibner et al., 2006). Inflammasomes have also been shown to accelerate the decline of thymic function (Youm et al., 2012). In summary, this array of observations shows the tight intricacy which exists between ECM and inflammation, pledging for its consideration in immunosenescence and aging.

Within this inflammatory framework, the high levels of IL6 consistently observed in the blood of the elderly may directly reflect the nuclear stress resulting from the ECM remodeling. Indeed, the magnitude of nuclear deformation is related to expression levels for a specific array of genes, the most transcribed of which are histones H4(A-D) and H3F, but also IL6 (Le Berre et al., 2012). Nuclear envelope rupture has been shown to cause DNA breakage and repair that might contribute to the DNA damage response (Zhang et al., 2015) (Raab et al., 2016), but exchanges of material between the cytoplasm and nucleus might also provide a source of internal DAMPs directly sensed along these various pathways.

Overall, the ubiquitous ECM modifications associated with collagen glycation and cross-

linking are probably directly or indirectly followed by a series of events leading to the chronic production of highly potent inflammatory cytokines, underlying the inflammaging and its consequences seen in the elderly.

5.2. T lymphocyte depletion and its link to homeostatic proliferation and autoimmunity

Chronic T cell loss induces three highly regulated processes of T cell replenishment in mammals which are: 1) the mature T cell egress from the thymus, 2) the clonal amplification of cells engaged in an immune response, and 3) the homeostatic proliferation of T cells.

In the elderly, as thymic function is absent, T cell compartment replenishment is dependent exclusively on homeostatic proliferation. In this process, existing T cells proliferate in the absence of exogenous antigen, due to their intrinsic self-recognition properties resulting from their previous positive and negative selection in the thymus (Vrisekoop et al., 2008) (den Braber et al., 2012) (Johnson et al., 2012). Homeostatic proliferation may, therefore, also be linked to the development of auto-immunity (Goronzy and Weyand, 2012) as the T cell repertoire is built on a principle of basic but limited recognition of self (Mason, 1998), known as auto-reaction [see (Pradeu, 2012)].

In normal adults, this basal autoreactive state does not lead to auto-immune diseases because of several mechanisms, collectively called “peripheral tolerance”, but mostly involving regulatory T cells, which inhibit effector T cell function and which have been shown to accumulate with age (Sharma et al., 2007).

Most of our insight into T cell dynamics replenishment originates from analyses of T cell reconstitution in the blood following peripheral lymphopenia, as observed during HIV infection, chemotherapy to treat cancer, transplantation and aging. Lymphopenia is known to break tolerance (Jones et al., 2013), as highlighted by reports for hematopoietic stem cell transplantation (Matsuoka et al., 2010). In these conditions, the T cells with the highest affinity for MHC plus self-peptides proliferate faster than those with a lower affinity leading to dysregulated immune system activation.

In mouse models, homeostatic proliferation after lymphopenia also induces the spontaneous proliferation of naive and memory T cells but with little auto-immunity (Le Campion et al., 2009), because of the concomitant expansion of T regulatory cells (Tregs) to control this phenomenon (Picca et al., 2006). However, if the expansions of these two populations were to be dissociated, then transient auto-immune disorders arise. This is what is observed in the immune reconstitution inflammatory syndrome (IRIS), found in HIV-infected patients with low CD4+ T cell counts given highly active antiretroviral therapy (Shelburne et al., 2005) or in NOD mice (Le Campion et al., 2009).

Tregs interact with dendritic cells in the lymph nodes, in which they suppress effector T cell priming, subsequently migrating to non-lymphoid tissues, in which they suppress effector T cell functions locally. The suppression exerted by Tregs is not specific to the antigen; it is, instead,

highly dependent on colocalization with the effector T cells to be suppressed (Antunes et al., 2008). Tregs migrate rapidly from the blood to sites of inflammation, highlighting their strong dependence on a normal migratory capability to mediate their suppressive function. Changes in their migration capacity, due to the ECM alterations known to occur in aging, cripple their regulatory functions, leading to higher levels of auto-immunity. Treg suppressive function is, thus, highly dependent on effective migration mechanisms, which may be disrupted by ECM alteration, thereby exacerbating inflammatory processes and partly accounting for age-related auto-immunity.

6. Conclusion

T cells are highly mobile cells with functions in immunity that are highly dependent on their ability to migrate particularly for those residing in tissues. We argue here that changes to T cell migration capacity due to well-characterized ECM changes during aging may play a key role in the aging process, by crippling interactions between immune cells and preventing their trafficking (Fig. 2). Studies of hereditary immunodeficiencies involving a lack of efficient actin remodeling have shown that T cell loss results from the death of migratory cells. In addition to the consequences of T cell death for inflammation, the progressive depletion of T cells leads to viral reactivation (herpes virus) and triggers mechanisms of T cell replenishment that may lead to some degree of autoimmunity. These mechanisms provide information about the consequences of ECM remodeling in fundamental immunology as well as some explanation for immunosenescence, but they may also serve as appropriate treatment targets. Early in 2015, two studies convincingly showed that providing the host with T cells against tumors in the context of a scaffold matrix created a favorable environment for the generation of effective humoral and cellular immune responses to tumor antigens (Stephan et al., 2015) (Weber and Mulé, 2015). This observation reflects also the existence of tertiary ectopic lymphoid organs, in synovial tissue from rheumatoid arthritis patients for example (Weyand et al., 2003), demonstrating here again, the three-dimensional nature of immunity.

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Figure captions

Figure 1: Relationships of immunosenescence with aging mechanisms and comorbidities. Aging mechanisms follow the nine hallmarks of aging established by Lopez-Otin (Lopez-Otin et al., 2013). External circles depict the co-morbidities associated with aging which also cooperate to modulate aging phenotype. The ECM and its alterations linked to aging will constraint immune cell mobility while inducing cell death. ECM alteration is a hallmark of aging and therefore a crucial process to better understand the phenomenon of aging. Fundamental mechanisms associated with ECM aging are represented in the expanded box, in relation with the altered cellular communications. ECM serves not only for the cells to migrate within, but also for growth factors storage and receptor anchorage as it is the case for integrins and CD44.

Figure 2: Role of extracellular matrix alterations in immunosenescence. The increase in ECM cross-linking with aging places constraints on the mobility of immune cells, accounting for the phenotype associated with aging. Other situations often encountered in clinical practice may also lead to this phenotype (hereditary defects of cell mobility, and T cell depletion as in HIV infection, immunosuppressive treatments or chemotherapy).

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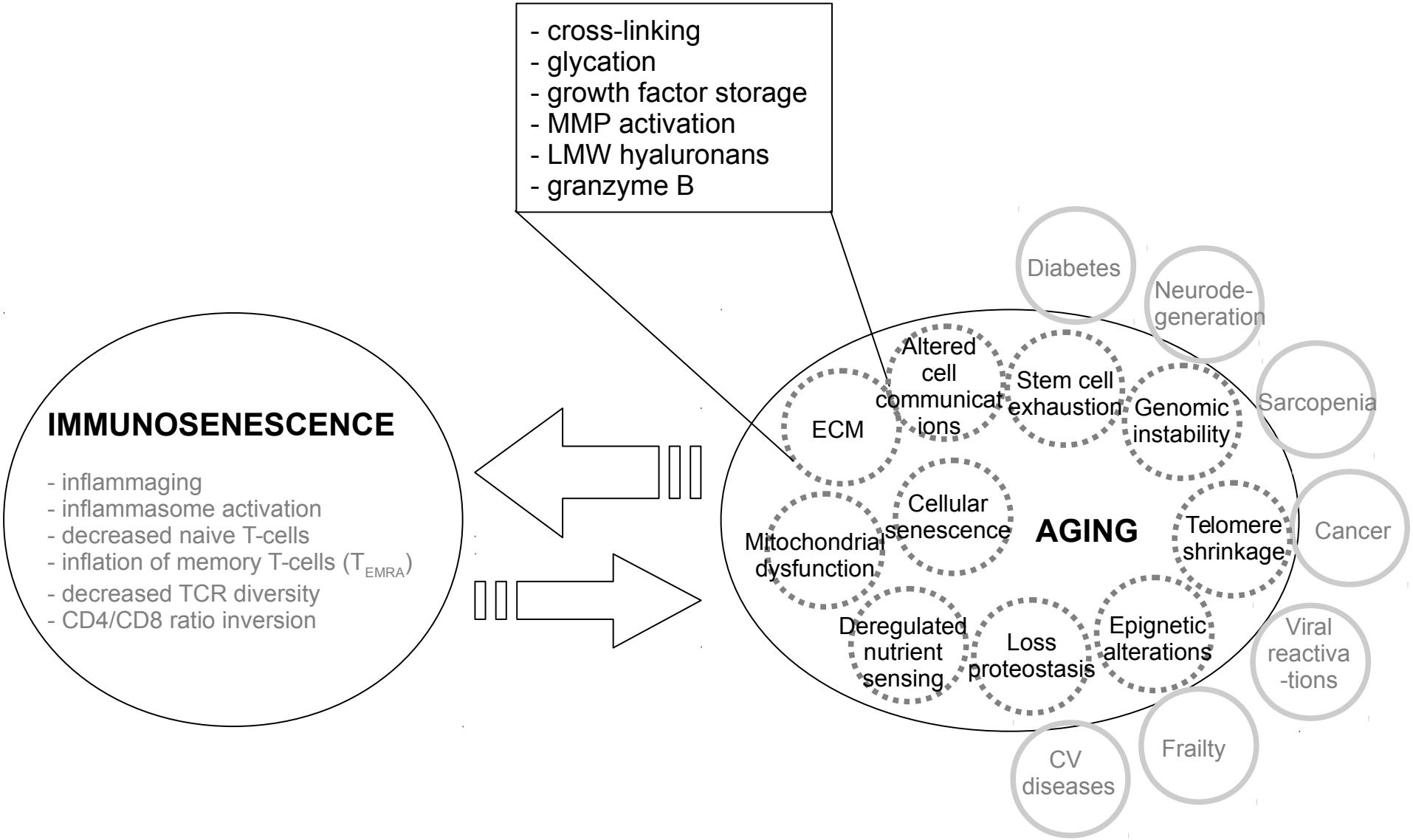
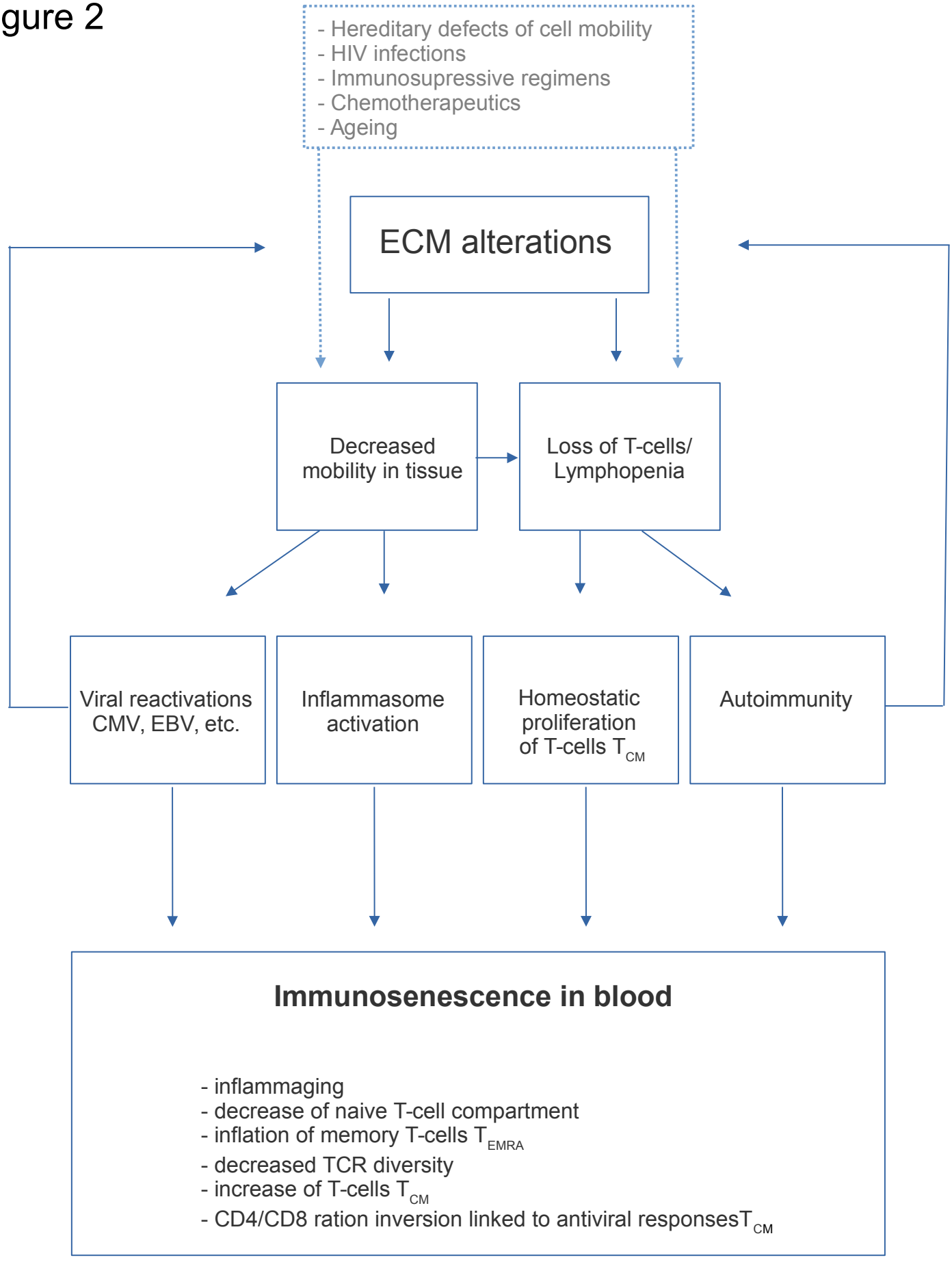

- cross-linking
- glycation
- growth factor storage
- MMP activation
- LMW hyaluronans
- granzyme B
IMMUNOSENESCENCE
- inflammaging
- inflammasome activation
- decreased naive T-cells
- inflation of memory T-cells (T_{EMRA})
- decreased TCR diversity
- CD4/CD8 ratio inversion
ECM
Altered cell communicat ions
Stem cell exhaustion
Genomic instability
Cellular senescence
AGING
Mitochondrial dysfunction
Telomere shrinkage
Deregulated nutrient sensing
Loss proteostasis
Epignetic alterations
Diabetes
Neurode-generation
Sarcopenia
Cancer
Viral reactiva -tions
Frailty
CV diseases

Figure 1

Figure 2


- Hereditary defects of cell mobility
- HIV infections
- Immunosupressive regimens
- Chemotherapeutics
- Ageing
ECM alterations
Decreased mobility in tissue
Loss of T-cells/ Lymphopenia
Viral reactivations CMV, EBV, etc.
Inflammasome activation
Homeostatic proliferation of T-cells T_{CM}
Autoimmunity
Immunosenescence in blood
- inflammaging
- decrease of naive T-cell compartment
- inflation of memory T-cells T_{EMRA}
- decreased TCR diversity
- increase of T-cells T_{CM}
- CD4/CD8 ration inversion linked to antiviral responses T_{CM}