Unraveling the syndrome of the age-associated diseases: Cancer, Cardiovascular, and Neurological disorders. Common pathways and novel therapeutic strategies

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Cardiovascular diseases and cancer are the most frequent causes of death in the industrialized world and their incidence increases significantly with age. Interestingly, autoimmunity is also seen with a higher frequency among older people. Is there a common pathogenic mechanism underlying this triad? One possible mechanism is the age-associated mutations that occur in all the cells of the human body capable of dividing. These mutations may lead to the formation of new proteins which can induce autoimmune reactions and inflammation that promote cancer and/or lead to an increased risk of cardiovascular disease. Here we review available evidence supporting the role of autoimmunity in the development of age-related diseases. If mutation-associated autoantibodies play a central role in the development of cardiovascular disease, cancer as well as neurological disorders, a new therapeutic option could be considered to switch...
Unraveling the syndrome of age-associated diseases: Common pathways and novel therapeutic strategies

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Abstract

Cardiovascular diseases and cancer are the most frequent causes of death in the industrialized world and their incidence increases significantly with age. Interestingly, autoimmunity is also seen with a higher frequency among older people. Is there a common pathogenic mechanism underlying this triad? One possible mechanism is the age-associated mutations that occur in all the cells of the human body capable of dividing. These mutations may lead to the formation of new proteins which can induce autoimmune reactions and inflammation that promote cancer and/or lead to an increased risk of cardiovascular disease. Here we review available evidence supporting the role of autoimmunity in the development of age-related diseases. If mutation-associated autoantibodies play a central role in the development of cardiovascular disease, cancer as well as neurological disorders, a new therapeutic option could be considered to switch off this key mechanism of the aging process. This also raises the question of whether successful treatment of autoimmune reactions, even at the subclinical level, can reduce the risk of cardiovascular disease, cancer, and other age-associated diseases.
Introduction

Aging, or senescence, is a feature of life characterized by the progressive deterioration of the physiological functions necessary for survival and fertility with increasing age (1). Various theories have been proposed to explain the process of aging (2–5). Still, nearly all of them coincide with the fact that the inevitable accumulation of cellular and molecular damage throughout life is the general cause of aging (6–8). This damage leads to the natural accumulation of genetic and epigenetic lesions (9,10) that manifest themselves only late in life. Age-associated diseases include cancer (11), atherosclerosis (12–14), type 2 diabetes (15,16) cardiovascular (17), and neurodegenerative diseases (18,19), as well as autoimmune disorders (20–22). Of the 150,000 people that die each day across the globe, about two thirds (100,000 per day) die of age-related causes (23). However, age-associated diseases are to be distinguished from the aging process itself, because all individuals of a species age or get old, but not all adult individuals’ experience age-associated diseases.

The consequence of the extended life expectancy is the increasing number of older people in developed countries, an "artifact" of human civilization (2). According to the WHO, the global number of centenarians is projected to increase 10-fold between 2010 and 2050. The consequence of an increasingly aging population is the rise of chronic and degenerative diseases resulting in a progressively higher susceptibility to chronic morbidity, disability, and frailty. Heart disease, stroke, and cancer have long been the leading contributors to the overall disease burden in high-income countries, but these and other chronic diseases are increasing in middle- and low-income countries as well (24,25). This increment in the elderly population and therefore in the number of people suffering from chronic diseases is expected to have economic and social costs and may eventually affect economic growth. The issue that needs to be addressed now is whether the increase in life expectancy will go along with a postponement of morbidity, disability, and functional limitations. The challenges of an aging population are also a major concern of philosophy (26): Which are the modern aims of medicine: To reduce suffering and forestall death? How are we going to respond as a society to the delay of aging? Which strategies are we going to be developed for elder care? Therefore, understanding the process of aging has become a public health priority.
The aging phenotype is characterized by the accumulation of mutations, increased autoimmunity and an "aged immune system" that does not respond to the immune challenge like before. The question is whether age-associated diseases might share a common pathogenic pathway. If indeed a common pathway can be discerned, the second question is whether there might be a preventive or therapeutic strategy for reducing the incidence and severity of some of the age-associated diseases and age-associated morbidity and mortality. Since the accumulation of mutations throughout life (27), which increases exponentially with age, leads to the development of autoimmunity, autoimmunity is also more frequent in the elderly population (20,22,28). Autoimmunity can generate damage in certain tissues and lead to the development of age-associated diseases, whose prevalence is foreseen to increase in the upcoming years as a consequence of lifespan extension. Here, we propose that autoimmunity should be evaluated as a therapeutic target for the prevention and treatment of age-associated diseases.

**Mechanisms of aging**

In the past few decades, the common cellular and molecular features associated with the ageing phenotype have been categorized into nine hallmarks, including: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (29,30). However, many of the hallmarks are not causes of aging, but rather secondary and later consequences of underlying molecular damage. Other researchers have identified seven common 'pillars' or mechanisms driving aging and age-related diseases: adaptation to stress, epigenetics, inflammation, macromolecular damage, metabolism, proteostasis, stem cells, and regeneration (31) which are interconnected and modulate each other. Impairment of anyone pillar fuels inflammation, which subsequently affects all the other pillars (32). The question of whether any of these specific manifestations of aging is or is not a root cause is very important because it will have an impact on the strategy adopted in the development of therapies to treat aging. Near all medical technology employed to date to treat age-related diseases fails to touch on the root causes of aging, however, and this is why these therapies are only marginally effective at best. They modestly ease suffering, but they cannot meaningfully prevent or turn back any aspect of the progression of aging (33). An interesting hypothesis arises from the
observation that human aging is characterized by a chronic, low-grade inflammation with high levels of pro-inflammatory markers in cells and tissues, named “inflamming” (34). These proinflammatory markers generate autoimmunity which is observed with a higher frequency among normal older people, and indeed autoantibodies are a common finding in a healthy elderly. Nevertheless, the precise etiology of inflamming and its potential causal role in contributing to age-associated diseases remain largely unknown.

**Age-associated clonal mutations in hematopoietic stem cells and solid tissues**

The human body contains approximately 100,000 trillion cells, with over 200 different cell types. Between 50 and 70 billion cells die each day in an average adult and the body’s ability to replace dead cells by new ones is key to the long lifespans observed nowadays. Almost all of our cells get replaced at different rates over the course of a life, but some tissues never replace cells. For example, in the blood system, the hematopoietic stem cells (HSC) produce mature blood cells at a rate of more than one million cells per second in the adult human (35). During each cell division there is an error rate of about three base pair mutations per cell cycle, resulting in three main base pair mutations per second. However, most mutations occur in irrelevant base pairs. In addition, telomere attrition being one of the hallmarks of aging further enhances the mutation rate with aging (29,36). Some of these mutations can eventually affect genes that contribute to oncogenesis. Since the older we get, the more mutations we accumulate (37), advancing age is the most important risk factor of cancer. Therefore, aging and cancer would share the same underlying mechanism; the accumulation of mutations. Cancer risk increases exponentially with age (38) and its incidence is expected to increase in the coming decades due to the growth and aging of the population (39). In order to cause cancer, the mutated cells must retain or reacquire stem cell properties to give rise to global proliferation which is one of the three essential pathophysiological hallmarks of cancer cells (40). The other two essential pathophysiological hallmarks of cancer are the block of differentiation and the acquisition of immortality (41). Tomasetti and Vogelstein (42) demonstrated the relationship between the cumulative number of stem cell divisions and cancer risk in different tissues of the human body. They showed that the variation in cancer risk among tissues is attributable to random mutations arising during DNA replication in normal, noncancerous stem cells. The molecular events
leading to the accumulation of clones with cancer driver mutations and the development of cancer have recently been reviewed in detail (37,42–44).

A series of recent studies have demonstrated that aging confers a predisposition to clonal hematopoiesis, that means the exponential acquisition of mutations in hematopoietic stem cells and their clonal propagation (45). Not surprisingly, the incidence of mutations correlated with the risk of hematologic cancers (46). Moreover, the incidence of clonal mutations also correlated with the risk of cardiovascular disease (17,47). Clonal proliferation is not only seen in the myeloid compartment of the blood system but also in B cells and plasma cells. More recently, clonal mutations have also been described in the esophagus demonstrating that age-associated mutations are present in all tissues whose cells are capable of dividing (11,48).

**Age-associated clonal proliferation of B cells and plasma cells: Monoclonal gammopathy, monoclonal B cell lymphocytosis, and malignant lymphomas**

Monoclonal gammopathy of undetermined significance (MGUS) is a monoclonal plasma cell disorder (49) frequent in the elderly. MGUS is a precursor to several lymphoplasmacytic malignancies, including immunoglobulin light-chain amyloidosis, multiple myeloma, and Waldenström’s macroglobulinemia. MGUS progresses to multiple myeloma at a rate of 1% per year. Recently, a novel subgroup of monoclonal gammopathy, “monoclonal gammopathy of clinical significance” has been differentiated from MGUS (50). In this case, the monoclonal paraprotein is stable with no impact on normal hematopoiesis and not requiring any treatment per se. However, the clone and its paraprotein are associated with potentially severe organ damage, due to the toxicity of the monoclonal immunoglobulin molecule or its light chain. This phenomenon is increasingly observed but still poorly recognized and frequently undertreated, although it should receive rapid specific intervention to preserve organ function. Efficient control of the underlying B-cell clone usually results in organ improvement (50). Monoclonal B-cell proliferation in otherwise asymptomatic patients has also been described and termed Monoclonal B-Cell lymphocytosis, or MBL (51). Although monoclonal T-cell proliferation has been described, their clinical significance remains to be determined. Similar to MGUS and MBL, the term T-cell clonopathy of undetermined significance has been proposed (52).
B-cell lymphomas frequently carry an idiotype which recognizes low-affinity autoantigens (53). Thus they can be considered as the malignant progression of a preexisting autoreactive B cell clone. Similarly, 33% of idiotypes in myeloma have been shown to recognize physiological lysolipids (54).

In summary, clonal proliferation of the myeloid lineage, as well as the lymphoid lineage, has been previously described. We hypothesize that these lymphoid clones similarly to myeloid clones have an effect on age-associated changes and diseases including autoimmunity.

**Mutations can generate neoantigens: induction of autoimmunity and inflammation**

Chronic inflammation has been described as a common pathogenic factor for age-associated diseases such as cardiovascular disease, cancer, arthritis, diabetes and metabolic syndrome (55,56) and probably also aggravates degenerative diseases like arthrosis (55). On the other hand, autoimmunity has been shown to increase with age (20,22,28). We hypothesize that the increase in autoimmunity in old people may be enhanced by the accumulation of mutations throughout life as observed in cancer patients (57,58). Autoantibodies directed to these neoantigens could also cross-react with endogenous antigens causing a chronic autoimmune inflammatory response (59). If autoimmunity and autoantibodies indeed are common in old people and contributing factors to age-associated diseases by causing inflammation, the question arises if these antibodies might also play a role in contributing to the development of age-associated diseases. For example, by binding to certain receptors that stimulate or inhibit important signaling pathways and in this way influence cellular functions. This has been previously observed in cancer, where antibodies not only play a role in inhibiting or killing cancer cells but also in stimulating cancer cell growth (60). Recently, a profound relationship between inflammation and the expression of the DNA repair-associated enzyme 8-Oxoguanine DNA glycosylase 1 (OGG1), which binds with high affinity to 8-oxoG in double-stranded DNA to initiate DNA base excision repair, has been demonstrated (61). This observation strongly supports the relationship between mutations, DNA repair, and inflammation.

**Age-associated changes in immunity**
An additional risk factor for autoimmunity and inflammation are age-associated changes in the immune system itself. Autoimmune diseases occur only in those individuals in whom the mechanisms regulating immune tolerance fail, resulting in self-reactivity that can cause tissue damage. For example, rheumatoid arthritis is an autoimmune disease that occurs in individuals with an aged immune system whose immunocompetence is declining (22). Recently, age-associated changes in the B cell compartment have received increasing attention. These changes in B cells, including the new phenotype, “age-associated B cells” (62) lead to complex dysfunction associated with inflammation (63–65). This newly discovered B cell subset expresses the transcription factor T-bet and exhibits a unique cell surface phenotype (66). It progressively accumulates with age and is associated with viral infection and autoimmunity in mice and humans (66–70). Interestingly, chronic inflammation has also been shown to accelerate aging by inducing telomere dysfunction (36).

Autoimmunity and cancer: A role of B cells in Cancer?

Cancer and the immune system interact in a black box

When a patient presents cancer, it means that immune surveillance has failed. The immune system was not able to contain cancer cell growth leading to cancer progression (71). However, it is not clear, whether the immune system has failed to recognize cancer antigens or whether its response has been inadequate. The immune system might not only fail to suppress cancer growth but could also stimulate cancer cell development and proliferation. Chronic inflammatory conditions, for example, enhance a predisposition to cancer development (72). Studies about cancer immunity have largely been focused on the role of T cells leading to novel treatment strategies. These immune checkpoint inhibitors block immune checkpoints on T cells or on tumor cells allowing autoreactive as well as cancer-reactive T cells to kill cancer cells. The translation of this concept to animal studies and human trials was recently recognized by the Nobel Prize (73).
Autoantibodies: Protective or harmful?

The fact that cancer cells undergo continuous evolution with respect to their genome, and their epigenetic features (74,75) results in the continuous generation of novel antigens. It is therefore not surprising that cancer patients exhibit a broad spectrum of anti-cancer antibodies, which appear to increase with progressive disease (76). Studies of B cell responses to cancer antigens using the Serex technology (77) demonstrated that IgG antibodies can be associated with both, a good (77,78) or poor prognosis in different cancer entities and stages. Antibodies including autoantibodies certainly can have agonistic functions stimulating tumor growth (60). In a rat model of pancreatic cancer, the B cell receptor blocking agent Ibrutinib has been shown to induce remissions and prolong survival (79). In a study by Kim et al. (80) B cell depletion augmented antitumor immune responses and immunotherapy in non-hematopoietic murine tumor models.

The mechanism of action of these autoantibodies on cancer cell growth has not been studied in detail. It has been demonstrated that autoantibodies directly stimulate cancer cells to grow (60). Agonistic monoclonal antibodies are frequently used clinically (81) as well as experimentally, e.g. anti-CDR and anti-CD28 antibodies to activate T cells (82). Furthermore, an indirect effect on cancer cell growth can be mediated by inflammatory reactions in cancer tissues and their microenvironment. Autoantibodies could also influence B regulatory cells (83). If autoantibodies against cancer cells are indeed harmful in many cancer patients the question arises whether a B cell depleting strategy could be beneficial. Considering clonal evolution of cancer cells, cancer is a “moving target” that constantly changes its antigen pattern, Martin et al. (84) suggested that the aging human B cell repertoire is associated with a failure of selection, e.g. elimination of autoreactive clones.

Linking cardiovascular disease, mutations, and autoimmunity

Clonal mutations in hematopoietic cells are potent and newly recognized contributors to cardiovascular risk

The presence of clonal hematopoiesis in peripheral-blood cells was associated with nearly a doubling in the risk of coronary heart disease in humans and with accelerated atherosclerosis
in mice (17). It has been proposed that the progeny of mutated hematological stem cells malfunctions and thus increases inflammation (47). Alternative pathways include malfunctioning endothelial cells derived from the mutated clones, neoantigens, and autoantibodies to mutated HSC cross-reactive endothelial cells could also contribute to increased inflammation. Inflammation is considered to be one of the major pathogenetic factors for cardiovascular diseases. These observations convincingly demonstrate that organs exist in an ecosystem where pathological alterations in one organ system can affect other systems. However, it is not completely clear whether the accumulation of mutations in the hematopoietic system is just an indicator of the damage accumulated also in other organs or whether the mutated hematopoietic cells directly contribute or generate the damage observed in other organs, e.g. the cardiovascular system. The increase in clonal hematopoiesis with age could be an indicator of aging in all organs. While the relationship and interactions between different organ systems have been known for a long time, we propose the name "cross-organ pathophysiology" to the association between the molecular damage in one organ with clinically relevant diseases in another organ.

**Autoimmunity and Cardiovascular disease: A role of B cells in cardiovascular disease?**

Zouggari et al. (85) demonstrated that mature B lymphocytes induce monocyte mobilization to the heart leading to the deterioration of myocardial function. These observations demonstrating the importance of antibodies have been confirmed by Keppner et al. in 2018 where they show that autoantibodies contribute to ischemic heart failure progression (86). Moreover, the importance of not only local but also systemic inflammation for cardiovascular events was recently demonstrated in two clinical trials. The association of influenza infection and acute myocardial infection does suggest that a systemic immune reaction can further enhance inflammatory events in atherosclerotic lesions (87). Furthermore, it has been demonstrated in a recent clinical trial, that blocking the Interleukin-1β pathway systemically with the anti-IL-1β antibody Canakinumab leads to a significantly lower rate of recurrent cardiovascular events than placebo and this effect was independent of the reduction in the lipid levels (88). The
association of systemic inflammation with increasing age “inflammaging” and its contribution to aging, cardiovascular disease, and frailty has recently been reviewed (56).

**Age-associated neurological disorders**

Aging is also a major risk factor for the most common neurodegenerative diseases including mild cognitive impairment, cerebrovascular disease, Lou Gehrig's disease, multiple system atrophy, Parkinson’s disease, Alzheimer's disease, stroke, transient ischemic attack, amyotrophic lateral sclerosis, Reutzfeldt–Jakob disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, as well as neurological disorders associated with other diseases such as diabetes mellitus (89). Several reviews describe the myriad aspects of age-associated neurological disorders (90–94). While much research has been focused on other age-related diseases such as cancer and cardiovascular disease (see above), there are few studies on the molecular biology of the aging brain (95). Available research does suggest that the aging process is associated with several structural, chemical, and functional changes in the brain as well as a myriad of neurocognitive changes. Recent reports in model organisms suggest that as organisms age, there are distinct changes in the expression of genes at the single neuron level (96). The importance of age-associated accumulation of genetic and epigenetic alterations should become an important research topic in the future. Misfolding of proteins is a common component of the proposed pathophysiology of many diseases associated with aging. The proposed mechanism for Alzheimer's is related to the accumulation of amyloid beta, in a similar mechanism to the prion propagation of Creutzfeldt-Jakob disease (97,98). An interesting approach for studying the brain in vivo is a machine learning MRI model described by Raffel et al. (99). Since brain cells rarely divide, their clonal proliferation is a rare phenomenon. Induction of immune responses, however, could be triggered by alterations in protein folding and posttranslational modifications (59,100).

Inflammation has been recently recognized as a pathogenic mechanism closely linked to neurodegeneration (101–106) The relationship between autoimmunity and neuropsychiatric disease (104) suggests that autoimmune processes play a more important role in neurological age-associated diseases than appreciated till now. A pathogenic role has also been assigned to systemic inflammation in neurodegeneration (101–103). This observation is, of course, reminiscent of the role of systemic inflammation in cardiovascular diseases. In the last decade,
an increasing number of anti-brain antibodies have been detected that can affect cognition and behavior (106). The most striking evidence is provided by tumor-associated autoantibodies causing paraneoplastic neurological disorders. These antibodies are cross-reactive to neuronal antigens expressed on cancer cells leading to neuronal cell death after antibody binding to neuronal antigens (105).

**Conclusions and Outlook**

Cancer incidence is subjected to inherited genetic factors, exposure to environmental carcinogens, and random errors occurring during DNA replication in normal stem cells, factors that are the determinants of mutations. While molecular aging rates appear to be linear, mortality increases exponentially with age parallel to the acquisition of mutations, strongly suggesting that the accumulation of mutations over time are at the root of age-associated diseases and mortality. The fact that the incidence of MGUS and MBL increases with age, supports the notion that age-dependent accumulation of genetic damage increases the risk of developing a clone with increased survival and proliferation potential in the B cell compartment. This was also demonstrated in hematopoietic stem cells and recently, in esophageal cells. Only those cells whose mutations confer a proliferative and survival advantage will be detected in clinical studies, as is the case for monoclonal gammopathy or malignant lymphomas. However, there is a much higher burden of genetic changes accumulating with age besides those that may induce cancer. The collateral damage of these "silent" genetic mutations, i.e. inflammation, and autoimmune phenomena, play a significant role in aging and age-associated diseases. B-cells and autoimmunity appear to be overlooked players contributing to cardiovascular diseases, carcinogenesis, neurodegenerative disorders, and atherosclerosis.

We propose the name “Omega Syndrome” (Fig 1) to refer to the set of most important players contributing to aging and the development of age-associated diseases. Mutations, autoimmunity, and inflammation are common to both, even when elderly individuals' do not experience a specific age-associated disease. The accumulated genetic and epigenetic damage throughout life can lead not only to functional alterations of cells and to carcinogenesis but is also a relevant factor for age-associated autoimmune phenomena. Subclinical effects of
autoimmunity on all tissues could be a relevant pathogenic factor contributing to age-associated changes (e.g. in the cardiovascular system and the brain) that may cause age-associated diseases like atherosclerosis or neurodegeneration.

Treatment strategies could be developed in the future to block the biological effects of these mutations, eliminating the mutated cells by pharmacological or immunological means at an early stage, before they produce harm. We suggest that autoimmunity should be evaluated as a therapeutic target for the prevention and treatment of age-associated diseases. Anti-B-CD20 antibodies, which are an effective treatment for the vast majority of autoimmune diseases and lymphomas of B-cell origin, could be excellent drugs to evaluate.

**Fig 1: The Omega syndrome.** This model presents the main and common players involved in aging and age-associated diseases. The aging process itself consists of the inevitable accumulation of cellular and molecular damage with time and manifests only late in life when the mutation probability in our cells increases exponentially. This leads to the development of autoimmunity and inflammation, which are more frequent in the elderly population. Autoimmunity can generate damage in various tissues accelerating aging or eventually leading to the development of age-associated diseases. Even if not all elderly individuals’ experience age-associated diseases they may experience the subclinical effects of autoimmunity on all tissues of the body.
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