Immunosenescence: implications for cancer immunotherapy in elderly patients

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ABSTRACT

The aging process produces functional and developmental changes in the immune system. Those changes may occur at different levels or at different moments, from lymphopoiesis up to the final response of the immune system facing a certain disease. The response of the adaptive immune system is most strongly affected by the aging process, particularly at the level of the effector T-cells. These changes can have a negative impact on the immune response of elderly patients during cancer immunotherapy. The present paper is an updated review of the bibliography on the most important modifications produced in the immune system during aging, as well as on the relevance of these modifications for the design of new strategies for cancer immunotherapy.

Key words: Aging, immunosenescence, cancer, immunotherapy

Introduction

The deterioration in the performance of the immune system due to aging has been named immunosenescence. One of the symptoms of this deterioration is an increased susceptibility to infectious diseases, cancer, and autoimmune disorders [1]. During aging there is a steady accumulation of functional defects in the immune system that gradually compromises its performance; for instance, the production of lymphocytes in the bone marrow and thymus decreases, ultimately reducing the amount of available naïve cells for replenishing the peripheral repertoire [2]. Additionally, there are oligoclonal expansions of effector T lymphocytes with specificities restricted to a narrow set of epitopes, related to infections acquired during the lifetime of the individual; the T-cell repertoire shrinks, and, in general, there is a decrease in the immune response. Although these age-related defects have been known for some time, most studies in this field have been limited to their description, and it is only recently that the focus has shifted towards the identification of the mechanisms underlying these processes. There has been a growing interest in recent years on the development of geriatric oncology, due to the evidence of several risk factors for cancer development at advanced ages, as well as the increase in life expectancy in many modern societies. A thorough analysis of all the information currently available on this topic would be useful for the design of new, specific strategies focused on increasing the efficacy of vaccinations in the elderly, restoring the immune function in immunocompromised individuals, and for the prevention and control of cancer.

This review describes the main findings of the last 10 years on the aging-related deterioration of the immune system, with the aim of providing information for the development of new schemes of specific immunotherapy for cancer treatment in elderly patients.

Effects of aging on thymopoiesis

The thymus is the site for maturation and differentiation of T-cells, also known as “the immunological clock of aging”. The involuting of this organ, and the decrease in the output of T lymphocytes, are two major changes that take place in the immune system in the course of aging.

Thymus involuting generally begins during puberty. However, it has been reported that the atrophy of the epithelial space begins during the second year of life in humans. Although there is functional thymic tissue at least until the age of 60, after 50 most of the parenchymal tissue has been replaced by fat. This involution results in a decrease in the production of T cells and their export to the secondary lymphoid organs additionally affecting the maintenance of the naïve cell repertoire in the peripheral T cell compartment [2].

The thymus receives a constant stream of incoming hematopoietic precursors derived from stem cells in...
the bone marrow. It has been observed that age brings about important changes, such as a decrease in replicative potential [3], which results in a diminished capacity for the renovation of stem cells. A number of authors consider that the changes with age in the compartment of intrathymic progenitor T cells are due, in part, to a decrease in the lymphopoiesis of T cells, since it has been shown that the bone marrow of older mice does not produce lymphocytes with high efficiency when transferred to a younger individual [4, 5]. This indicates that the intrinsic defects accumulating with age are deleterious for the potential development of these cells.

The thymus contains a heterogeneous population of stromal cells that support the development of T cells. It has been speculated that age leads to the selective loss of one or more of these populations, as well as to detrimental changes in their size and functionality. This may be attributed to a reduction in the synthesis of key factors for T cell lymphopoiesis, such as IL-7 [6, 7], which has been linked to thymus involution.

Several authors have noted that the organization and maintenance of the thymic microenvironment depends on signals produced in the mature T lymphocyte [8, 9]. Therefore, it is believed that the initial reduction in T cells due to age-related defects in the early progenitors of the T lineage might affect the viability or functionality of the stromal thymic cells, thus compromising their potential to contribute to thymic microenvironment. This would, in turn, have a negative impact on the progenitor cells that would lead to the reduction of the T cell population [10].

Phenotypic analyses of lymphoid cells and their microenvironment have proven that thymus involution is mainly caused by quantitative changes. Although the total volume of the thymus decreases with age, its main lymphocyte subpopulations are preserved during the lifetime of the individual, both in cortex and medulla.

It has also been proven that extrathymic factors, such as zinc, cathepsin L, melatonin, thyroid hormone and growth hormone, are important for the maintenance of thymic functionality [11-13]. The interaction between developing thymocytes and thymic stromal cells can be sensitive to changes in the endocrine system, since both express receptors to one or more hormones, including the growth hormone and insulin-like growth factor I [14, 15]. These hormones have an antipoptotic effect on thymocytes and, additionally, stimulate the synthesis of cytokines by the thymic stromal cells.

Studies performed on rodents have shown that lymphopoiesis is stimulated by these hormones [14, 16], and the administration of growth hormone in humans increases the size of the thymus. However, this procedure does not restore the amount of thymic T cells to the levels found in younger mice [14]. Other authors have reported that the administration of IL-7 to mice can also increase the number of thymic T cells, but again, not to the levels found in young individuals [17, 18]. These findings, considered together, evidence that thymic involution is a multi-factorial process, and illustrate why reversing the changes occurring in the population of peripheral T cells with simple interventions with hormones or similar treatments is hardly a trivial task.

### T cells

The critical changes that characterize the immunosenescence process take place mainly in T cell populations. The three most important alterations observed are:

1. A decrease in the number of naïve cells, due to diminished levels of lymphopoiesis.
2. An increase in the number of memory cells, leading to an increase in the production of cytokines.
3. The accumulation of dysfunctional activated effector cells with a limited repertoire [19].

The T cells produced in the thymus migrate to different sites in the secondary lymphoid organs. The number of these cells does not change much with aging but, there is a significant reduction in the responses mediated by CD4 and CD8 T cells [20, 21].

One of the main reasons explaining the reduction with age of cell-mediated immunity is the substantial reduction in the fraction of naïve T lymphocytes, with a simultaneous increase in memory T cells [22]. The net effect of the reduction of peripheral naïve T cells is the shrinkage of the available repertoire, and, consequently, a poorer response to the appearance of new antigens.

As mentioned above, the fraction of T cells with a memory phenotype increases with age. This change has been particularly well studied in CD4 T cells. The analysis of CD4 T cells obtained from aged animals which have been depleted of their peripheral populations and reconstituted with precursors from young individuals has shown that the new CD4 T cells in the old animals are mainly memory cells with a CD44+CD57– phenotype, producing IL-2 and with a cytokine profile characterized by high levels of gamma IFN, IL-2 and IL-5. This suggests that the aged microenvironment of the host leads to an accelerated maturation of the naïve CD4 T cells towards a memory state [1].

It has also been reported that age produces not only alterations in the thymic microenvironment, but in biochemical and molecular mechanisms of the T cells as well: a decrease in transmembrane signaling upon the engagement of the T cell receptor, changes in tyrosine kinase activity due to a reduced activation of the raf-1 and MEK-ERK kinases, and a decrease in the CD28-mediated activation of the JNK kinase. Among other changes occurring downstream to TCR stimulation, there are reductions in transcriptional factors [22-24] that play an important role in the expression of genes involved in the induction of the immune response [25].

The proliferation of T cells requires the synthesis of IL-2 and the presence of its receptor (CD25) [26, 27]. However, aging reduces the expression levels of this receptor, and the reduction in the size of the naïve lymphocyte populations also reduces the production of IL-2 [28]. Additionally, the existence of a chronic inflammatory state at older ages, caused by an increase in the levels of IL-6 and TNF alpha, has been reported [29]. During this state the sensitivity of CD4+ and CD8+ cells to TNF, alpha-induced apoptosis increases. Chronic exposure to TNF alpha can lead to the loss of CD28 expression in naïve CD8 T cells and central memory cells. Whereas effector T cells are resistant to apoptosis under these conditions, naïve or central memory cells are not [30].

Another important alteration taking place in T populations is the accumulation of terminally differentiated effector cells that are reactive against a particular virus, but have an extremely limited TCR repertoire [31]. Often there is an oligoclonal expansion, preferentially involving CD8 T cells [32, 33], which are reactive against Cytomegalovirus (CMV) and Epstein Barr (EBV) [34, 35]. In humans, this expanded population appears to be resistant to apoptosis, it has lost the expression of the CD28 co-stimulatory molecule, it has shortened telomeres, and it has suffered a reduction of its proliferative capacity [36].

Longitudinal studies in healthy, elderly individuals, have shown that aging produces an inversion of the CD4:CD8 ratio, associated to an increase in mortality [37]. It is known that doubling the number of CD8 T cells after repeated stimulation cycles leads to the appearance of activated effector cells with a CD28-, CD27-, CD45RA+, CD57+ phenotype [34, 38]. These dysfunctional CD8+ cells can reduce the repertoire of available T cells for responding to new infections or neoplasias.

Several authors have reported a specific decrease in the response to immunizations in elderly individuals, due to a reduction in naïve cells. As age increases, the number of naïve CD45RA+ CD8 T cells decreases, with an associated increase in CD45RO+ memory CD8 T cells [28] and a reduction in the expression of the CD27 and CD28 markers, which indicates a high degree of differentiation of CD8 T cells in these individuals [39-41]. It has been hypothesized that memory CD8 T cells might lose their capacity for replication due to telomere loss, which can restrict their functionality or persistence during aging [42]. The naïve and memory CD8 T cells from older individuals have significantly shorter telomeres than their homologous counterparts from younger individuals [43, 44], and this phenomenon, especially in the case of clones recognizing persistent antigens, can eventually limit their expansion. Since the latter can become problematic for older individuals who have had multiple encounters with the same antigens throughout their life, chronic viral infections can play a major role in the establishment of replicative senescence.

**Replicative senescence and the role of antigenic load**

The loss of CD28 in the T cells from aged individuals can have a substantial impact in their functionality, since this molecule is involved in several key processes; including the transcription of IL-2 genes IL-2 [45], apoptosis, cellular adhesion and the regulation of telomerase activity [46-49]. These cells are characterized by a reduced proliferative capacity and short telomeres, indicating that they may have reached a stage in which human cells can no longer proliferate and therefore, are irreversibly impaired in their capacity for growth and adoption of functional changes. The latter phenomenon is known as replicative senescence [50, 51].

Replicative senescence is typical of CD8 T cells. The expanded CD8+CD28- cells are usually oligoclonal, and most of them are positive for CD57. During cell culture experiments in which CD4 and CD8 T cells from the same donor have been subjected to identical stimulation protocols, it has been observed that there are no further increases of telomerase activity in the CD8 T cells after the fourth encounter with the antigen, and most of these cells do not express CD28. On the other hand, the CD4 cells from the same donor, having experienced the same number of replication events, show high levels of antigen-induced telomerase activity and the expression of CD28 in a high percentage of the population [49]. Senescent CD8 T cells remain viable and metabolically active for long periods of time, preserving their antigen-specific cytotoxic capacity [1, 50]. In spite of the loss of the CD28 co-stimulatory molecule –characteristic of T cell replicative senescence– these cells retain other T cell markers indicating their cellular lineage. Senescent T cells not only have shortened telomeres and detectable telomerase activity, but also display a significantly reduced response to thermal shock and an increased resistance to apoptosis [50]. Being effector cells that have entered a terminal stage of differentiation, they produce gamma IFN, but their levels of IL-2 synthesis are markedly reduced, in contrast to CD8+CD28+ T cell clones in which the reverse is true [1].

It has been proven that there is a correlation between a high proportion of CD8+CD28- and CD45RA+CD27- T cells, and seropositivity to CMV [52, 53]. This seropositivity suggests that in healthy elderly individuals there is a bias of the CD8 T cell repertoire towards a large expansion of specific clones recognizing a restricted number of CMV epitopes which no longer express CD28 and CD27 [54]. Such a situation leads to the expansion and accumulation of dysfunctional virus-specific T cells, thereby reducing the repertoire of available functional T lymphocytes for responding to new antigens [55]. The chronic stimulation of the immune system (antigenic stress), caused by infections occurring earlier in life, is considered by many authors to be the most important cause of immunosenescence, which is characterized by a reduction in immunological space and a restriction of the T repertoire, and ends up being substituted by quiescent antigen-experienced cells [56].

There is evidence that a persistent exposure to infectious agents leads to a faster senescence of the immune system. This, as explained above, decreases the expression of important molecules for T cell activation and reduces their functional capacity, leading to a clonal expansion that fills the immunological space and results in telomere shortening, and the subsequent inability to proliferate. Most elderly persons have trouble coping with infections, due to senescence [57]. It is important to point out that in people reaching an age of 100 or more without significant health disorders, the functionality of the immune system is well preserved, with parameters resembling those of much younger persons [58]. This suggests that their longevity is due, at least in part, to a slower progress of immunosenescence, in spite of the remodeling that age imposes on the immune system.

The facts exposed above underscore the need for reducing the chronic stimulation of the immune system when treating infections that cause chronic antigenic loads. This includes the treatment of intestinal parasites and vaccination against the most common viral infections in man, such as EBV and CMV.

B cells

The reduction of B cell lymphopoiesis, in a situation paralleling that of the thymus, may be produced both by intrinsic defects in B cell progenitors and by age-related changes that negatively affect the potential of the bone marrow microenvironment to support their growth and differentiation. The decrease in the generation of B cells of older mice reconstituted with bone marrow transplants from younger donors [59, 60], and an inadequate level of IL-7 secretion by the aging stromal cells [61], support the notion that aging brings about an accumulation of microenvironmental defects.

The steady input of B cells into the spleen, and their later selection within the marginal and follicular zones, guarantee a constant replenishment of splenic B cells, as well as the maintenance of repertoire diversity [62]. Aging produces alterations in peripheral B cells in two important ways: The number of B cells migrating from the bone marrow to the spleen is reduced, and there is an accumulation of cells of the B lineage in the transitional and mature compartments of the spleen [63, 64]. Many of the latter cells are experienced memory B lymphocytes, which have moved on to fill the peripheral niches left by the reduced production of follicular B cells [65].

These changes in the composition of the peripheral B cell population have a consequence for humoral immunity: a rise in the incidence of autoantibodies [66] and a concurrent reduction of antibody response to foreign antigens [1, 67]. In studies in mice, it has been observed that aging brings about a gradual decrease in the formation of germinal centers [68]. Several authors have reported that the duration of the humoral response in older persons is comparatively shorter than in young individuals, having less protective immunoglobulins with lower titers and decreased longevity [69-72]. Besides, it has been described that the proportion of IgM antibodies secreted by the B cells of elderly persons is higher, and that the set of V region genes being used is different to that employed at younger ages [73, 74]. Aging also decreases the expression of the B7 (CD86) co-stimulatory molecule [68], and propitiates the appearance of B cell receptor signaling defects [75].

The problems produced by aging on the functionality of the helper T cells can also contribute to the reduction of the capacity to mount a vigorous, high-affinity antibody response in the germinal reaction centers of elderly persons [68]. It has been found that the expression of CD40, an important molecule for the interaction of T and B cells, is reduced in the latter.

Recently, Eaton et al. reported a marked reduction on the expression levels of CD154 (also known as the CD40 ligand, or CD40L) in activated helper T cells from elderly mice [76]. Since the interaction between B and T cells via CD40 and CD145 is necessary for the formation of germinal centers and antibody class switching, this might be an explanation for the poor antibody responses observed in the vaccination of older persons. A study on elderly patients vaccinated against influenza virus showed that elder vaccinees fail to develop adequate antibody titers, thus remaining only marginally protected, or exposed to severe episodes of influenza infection in spite of the vaccine [77, 78].

Innate immunity

The innate immune system also deteriorates with age in humans and animals. Although the studies published on this system are less advanced than those focusing on adaptive immunity, several age-related changes have been described. For instance, the increase in B1 cells (producers of autoantibodies) with age might explain the increased frequency of self-reactive immunoglobulins in the elderly [65].

There is evidence demonstrating a reduction of the functional potential of monocytes and macrophages in older mice. The comparison of human monocyes from young and old donors showed that in the latter there was a reduction in the level of cytotoxicity against tumor cells after activation with LPS, which was associated to a decrease in IL-1 secretion and the production of oxygen reactive intermediaries, such as NO; y H2O2 [79]. Furthermore, there were alterations in the secretion of other chemokines and cytokines, such as IL-6 and TNF alfa, and a significant reduction of the expression of Toll-like receptors, both in spleen macrophages and in the activated peritoneal macrophages of old mice [80, 81]. These phenomena would have a negative impact on antigen presentation, and could trigger an inadequate activation of the innate or adaptive immune functions [82].

As in other cellular populations, the microenvironment in an older host can certainly influence the differentiation and the behavior of antigen-presenting cells. It has been observed that IL-10, a key cytokine that suppresses cell-mediated immunity and the maturation and function of dendritic cells, is up-regulated in healthy old individuals [83]. The process of aging also affects the migratory capacity of dendritic cells [84], and their numbers in epidermal decrease [85, 86].

Other studies related to the variations in innate immunity during aging indicate that the number of natural killer (NK) cells increases with age; however, their cytotoxicity is reduced [87]. In fact, it has been observed that NK cells from old persons secrete less IFN gamma and chemokines in response to IL-2 and IL-6 [88].

The Immune Risk Phenotype as an Integrating Element

Longitudinal studies conducted on a Swedish population of very old adults (more than 80 years old) [89] analyzed the changes in several immunological parameters related to aging, monitoring their behavior in time with the goal of establishing predictive factors for longevity [90]. These analyses yielded a set of parameters whose value can be used to predict the mortality and morbidity of a relatively homogeneous population within a time period of two years [91]. This set of parameters, associated to a poor immune function [25], has been called the Immune Risk Phenotype (IRP) [92] (Table 1).

The seropositivity to CMV was later associated to the IRP [93, 94]. It has been described that in some older individuals there is a clonal expansion of CMV-specific CD8 cells. These clones are dysfunctional, more resistant to apoptosis, and occupy a relatively large portion of the immunological space, being therefore harmful for the immune system [95].

Currently, several authors have hypothesized that the advance towards an IRP or the permanence in this
status with aging is greatly influenced by the nature of the individual response to CMV infection. Studies with persons of more than 80 or 90 years old have confirmed the presence, in this population of a marked expansion of CD8 CD28- cells, with receptors for a CMV epitope that is immunodominant in humans [34]. A high proportion of these CMV-specific cells also expressed high levels of the lectin-like G1 receptor, which is a negative regulator for killer cells (KLRG-1) [96]. This molecule is present in terminally differentiated senescent cells which, in spite of retaining their cytotoxic functionality, have a reduced capability for the secretion of cytokines such as IFN gamma.

These studies in very elderly persons also showed that the IRP behaved independently from the health status of the individual during the time in which the measurements were taken (2 years) [97]. The clinical relevance, in a pragmatic sense, of these IRP parameters has been an issue for some years [98]. The clinical relevance, in a pragmatic sense, of these IRP parameters has been an issue for some years [98].

The evidence suggests that at least some of the mechanisms used by cancer cells to escape the surveillance of the immune system might be more effective in older hosts. One of these mechanisms is the secretion of Fas ligand (FasL) and its receptor (FasR) [108]. It has been reported that the increase in the expression of FasR in aged leukocytes may facilitate the immune escape of FasL-expressing tumors through the induction of apoptosis in tumor-infiltrating leukocytes.

Another mechanism allowing tumors to escape from the immune system is the secretion of immunosuppressive cytokines, such as IL-10 and TGF beta, by cancer cells. These cytokines can suppress the inflammatory response of T cells and cell-mediated immunity, which are indispensable for tumor control and the destruction of cancer cells. Usually, the production of these cytokines is higher in the leukocytes of older persons, and their higher concentration might thus reduce the immune response of the host against the tumor [109].

The usefulness of cancer immunotherapy may look controversial in the light of the relationship between immunosenescence and tumor escape from immunosurveillance. Unlike most vaccines against infectious agents, which are mostly prophylactic, the cancer vaccines currently under development can be used on a wide array of scenarios, ranging from cancer prevention and the treatment of neoplastic lesions after early diagnosis, to their use in minimal residual disease. The NK and NKT cells are also actively involved in the response to certain immunotherapies.

Table 1. Immune Risk Phenotype (IRP)

<table>
<thead>
<tr>
<th>IRP</th>
<th>Positive IRP</th>
<th>Negative IRP</th>
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<tbody>
<tr>
<td>CD4:CD8 ratio</td>
<td>&lt; 1</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Proliferative responses of T cells to mitogens</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Number of CD8+, CD28-, CD57+ T cells</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Number of B cells</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Response to CMV</td>
<td>IgG seropositive</td>
<td>Seronegative</td>
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molecularly defined immunodeficiencies has led to a progress in the understanding of the complex relationship between this system and the cancer process [103]. Studies on IFN gamma or perforin in knockout mice have shown that the absence of these molecules, which are paramount for the proper functionality of T cells, decreases the susceptibility of the host both to spontaneous or chemically induced tumors [104, 105]. The NK and NKT cells are also actively involved in cancer immunosurveillance. One of the first experiments to prove this fact used a monoclonal antibody (anti NK 1.1) to deplete this population in the C57 BL/6 mouse strain, showing that the treated mice were more susceptible to methylcholanthrene-induced tumorigenesis than the untreated controls [106]. The accumulated data gathered so far indicates that immunosurveillance is not restricted to animal models, but it is also present in human beings [102, 107].

The incidence of cancer rises disproportionately at older ages, both in Cuba and in many developed countries. Cancer is one of the leading causes of death, especially in the age groups of 46 to 75. In spite of the existence of a large body of research on the topic, the relationship between aging and cancer has not yet been satisfactorily elucidated.

In earlier decades, the prevailing scientific opinion defended the concept that the conversion from a normal to a cancer cell was a relatively frequent event, with the resulting malignant cells being eliminated by the constant surveillance of the immune system of the host. According to this concept, the development of cancer cells into a clinically significant cancer would occur only if this immunosurveillance failed, due to aging or other reasons [100]. However, whether the rise in cancer incidence seen in the older population is mainly due to the deterioration of the immune system is still under discussion [100].

Although the idea of immunosurveillance was initially conceptualized by Paul Ehrlich in the first decade of the XX century [101], much of the research on the topic conducted ever since have, however, failed to prove the existence of such a system. Nonetheless, in recent years the concept that the immune system plays a critical role in the development of cancer has gained general acceptance [102]. The development of tumor models in mice with
The remodeling of the immune system due to the aging process suggests that the vaccination models with proven efficacy in young adults may not be as efficient with an older target population. It has been proven that in aged mice there is a reduction in the number of naïve T cells and their conversion to a memory phenotype [114-116], a deregulation of the Th1 and Th2 responses with a bias towards the Th2 phenotype, and a deterioration in antigen presentation to the T lymphocytes by the APCs, all of which illustrate the multiple deleterious effects of age in the immune system. These phenomena have a negative effect on the different cellular populations involved in the activation of the immune response against cancer [117, 118]. It has also been observed that the signals produced by the components of the innate immune system, which are required to lead the adaptive immune response, can be inadequate or misdirected in older individuals, having a negative influence on the clonal and specific adaptive response.

There is a consensus on the low efficiency of vaccines in the older adult. The latter is supported by the evidence from several vaccines against different infectious agents, such as the influenza virus [119, 120], the polysaccharide-based vaccine against pneumococci [121], tetanus [122], and combined Hepatitis A and B vaccines [123]. More than 50 cancer vaccines have been reported to enter the phase of clinical trials as of today. Most of these have been small, non-randomized trials focused on the evaluation of safety, immunogenicity and long-term responses for each product. Table 2 shows some of the products of this field in more advanced development stages [124]. Although it can be stated that the technology for generating an immune response against tumor-associated antigens and to measure this response has, in general, been developed, the efforts invested in this direction have failed to achieve the cure, or at least an increase in the survival, of cancer patients.

Two of the possible causes for the failure of clinical trials in their most advanced stages are the use of experimental models that do not represent clinical reality, and the intrinsic complexity of the immune system. In fact, most cancer vaccine candidates have been selected using experiments in young, healthy mice, transplanted with exogenous tumoral cells. Unsurprisingly, most of these vaccines are very effective in these models [124].

There are no clinical data on the relationship between the efficacy of cancer vaccines and the aging process. Some direct evidences on the reduction of their efficacy in models of older animals have recently been published. A study on the effect of mammary tumor cells modified to produce IL-2 to induce an antitumoral response capable of rejecting the tumor cells modified to produce IL-2 to induce an antitumoral response capable of rejecting the tumor [125]. All these immunotherapeutic tools have been shown to have severe limitations upon their introduction in clinical trials. A number of authors have recently suggested the possibility of using normally expressed self antigens as a target for cancer immunotherapy. Such is the case of the p185 protein, which is the product of the Her-2/neu oncogene and is also known as mucin 1; it is an epithelial glycoprotein that is overexpressed in 90% of adenocarcinomas. The same can also be said of the therapies based on the epidermal growth factor (EGF) and its receptor (EGF-R) [129-131]. These therapies have yielded mixed results in clinical trials, and whether immunotherapies using poorly immunogenic self antigens will be successful in the coming years remains unknown [124]. Recent, unpublished results from our group showed that the survival advantages conferred by vaccination with EGF to non-small cell lung cancer patients are confined only to individuals under 60 years old.

Although the data gathered so far is not enough, the available evidence suggests that the use of cancer vaccines in elderly patients may not be as effective as in young individuals, due to the effects of age on the activation of the specific immune responses. Therefore, there is a need for the development of techniques for the therapeutic manipulation of immunosenescence, with the goal of finding effective treatments against cancer in elderly patients. This goal will require a deeper understanding of the mechanisms underlying the process of immunosenescence.

**Conclusions**

The changes that take place with age on the immune system have been extensively described during the last decade. Much must still be discovered on the mechanisms underlying those changes, especially at the genetic and molecular levels. The data gathered so far indicate that adaptive immunity is the immune subsystem most highly affected by aging. The innate immune system seems to be only moderately affected, although it has been proven that age does affect some of its pathways. However, since it has become clear that an optimal immune response depends on a coordinated cooperation between both systems, a deterioration of one part will be obviously detrimental for the functionality of the other.

The age-related deregulation of the immune system may contribute to morbidity and mortality. The

### Table 2. Cancer vaccines: The Most advanced projects in clinical trials

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacuter</th>
<th>Anatomical location</th>
<th>Current status</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melacine</td>
<td>Corixa</td>
<td>Melanoma</td>
<td>Market</td>
<td>No influence on survival; improvement on quality of life</td>
</tr>
<tr>
<td>Theratope</td>
<td>BioMirra</td>
<td>Breast</td>
<td>Phase III</td>
<td>No influence on survival</td>
</tr>
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<td>Dendreon</td>
<td>Prostate</td>
<td>Phase III</td>
<td>Not available yet</td>
</tr>
<tr>
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<td>Small-cell lung</td>
<td>Phase III</td>
<td>Not available yet</td>
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<td>CancerVax</td>
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<td>Phase III</td>
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<tr>
<td>Oncophage</td>
<td>Antigenics</td>
<td>Kidney</td>
<td>Phase III</td>
<td>Not available yet</td>
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