Chapter 8
Immunosenescence and Cancer

Gisele W. B. Colleoni and Valquiria Bueno

Abstract The probability to develop invasive cancer increases enormously for individuals aged 70 years and more. In addition, cancer has been the first cause of death for individuals aged 60–79 years. In oldest age individuals (80 years and more) cancers such as breast and colorectal are mostly diagnosed at a metastatic stage with the low survival compared to other age groups. The treatment of cancer in old individuals is a challenge and a further knowledge of the tumor development in aged host immune system is crucial to develop individualized therapy and thus benefit this population. The lifelong exposition to carcinogens and insults increases the risk for cancer development and a physiological induction of cell senescence facilitates the clearance of damaged cells by the immune system. However, senescence seems to play a dual role leading to the clearance of tumor cells but also inducing proliferation and induction of tumor vascularization. Immunosenescence is another age-related event linked to cancer progression both for the decreased immunosurveillance and for the chronic low-grade of systemic inflammation (inflammageing) observed in ageing individuals. In this context, cancer immunotherapy has been administered aiming the enhancement of the immune response against the tumor but only a fraction of patients has achieved long lasting remissions. Senolytics such as dasatinib and querceting have been developed to selectively kill senescent cells and potentiate anticancer therapies.

Keywords Ageing · Cancer · Immunosenescence · Inflammageing

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Abbreviations

ARG1	Arginase 1
B-ALL	B cell Acute Lymphoblastic Leukemia
BCG	Bacille Calmette-Guerin
Bregs	B Regulatory cells
CAR	Chimeric Antigen Receptors
CMV	Cytomegalovirus
COVID-19	Coronavirus 19
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DC	Dendritic cells
DNA	Deoxyribonucleic Acid
gMDSC	Granulocytic Myeloid-derived suppressor cells
HPV	Human Papillomavirus
IDO1	Indoleamine 2,3-dioxygenase
IL-10	Interleukin 10
iNOS	Inducible Nitric Oxide Synthase
l-Arg	**L**-Arginine
M1	Macrophage type 1
M2	Macrophage type 2
mMDSC	Monocytic Myeloid-derived suppressor cells
MDSC	Myeloid-derived suppressor cells
MHC class I	Major histocompatibility complex class I
MHC class II	Major histocompatibility complex class II
NK	Natural killer
Nor-NOHA	N-hydroxy-nor-L-arginine
PD-1	Programmed death 1
PD-L1	Programmed death-ligand 1
ROS	Reactive Oxygen Species
TAA	Tumor-associated antigens
TAM	Tumor-Associated Macrophages
TCR	T cell receptor complex
TGF-β	Transforming Growth Factor beta
Th1	T cell helper 1
Th2	T cell helper 2
Tregs	T regulatory cells
USA	United States of America
UV	Ultraviolet

8.1 Cancer and Ageing

A USA study showed that the probability to develop invasive cancer in all sites during the period 2014–2016 for individuals aged 50–59 years was 6.2% for men and 6.4% women, whereas for individuals aged 60–69 years the probability was 13.3% and 10.2% respectively. These probabilities increased enormously for the individuals aged 70 years and more to 32.7% (men) and 26.7% (women). Breast (7.0%), lung (6.0% men and 4.8% women), prostate (8.2%), and colorectal cancer (3.3% men and 3.0% women) were the most incident sites for the population aged 70 years and more. In addition, cancer was the first cause of death for male and female aged 60–79 years and second cause of death for the age of 80 and more (Siegel et al. 2020). The higher incidence of cancer development and death in individuals older than 60 years compared to younger counterparts are not exclusive of the USA population but have been a common finding around the world (Bray et al. 2018). In Americans aged 85 years and more (oldest age), DeSantis et al. (2019) observed that some cancers (i.e. breast and colorectal) are mostly diagnosed at a metastatic stage with a relative lowest survival of any age group.

The treatment of cancer in oldest age individuals is a challenge due to comorbidities, decrease of the functional reserve, impaired cognition, reduced immunosurveilance, and polypharmacy which could increase the risk of toxicity to cancer therapies. A further knowledge of how tumor cells develop and escape from the aged host immune system could lead to individualized oncology and thus benefit older individuals.

8.2 Cancer Initiation and Progression

Considering that the human organism is exposed to carcinogens and insults capable to transform healthy cells in tumor cells, the lifelong exposition to these agents will increase the probability to develop malignancies (Fulop et al. 2010; Sportès and Hakim 2009). The common carcinogens such as tobacco, obesity, sedentarism, alcohol consumption, exposure to ultraviolet sunlight or tanning devices (http://cancerprogressreport.org/) could be avoided or reduced and therefore, many cases of cancer are preventable. However, several years of DNA damage in healthy cells disrupts their physiological growth and induces the development of malignant tumors. As a consequence, cancer cells present thousands of mutations, but only a small subset are "drivers" that trigger tumor growth and allow cancer cells to survive. Therefore, accumulation of mutations can be considered an age-related event that impact the pathogenesis of malignancies (Hanahan and Weinberg 2011). Another age-related cause that leads to tumor development is the lower efficacy of the immune system with decreased immunosurveillance and impaired immunity against tumor antigens (Foster et al. 2011) (Fig. 8.1).

One mechanism that fight cancer initiation and progression due to continuous DNA damage is the physiological induction of cell senescence which facilitates the clearance of damaged cells by NK cells, macrophages, and T cells (Burton and Stolzing 2018). Oncogene activation induces senescence and cell cycle arrest inhibiting thus a benign tumor progression to malignant tumor (Wajapeyee et al. 2008). In addition, the loss of tumor suppressor genes (TSG) can also induce cell senescence (Ahmad et al. 2011).

The senescence-associated secretory phenotype (SASP, cytokines and chemokines) activate innate and adaptive immunity for the clearance of tumor cells (Vicente et al. 2016). However, SASP play a dual role in the tumor microenvironment and can also induce tumor cell proliferation and induction of tumor vascularization (maladaptive senescence) (Toso et al. 2015). In addition, SASP is capable to attract myeloid-derived suppressor cells (MDSCs) which infiltrate the tumor microenvironment, block the immune response, and impairs the chemotherapy-induced senescence (Jackson et al. 2012).

Therapy induced-senescence (TIS) has been used to treat cancer and it can both impair the proliferation of tumor cells (Ewald et al. 2010) but also, some chemotherapy agents prevent the destruction of senescent tumor cells from the immune system. In addition, TIS enhances the process of ageing in normal cells of the patient (Marcoux et al. 2013).

8.3 Cancer and Immune System

Immune cells are attracted to tumor microenvironment and recognize molecules in senescent cells such as the receptor for CD58/ICAM (recognized by NK cells); macrophages express receptors (CD36, IgM, SIRPα, and leptins) for glycans, lipids, and vimentin that are present in senescent cells; T cells recognize antigens via TCR (Vicente et al. 2016; Burton and Stolzing 2018). Cytotoxic NK kills senescent cells via granules secretion (Sagiv et al. 2013). Macrophages polarized to M1 are essential for the adequate function of CD4+ T cells and for the phagocytosis of senescent cells (Kang et al. 2011).

During the ageing process, changes occurring in the immune system alter the immunity, increasing thus the susceptibility to cancer development (Isidori et al. 2018) (Fig. 8.1). In older individuals the different subsets of NK cells are redistributed, there is a reduced expression of activating receptors, and the cytotoxicity is impaired. NK activating receptors are also altered in cancer patients suggesting that age and cancer may have a synergistic action in NK cell by decreasing tumor immunosurveillance (Tarazona et al. 2017). T cells present senescence, anergy, and exhaustion which contributes differently for cancer progression. The reduced percentage of naïve T cells and increased percentage of effector memory T cells (mainly terminally differentiated CD8+) are common findings in aged individuals (Alves et al. 2018) and in addition to the reduced diversity of the TCR (T cell receptor) that impairs the

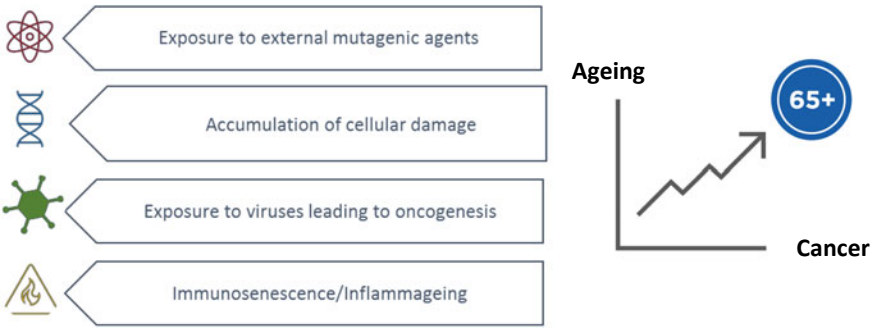

Fig. 8.1 Ageing and cancer: findings and risk factors

response to new cancer antigens (Foster et al. 2011), have been suggested as risks for the development of cancer.

The tumor microenvironment (TME) contains senescent tumor cells, stromal cells, proliferating tumor cells (non-senescent), and immune system cells. Tumor cells present suppressive mechanisms that act on healthy cells before the infiltration of cells from the immune system (Lowe et al. 2004). As T cells (CD4 and CD8) infiltrate the TME, they act as the main eliminators of tumor lesions (elimination phase). The incapacity from the immune system to total clearance of tumor cells but with prevention of tumor outgrowth (equilibrium phase), generates variants of tumor cells which are less immunogenic and thus maintained occult. Tumor cells with less immunogenic capacity expand and reach clinical stages (escape phase). Elimination, equilibrium and escape are phases described for the cancer initiation-progression and are known as cancer immunoedition (reviewed in Ostroumov et al. 2018). Thus, either tumor cells can be suppressed by the immune system or they can escape from immunosurveillance. As example Katlinski et al. (2017) showed that colorectal cancer cells resisted to cytotoxic (CTL)-mediated growth control by downregulation of interferon receptor chain (IFNAR1). In prostate and breast cancer patients with residual drug resistant tumors it was shown that MMPs in senescent cancer cells play a role to avoid immune recognition by NK receptors (NKG2D) cell (Muñoz et al. 2019). TME can also drive T cells to exhaustion causing loss of the effector function and upregulation of receptors of inhibition in T cells (Wherry et al. 2015) which leads tumor cells to escape from immune attack (Figs. 8.2 and 8.3).

Considering that "tumor promoting inflammation" is one of the Hallmarks of Cancer, some cells of the immune system with inflammatory profile are crucial as they provide conditions within the TME that contribute for tumor growth (Hanahan and Weinberg 2011). Therefore, angiogenesis, proliferation, and tissue evasion are facilitated in tumor cells due to the inflammatory cells support. As an example, macrophages polarized as M2 (anti-inflammatory) has been linked to immune suppression, angiogenesis, and tissue remodeling (Mantovani and Sica 2010). In this

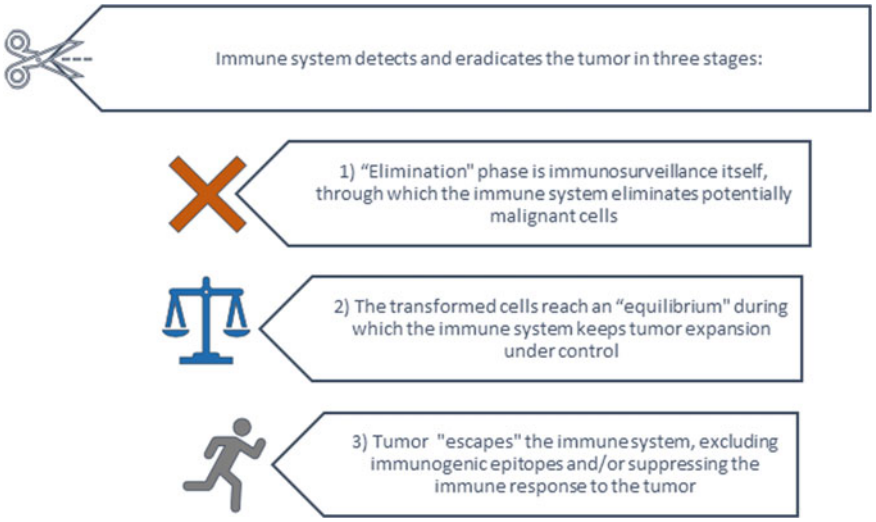

Fig. 8.2 The three phases of cancer immuno-editing: elimination, equilibrium, and escape

context, ageing has been associated with a chronic low-grade of systemic inflammation and thus, cancer and ageing could be linked by the inflammatory process (review in Leonardi et al. 2018).

The most studied group of cells in cancer in the last few decades which are also linked to inflammatory processes are myeloid-derived suppressor cells (MDSCs). In older healthy individuals, two different groups demonstrated an increase in the number of MDSC (Verschoor et al. 2013; Alves et al. 2018) and the maintenance of their suppressive capacity (Magri et al. 2020). These findings suggest an increased suppressive action on the immune system during the ageing process, thereby favoring tumor development. On the other hand, as the tumor itself induces emergency myelopoiesis, and in turn MDSCs, it is difficult to distinguish between the role played by age and by the tumor in the increased frequency and suppressive action of MDSCs. Some studies have shown that MDSCs contribute to tumor progression through suppression of tumor-specific T cell responses, stimulation of tumor angiogenesis, or facilitating tumor cell metastasis. Considering all available cancer therapies, their impaired efficacy has been related, at least in part, to the accumulation of MDSCs and their contribution to an immunosuppressive microenvironment (Shipp et al. 2016; Marvel and Gabrilovich 2015).

Since MDSCs are enhancers of other immunosuppressive cells, such as regulatory T cells (Tregs) and B cells (Bregs), we can assume that MDSCs remodel the immune system, preventing excessive inflammation during the aging process (Salminen et al. 2019).

MDSCs cause suppression of immune cells via oxygen species (ROS) generated by g-MDSCs (granulocytic MDSC), nitric oxide (NO) generated by m-MDSCs (monocytic MDSC), production of arginase and also by secretion of cytokines such

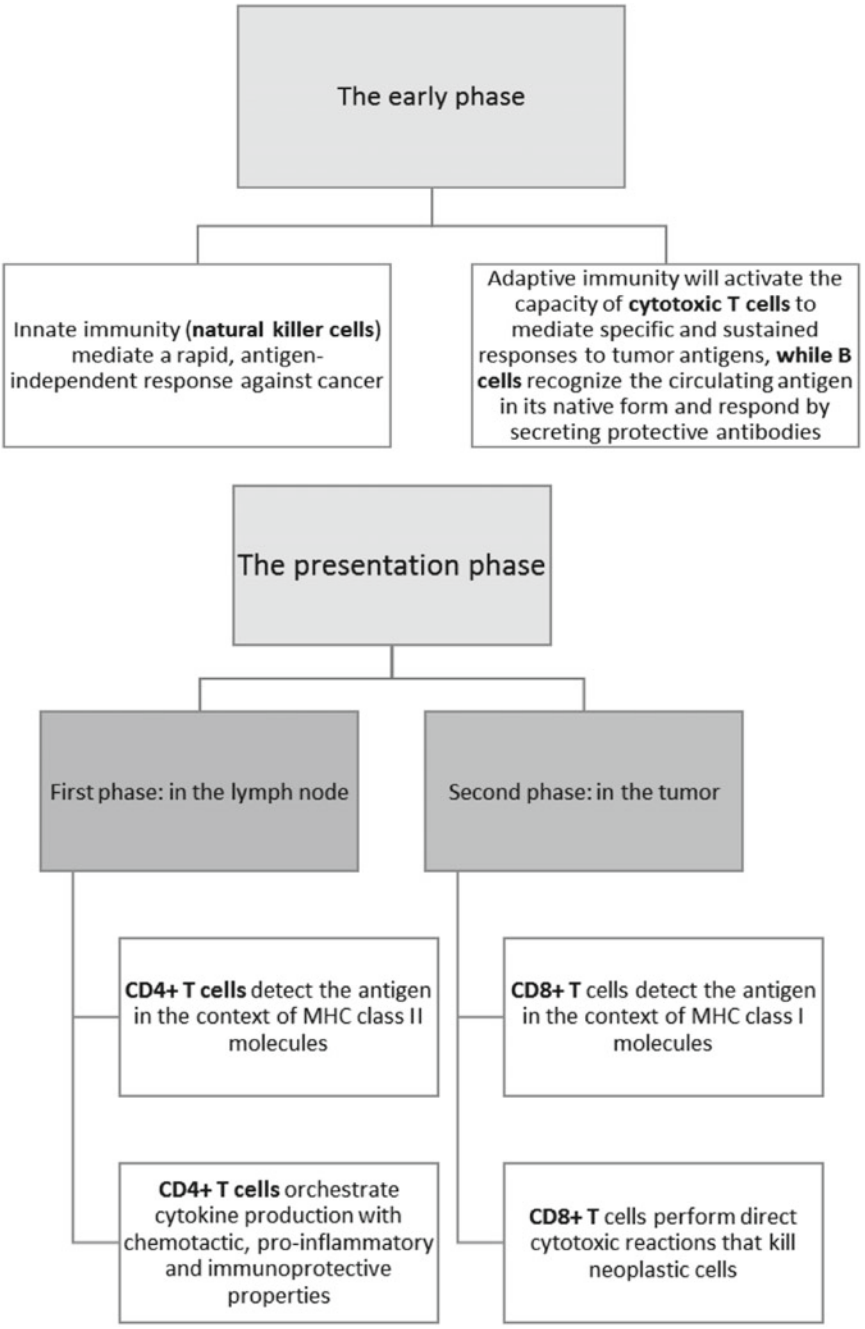

Fig. 8.3 The early and presentation phases of the immune system against cancer

as IL-10 and TGF-β. Arginine is used metabolically by MDSC and, therefore, by removing this substrate from the microenvironment that is also used by T cells, MDSC interferes with T cell proliferation. The consumption of L-arginine (Arg) to produce arginase 1 (ARG1) represents a well-known immunoregulatory mechanism explored by MDSCs and also M2 macrophages (Mondanelli et al. 2019). Another via used by MDSCs is PD-L1- and cytokine-dependent inhibitory mechanisms that inhibit the antitumor effector T cell response (Timosenko et al. 2017).

In cancer MDSCs and DCs overexpression of ARG1 and IDO1 contribute to the reduction of the host anti-tumor immunity (Mondanelli et al. 2019). The use of arginase inhibitors such as Nor-NOHA (N-hydroxy-nor-L-arginine) abrogated the arresting effects of arginase on T-cell proliferation and allowed lymphocyte-dependent tumor reduction (Rodriguez et al. 2017). In addition, as MDSCs polarizes macrophages toward the M2 phenotype, arginase inhibitors could have a double effect in favor of T cells proliferation and preventing the expansion of immunosuppressive TAMs (Mussai et al. 2013).

Considering that the relationship between the immune system and cancer is dynamic and complex, it is not a surprise that cells from the immune system can play dual role in cancer development. The immune system can not only suppress tumor growth by destroying cancer cells and inhibiting their outgrowth, but also promote tumor progression by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth. Human tumors harbor a multitude of somatic gene mutations and epigenetically dysregulated genes, the products of which are potentially recognizable as foreign antigens. The immune system must recognize danger signals and respond accordingly. In this scenario, immune escape and immunotolerance are considered the main mechanisms linked to cancer development (Hong et al. 2019). Therefore, it is essential to further understand the changes occurring in the immune system that could contribute for cancer development and response to current therapy.

In this context, cancer immunotherapy has been developed aiming the enhancement of the immune response against the tumor. The common feature of the immunotherapy is increase T-cytotoxic lymphocytes capability to attack tumor cells (Pisconti et al. 2018).

Immunotherapy approaches aim: (1) “trigger” powerful T cell responses via immune control point block (checkpoint); (2) infusion of immune cells that fight tumors in the body (adoptive cell therapies); (3) be prophylactic or therapeutic (cancer vaccines) (Waldman et al. 2020).

Monoclonal antibodies against the CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed death 1)/PD-L1 (programmed death-ligand 1) resulted in antitumor responses by regulation of activation at various stages of the immune cycle (Pisconti et al. 2018). However, despite the clinical efficacy of checkpoint block, most cancer patients do not yet have long lasting benefits from these therapies: many important types of tumor do not or minimally respond to checkpoint block, including pancreatic cancer, to most colorectal and prostate tumors.

Even in responsive tumors, such as melanoma or lung cancer, only a fraction of patients will achieve long lasting remissions.

Animal models suggest that tumors often activate several receptors in the immunosuppressive pathways. Antibodies to PD-1 / PD-L1 and CTLA-4 showed that the response to blockage in one pathway does not exclude the response to the other. Thus, combining two checkpoints with ipilimumab and nivolumab conferred a significant survival benefit in patients with metastatic melanoma and advanced renal cell carcinoma, leading to FDA approval for these conditions. In addition, some of these tumors may respond to the blocking of alternative checkpoint receptors (Dougan et al. 2019).

Allogeneic hematopoietic stem cell transplants for leukemia represented the first effective adoptive transfer approach clinically implanted, and clinical positive results were mediated by the graft of T cells against the tumor (Waldman et al. 2020).

T-cell chimeric antigen (CAR) receptors are chimeric proteins that assemble a signaling portion similar to the T cell receptor complex (TCR) and the variable domain of an antibody directed to an antigen of interest. CAR T cells designed with specificity for the CD19 cell surface molecule, which is expressed by all B cells, have been successful in treating B cell malignancies. The first clinical implantation of second generation CD19-specific CAR T cells led to durable responses in chronic lymphocytic leukemia (Waldman et al. 2020).

Prophylactic vaccines are used for the prevention of infection with oncogenic viruses. Vaccines against hepatitis B and human papillomavirus reduced the incidence of hepatocellular carcinoma and cervical cancer, respectively. Therapeutic vaccines action is based on the immune system cells which eliminate disease-causing cells that are already neoplastic. The bacillus vaccine Calmette-Guérin (BCG, attenuated *Mycobacterium bovis*), which is generally used as a prophylactic vaccine against tuberculosis, has been reused as a primitive therapeutic vaccine for bladder cancer. Tumor-associated antigens (TAAs) which are highly expressed in tumor cells but not in normal tissues led to new approaches based on therapeutic vaccines, and are in clinical trials for specific tumors, associated or not with other immunotherapies (Waldman et al. 2020).

In summary, despite the promising results of immunotherapy, a minority of cancer patients achieve long-lasting responses against tumor. Therefore, immunotherapies are in expansion mainly approaching checkpoints (Dougan et al. 2019. Moreover, the decline in the incidence of some common cancers after age 80, such as prostate and breast cancer, has directed research for the further understanding of the age process and its effect on the immune system. Senolytics such as dasatinib and querceting have been developed to selectively kill senescent cells and potentiate anticancer therapies (Birch and Gil 2020).

In conclusion:

- Cancer is a leading cause of morbidity and mortality worldwide
- > 50% of new cancer cases are diagnosed in people aged 65+ years
- Exposure to carcinogens and accumulation of cellular damage are important cancer risk factors in all populations, mainly in 65+ patients
- Immunosenescence is extremely important for cancer development, including immunotolerance and immune escape
- Immunotherapy is an important tool to enhance loss of function in immune system in cancer patients, in special in old individuals

Compliance with Ethical Standards

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Conflict of Interest All authors declare they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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