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The immune system: endogenous anticancer mechanism

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1. ABSTRACT

The genetic alterations acquired by cancer cells are identified by diverse immune mechanisms, creating a complex network of interactions that can either favor or control tumor growth. Defects and impairments in the immune system are associated with cancer development. Compelling new evidences are also available regarding the protective value of anti-tumor adaptive immune responses, both local and systemic, developed by the host. More recently, the identification of new subsets of T helper, T cytotoxic, and dendritic cells, unraveled new forms of interactions between immune and tumor cells. The immune system is a powerful ally in the control of cancer development, metastasis and recurrence, due to two important properties that are absent in most anti-cancer treatments – specificity, and long-lasting memory. These properties are being increasingly explored in cancer therapy, from the wide use of monoclonal antibodies to the still experimental dendritic cell based therapies. Now, more than ever, the preservation as well as the recruitment of immune responses in the host constitute important approaches to be applied in cancer therapy.

2. INTRODUCTION

It was long assumed that cancer was a cell-autonomous multistep genetic disease. The genomes of tumor cells in the tumorigenesis process are consistently altered at multiple sites and these genetic alterations drive the progressive transformation of normal cells into malignant derivatives (1). There are six major alterations in cells physiology that collectively dictate malignant growth: (1) Self-sufficiency in growth signals; (2) Insensitivity to growth-inhibitory signals; (3) Evasion of programmed cell death; (4) Limitless replicative potential; (5) Sustained angiogenesis; (6) Tissue invasion and metastasis. Each of these six changes represents the successful breaching of an anticancer defense mechanism hardwired into cells and tissues; consequently these are the six hallmarks of cancer.

The tumor cell microenvironment is made up of stromal and immune cells that can play a significant role in cancer initiation, development, growth, and metastasis (2-4). Immunological pressure, working as an endogenous anticancer mechanism, prevents the outgrowth of malignant cells. Paul Ehrlich in 1909 was the first to propose the

concept of immuno surveillance, in which the immune system would scan for nascent transformed cells raising continuously in our bodies and eradicate these transformed cells (5). By 1950's, Burnet and Thomas postulated, based on experimental evidence from tumor transplantation models, that tumors could be repressed by the immune system. Such findings strongly suggested the existence of tumor-associated antigens and formed the basis of the immune surveillance concept (6).

However, in 1970s, immune surveillance was strongly criticized. This hypothesis was formally tested in CBA/H immunodeficient nude mice, which were found to develop spontaneous tumors and chemical carcinogen methylcholantherene (MCA)-induced sarcomas in an equivalent manner to wild-type control mice (7, 8), suggesting that the immune response was not important to tumor control. At that time, these experiments were so convincing that they essentially caused a negation of the cancer immuno surveillance hypothesis. Only now, in retrospection, it is appreciated that there were several caveats associated with these initial experiments. Nude mice that lack a thymus are not entirely immunodeficient, containing NK cells and even low numbers of some functional populations of T cells, which are important to control tumor growth. In addition, the CBA/H strain of mice used in the MCA carcinogenesis experiments expressed a highly active isoform of the enzyme that metabolized MCA to its carcinogenic form. Thus, it was possible that any protective effect of the immune system was covered by the overwhelming efficiency of MCA-induced cellular transformation in the CBA/H strain (9)

Interest in the field of cancer immune surveillance was renewed as a result of studies published approximately 10 years ago, which demonstrated that the immune system can protect against tumor onset and be manipulated to reject established tumors. One important study demonstrated that use of neutralizing antibody to Interferon gamma (IFN-g), an important pro-inflammatory effector cytokine, caused accelerated tumor growth in tumor-bearing mice compared with control, antibody-treated, wild-type mice (10). The finding that IFN-g enhanced tumor cell immunogenicity by up-regulating tumor cell major histocompatibility complex (MHC) class I antigen processing and presentation was particularly important in demonstrating that rejection of these types of tumors was dependent on the development of anti-tumor immunity (11, 12). In addition, mice lacking perforin, an important effector molecule for the cytotoxic function of CD8+ T cells, showed an increased incidence of spontaneous B cell lymphomas compared with wild-type mice (13).

An extensive amount of experimental data from various mouse models of cancer, together with convincing, correlative clinical data from human patients has provided unequivocal evidence that cells of the immune system, innate and adaptive, are required for the prevention of cancer (3). The avoidance of immuno surveillance has thus been proposed to be the seventh hallmark of cancer.

However, tumors can and do arise in the presence of a functional immune system. This could be explained by immunomodulatory properties of cancer and/or tumor recruitment of cells that would hamper immune function within the tumor microenvironment. In addition, it has become evident that both innate and adaptive immunity have a "dark" side and can promote tumor progression. In particular, chronic inflammation, which has long been associated with increased tumor risk, is involved in polarizing immunity towards those effectors that facilitate tumor growth (reviewed in details in (14))

In fact, the dual nature of the immune system to hamper and aid tumor growth has led to the refinement of the cancer immuno surveillance hypothesis into one now termed cancer immunoediting (15-17). During immunoediting, the immune system destroys many pre-cancerous and malignant cells; however, some cells escape the immune response and give rise to progressively growing tumors. Immunoediting is thought to continue throughout the existence of the tumor, so it is very possible that the phenotype of an established tumor has been mainly shaped by the host's immune response.

It was demonstrated by Swann *et al* that inflammatory-induced cancer and cancer immunoediting can indeed occur in the same mouse tumor model during primary tumorigenesis (18). As a result, the immune system has the potential to either promote or delay tumor onset and progression, and the effectiveness of immune surveillance and the efficacy of immunotherapy depend on the balance between these diametric opposites.

The cancer immunoediting process is envisaged to consist of three phases: elimination, equilibrium, and escape. These have been termed the "three Es of cancer immunoediting". The elimination phase of cancer immunoediting is exactly the same process described in the initial theory of tumor immune surveillance, whereby the immune system detects and eliminates tumor cells that have developed as a result of failed intrinsic tumor suppressor mechanisms. The process of elimination involves innate and adaptive immune responses to tumor cells. The elimination phase can be complete, if all tumor cells are cleared, or incomplete, if only a portion of tumor cells are eliminated, and a temporary state of equilibrium ensues between the immune system and the developing tumor.

During equilibrium tumor cells either remain dormant or continue to evolve, accumulating further changes, such as DNA mutations or changes in gene expression. Such changes can modulate the tumor-specific antigens, and this process leads to the immune selection of tumor cells with reduced immunogenicity, which may occur over a period of many years (9). Chemically induced sarcomas in both nude and severe combined immunodeficiency (SCID) mice were more immunogenic than similar tumors from immunocompetent mice (19, 20). These findings suggest that the original tumor cells induced in normal mice and selected by a T-cell-mediated selection process have been adapted to grow in a host with a functional T-cell system, which has eliminated highly

immunogenic tumor cells, leaving low-immunogenic tumor cells to grow. Adaptive immunity plays an important role in occulting cancer cells in an equilibrium state as was demonstrated by Koebel and cols (21).

The pressure exerted by the immune system during the equilibrium phase is sufficient to control tumor progression, but eventually, the process results in the selection of tumor cell variants that are able to resist, avoid, or suppress the antitumor immune response, leading to the escape phase. During the escape phase the immune system is not able to contain tumor growth due to the induction of central or peripheral tolerance. Central tolerance refers to the process by which self-reactive T cells are deleted or converted to a regulatory phenotype in the thymus (22). Clearly, central tolerance fails to eliminate all tumor and/or self reactive T cells, as is evident by the presence of tumor-specific T cells that recognize non-mutated self antigens (23).

When T cells specific for tumor antigens escape central tolerance, tumor growth can induce T cell tolerance in the periphery. One example where tumor growth clearly primes an antitumor immune response that ultimately fails to control tumor growth is that a mouse challenged with a given tumor will reject a subsequent challenge with the same tumor at a distant site, despite the fact that the initial tumor continues to grow (24-26). It has been suggested that T cells from cancer patients have decreased function, due to down regulation of the z chain of the T cell receptor (TCR) and Natural killer (NK) cells receptor (27). However, immunosupression is not a clinical finding commonly associated with cancer. How could that be explained?

Many factors in the tumor microenvironment have been shown to contribute to tumor escape (28). Tumors can express and secrete molecules that lead to immunosupression directly inhibiting the effector cells, or yet recruiting immunosuppressive cells such as regulatory T cells (Tregs) or myeloid derived suppressor cells (MDSCs). Interestingly, tumors may have mechanisms of active tolerization of responses against tumor antigens, sparing responses to other antigens (29). Consequently, it is possible that tumors evolve strategic immunomodulatory mechanisms that affect the anti-tumor response, and yet do not render the host susceptible to infections.

The heterogeneous immune escape strategies and immunomodulatory properties of tumors, as well as the unpredictable responses that tumors present to immunotherapy, suggest that there may be considerable diversity in interactions between tumor and immune cells. Understanding these interactions is of supreme importance to the development of new cancer therapy strategies. The activation of innate and adaptive arms of the immune system by the tumor is dependent on neo-antigens, created by genetic alterations of tumor cells as well as 'danger signals' from damaged or death cells presented in the correct context.

3. THE INNATE ARM – INITIAL RECOGNITION

The initial recognition of tumor cells, or how the unmanipulated immune system can be activated by a developing tumor, has been the object of controversy. Some consider that cellular transformation does not provide sufficient pro-inflammatory signals to activate the immune system in response to a developing tumor, as postulated by the danger hypothesis. The danger hypothesis suggests that the prime role of the immune system is to react to cellular or tissue distress, as opposed simply to non-self (30). Activation of T cells does not occur in the absence of appropriate co-stimulation, which often results in no immune response (anergy) and tolerance (31). More recently some molecules, such as HMGB1 and HSPs, have been proposed to represent endogenous danger signals or damage-associated molecular patterns (DAMPs) from tumors (32, 33). In cancerous conditions, cells dying via non-apoptotic pathways, mainly necrosis, release DAMPs into the extracellular space. These molecules can be released by dying tumor cells and bind to different receptors such as toll like receptors (TLRs), advanced glycosylation end product-specific receptor (RAGE), CD91, LOX1, or CD40, can also stimulate the immune response. DNA-binding molecule high mobility group box 1 (HMGB1) is a DAMP and has been shown to be released from both irradiated and doxorubicin treated tumor cells (34). HMGB1 plays an important role in activation of dendritic cells (DCs) through TLR4 or RAGE (35, 36). However, HMGB1 can also contribute to tumor progression binding TLR4 and TLR2 (37).

Furthermore, it was described that calreticulin exposure in cancer cell death affects tumor immunogenicity (38). Also, necrotic tumor cells can release heat shock proteins (HSPs), such as HSP70, HSP90, and gp96, which stimulate the pattern recognition receptors TLR2 and TLR4. HSPs may facilitate the interaction with surface receptors of antigen-presenting cells (such as CD91, LOX1, CD40) and reportedly mediate the transfer of antigenic peptides from the stressed cell to the antigen-presenting cell (39)

For the innate immune response, several effector cells such as NK, NKT, and ((T cells are activated by inflammatory cytokines, which are released by the growing tumor cells, macrophages and stromal cells surrounding the tumor cells (40). One mechanism by which gamma-delta T cells might control tumor development is through natural killer group 2, member D (NKG2D) recognition of the stress ligand retinoic acid early transcript (RAE1) expressed by tumor cells. Mice lacking gamma-delta T cells are highly susceptible to multiple regimens of cutaneous carcinogenesis (41). In addition, acute upregulation of an NKG2D ligand RAE1 promotes rapid reorganization of a local immune compartment, with the contribution gamma-delta T supporting a initial immuno surveillance (42).

NK cells express both activator and inhibitory receptors that recognize ligands, including cellular stress ligands and MHC class I molecules (43). These receptors provide a balance of signals leading to either activation or inhibition of the NK cell. These recognition receptors allow NK cells to recognize altered malignant cells. Since the seminal discovery that NK cells can eliminate endogenous

Table 1. Murine dendritic cells subsets

cDCs			***pDCs***
Mono DCs	*CD11b+*	*CD11b-*	*pDCs* B220+
Monocyte derived inflammatory DCs	CD4+	CD8+	
	CD4-CD8-	CD103+CD207+	
	Classic Dermal (CD205+)		
	Langerhans Cells (CD207+ CD205+)		

cells with decreased class I MHC expression (44), a range of NK anti-tumor functions were described. NK and NK T cells mediated killing of the tumor cells by perforin (13), death-inducing molecule (FasL) and TNF-related apoptosis-inducing ligand (TRAIL) (45) releasing tumor antigens, which lead to adaptive immune responses. In addition, NK mediated perforin production is critical for the rejection of tumor cells expressing NKG2D ligands, defining NKG2D as a cytotoxicity inducing receptor (46). NK and NKT cells also produce chemokines that are important for the recruitment of effector T cells, B cells, neutrophils and other NK and NKT cells to the disease site. IL-2- or IL-12-activated NK cells secrete several T cell-recruiting chemokines, including MIP-1-a, MIP-1-b, IL-8, macrophage-derived chemokine, and RANTES (47). NK or NKT-derived IFN-g also upregulates expression of the chemokine receptor CXCR3 that mediates the subsequent recruitment of CXCR3+ T and NK cells to infected tissues (48). The early production of chemokines by NK and NKT cells is likely to have a profound role in shaping the ensuing inflammatory response. In the crosstalk between NK cells and DCs, NK cells promote the maturation of DCs resulting in the enhancement of antigen presentation to naive T cells (49).

Neutrophils are innate immune cells which migrate immediately to sites of tissue damage or inflammation, but some studies have shown that these cells could have anti-tumor effects (50). The recruitment of neutrophils to the tumor site, at their ‘‘N1’’ polarization, lead to antitumor activity. Conversely, in the presence of ‘‘N2’’ polarized neutrophils, the result is tumor growth. Interestingly, it was demonstrated in models of lung cancer the N1-N2 polarization of tumor infiltrating neutrophils are driven by TGF-b to acquire a polarized N2 protumor phenotype. After TGF-b inhibition, a shift to N1 occurs with acquisition of antitumor activity *in vitro* and *in vivo* (51). In study, the neutrophil/lymphocyte ratio in peripheral blood was a good indicator of tumor progression (52), however an excessive production of neutrophils may be unfavorable to anti-cancer immunity (53).

More recently, investigators have focused on the ability of macrophages to infiltrate solid tumors and modulate T-cell and stromal activity to either favor or inhibit tumor growth (54). Whether tumor associated macrophages (TAM) can be converted from the pro-tumorigenic M2 type to the pro-inflammatory M1 type to attack tumors is still under investigation (55, 56). Emerging evidence suggest that in human myeloid leukemias, macrophage phagocytosis is a critical mediator of tumor immunosurveilance. These cancers can escape such immuno surveillance by up-regulating CD47, a potent ‘‘don’t eat me’’ signal (57).

Immature DCs ingest necrotic tumor cells at the tumor site, acquiring a mature phenotype under appropriated pro-inflammatory conditions and migrating to tumor draining lymph nodes (TDLNs). In the TDLNs, the DCs present tumor antigens to naïve CD4+ and CD8+ specific T cells which expand and differentiate to effectors and memory T cells. Accordingly, DCs play a pivotal role in the initiation, programming, and regulation of tumor-specific immune responses (58, 59). Nevertheless, surprisingly little is known about the role of different DC subsets in cancer initiation and progression in patients.

In mice, there are two main pathways of ontogeny for DC derived from hematopoietic progenitors – see Table 1. One promotes the differentiation of myeloid DC (mDC) also known as conventional DCs (cDC) and the alternate pathway generates plasmacytoid DC (pDC). The cDC subsets in mice can be subdivided into migratory versus lymph node resident cDC. Thus, cDC subsets included the CD11b+ DCs; the CD11b– DCs; and the monocyte-derived inflammatory DCs. Several DCs fall into the CD11b+ DC group, including the CD4+ and CD4–CD8– lymphoid tissue–resident DCs; the classic dermal CD11b+ DCs and their counterparts in the lung and other tissues and the Langerhans cells (CD107+). The CD11b– DC group would include CD8α+ DCs of the lymphoid tissues and the CD103+ langerin+ (CD107+) DCs of the skin, lungs and other tissues. These four groups could be generalized to have broad specializations, with pDCs promoting innate immunity; the CD11b+ DCs stimulating CD4+ T cell help, potentially focused on humoral immunity or responses to extracellular parasites; the CD11b– DCs being dedicated to priming cytotoxic T cell immunity and responses to cell-associated antigens; and the monocyte-derived inflammatory DCs controlling events directly in inflamed tissues, including antigen presentation at effector sites and the initiation of local secondary responses (60).

Most data on subsets of DCs involved in cross-presentation to CD8 T cells, which involves the uptake and processing of exogenous antigens within the major histocompatibility complex (MHC) class I pathway, have been generated in mice (reviewed in (61)). It is generally accepted that migratory DCs (trafficking from the ports of entry or peripheral tissues to LN) carry the antigens (self/tumoral or nonself) to the lymph nodes and operate a transfer to resident CD8a DC that will ensure cross-presentation of the exogenous antigens into MHC class I molecules, the carrier being capable of presenting into MHC class II molecules (62). The DC subset expressing CD8a is particularly effective in cross-presentation to CD8 CTL (61).The CD8a subset of DC appears to originate from the CD8a negative subset by a maturation process involving up regulation of not only CD8a but also the C-type lectin DEC-205 and CD24 (48). The dominant role of this subset in cross-presentation is not due to differences in

Table 2. Human dendritic cells subsets

cDCs	pDCs
Dermal (CD1a+)	pDCs BDCA- 2 and 4+
CD14+	
Langerhans Cells	
CD141+DNGR-1+	

antigen capture but rather to a greater processing efficiency (63). For instance, a yet unknown preformed molecule that remains associated with necrotic cells (and hence is likely a part of the insoluble cytoskeleton) serves as a ligand for the SYK-coupled C-type lectin receptor Clec9a. Clec9a is expressed on CD8α+ dendritic cells that stimulate the cross-presentation of antigens associated with dead cells (64, 65).

Similarly to mice, humans have two major subsets of DCs, the mDCs and the pDCs. The mDCs comprise different subsets with unique localization, phenotype and functions (review in detail in (66), see also Table 2). In human skin, the epidermis hosts Langerhans cells, whereas the dermis contains CD1a+ DCs and CD14+ DCs. The latter DC subset is involved in the generation of humoral immunity, partly through secretion of interleukin (IL)-12, which stimulates the differentiation of activated B cells into plasma cells and also promotes the differentiation of naïve CD4+ T cells into T follicular helper cells a CD4+ T-cell subset that promotes antibody responses. In contrast, Langerhans cells efficiently prime antigen-specific CD8+ T cells, possibly by means of IL-15. The functions of the predominant CD1a+ dermal DCs are as yet unknown. A particular human DC subset identified by co-expression of CD141 (thrombomodulin, BDCA-3) and the C-type lectin CLEC9A (DNGR-1), is the human counterpart of mouse CD8a+ DCs present in secondary lymphoid organs such as tonsils and spleen and has the ability to cross-present antigens (67, 68)

Cancer is often associated with an environment that does not favour the DC activation events required for proper effector CD4+ and CD8+ T cell activation. DC phenotypes in cancer tissue and draining lymph nodes usually present an ‘‘immature’’ phenotype and MDSCs and TAMs adversely affect DC function. Head and neck squamous cell carcinoma diminishes the capacity of pDC to respond to TLR9L for IFN type 1 secretion (69). The prognostic relevance of DC during tumor progression has also been approached in immunohistochemistry analyses, and peritumoral infiltrates of maturing DC in clusters with activated T cells were reported to be associated with a favourable outcome (70).

4. THE ADAPTATIVE ARM – MEMORY DEVELOPMENT

Tumor antigen specific CD4+ and CD8+ T cells primed by DCs in the TDLN home to the primary tumor site, where they exert their effector functions. Cytotoxic CD8+ T cells eliminate the tumor antigen expressing tumor cells and this elimination is enhanced by the secreted IFN-g. IFN-g exerts a limited cytotoxicity via antiproliferative (71) and anti-angiogenic effects (72) and induces apoptosis (73).

During TCR activation in a particular cytokine milieu, naïve CD4 T cells may differentiate into one of several lineages of T helper (Th) cells, including Th1, Th2, Th17, and iTreg, as defined by their pattern of cytokine production and function. Some studies have also described TGF-b-producing Th3 cells, IL-10-producing TR1 cells, IL-9-producing Th9 cells, and T follicular helper Tfh cells, however cells may not be members of lineages that are distinct from Th1, Th2, Th17, and Treg cells but that rather represent diversity within Th lineages (74). Th1 facilitate tissue destruction and tumor rejection by providing help to CD8 T cells.

Recently identified Th17 cells, produce IL-17, a pro-inflammatory cytokine which plays a dual role in antitumor immunity, since inflammation appears to be a necessity for both metastasis and elimination of tumor cells (75). On the one hand, IL-17 promotes an antitumor cytotoxic T cell response leading to tumor regression. Th17- polarized cells were found to be more effective than Th1 cells in eliminating large established tumors (76). In addition, IL-17 has been shown to inhibit the growth of hematopoietic tumors such as mastocytoma and plasmocytoma by enhancing CTL activity (77). Also, it has been shown that the proliferation and angiogenesis of head neck squamous cell carcinoma are impaired in the presence of Th17 cells (78). On the other hand, IL-17 promotes tumor growth. Apart from a minor direct effect on the proliferation and survival of tumor cells (79), as not all tumor cells express IL-17 receptor and respond to IL-17, the major pro-tumor role of IL-17 in inflammation-associated cancer relies on its pro-angiogenic property of surrounding endothelial cells and fibroblasts (80, 81). Upon activation by IL-23, Th17 cells produce IL-17, which exacerbates inflammation by inducing IL-6, TNF-a, granulocyte colony stimulating factor G-CSF, and other acute phase proteins.

Several studies have revealed that Tregs, which are physiologically engaged in the maintenance of immunological self-tolerance, play critical roles for the control of antitumor immune responses (82). These studies have shown the presence of a large number of Tregs in a variety of tumors and the enhancement of natural as well as vaccine-induced antitumor T-cell responses by systemically or locally removing Tregs (83, 84). In addition to the CD4+CD25+Foxp3+ natural Tregs that develop in the thymus along with other T cells, Tregs can also be induced in the periphery. First, antigenic stimulation of naïve T cells in the presence of Interleukin 10 (IL-10) induces the generation of Type 1 Tregs (Tr1). These Tr1 cells do not express Foxp3 but produce IL-10 and TGF-b as their major immune suppressive mechanism (85). Second, antigenic stimulation of naïve T cells in the presence of transforming growth factor-b (TGF-b) induces the generation of T helper 3 (Th3) cells *in vivo* and *in vitro* (86), which subsequently produce TGF-b as their major immune suppressive mechanism. In addition to IL-10 and TGF-b, it has also been shown that IL-4 and IL-13 can induce the generation of Foxp3+ Tregs from naïve CD4 T cells in a process that is independent of IL-10 or TGF-b (87). The discovery that the early differentiation of Treg and Th17 cells from naive

CD4+ T cells shares a requirement for TGF-b indicated that there is substantial plasticity in the early and late stages of Th17 and Treg cell development (88).

T cell immunity to several tumor antigens, such as Human epidermal growth factor receprto 2 (HER-2/neu), carcino-embryonic antigen (CEA), Cell surface associated mucin 1 (MUC1) and NY-ESO-1, has been reported (89, 90). However, the tumor remains not totally controlled by the immune system, one of the reasons being that, unlike pathogens, they do not express potent rejection antigens. Tumor vaccination aims at stimulating a systemic immune response targeted to mostly weak antigens expressed in the disseminated tumor lesions. Paramount challenges in developing effective vaccination protocols are the identification of potent and broadly expressed tumor rejection antigens. Interesting, some tumor types exhibit a particular type of genetic instability referred to as microsatellite instability (MSI), where defects in DNA mismatch repair mechanisms lead to the duplication or deletion of short repeated sequences of DNA known as microsatellites. The high rate of mutation in MSI-H tumors has been shown to result in the generation of a number of novel tumor antigens that can be recognized by infiltrating B cells (91), CD4+ T cells (92), and CD8+ T cells (91) and this infiltration is associated with a favorable prognostic. An alternative approach in which the expression of new, and thereby potent, antigens are induced in tumor cells by inhibiting nonsense-mediated messenger RNA decay was proposed by Fernando Pastor and colleages (93). Small interfering RNA (siRNA)-mediated inhibition of nonsense-mediated messenger RNA decay in tumor cells led to the expression of new antigenic determinants and their immune-mediated rejection.

Although several studies have shown that naïve CD8+ T cells can become activated in the TDLN during tumor outgrowth, whether naïve CD8+ T cells are activated in the tumor mass itself remains to be established. Recently, Thompson and colleagues have shown, in a murine model, that naive tumor-specific CD8+ T cells can infiltrate the tumor, and be activated *in situ*, acquire an effector phenotype and proliferate in response to a specific antigen. To directly show that OT-I T cells were activated in the tumor and not in the draining lymph nodes, lymph node development was inhibited in mice *in utero* (94)

B cell antibodies (Ab) responses were thought to contribute modestly, if at all, to tumor immunity (95), whereas Ab production may contribute to chronic inflammation that enhances tumor development (96, 97). However, in a recent study it was demonstrated that B cells are required for optimal CD4 and CD8 T cells tumor immunity. They show that depletion of B cell enhances B16 melanoma growth (98)

An important attribute of the adaptive immune system is the ability to remember a prior encounter with an antigen; an ability termed immunological memory. Bigger, better, and stronger responses are mounted upon a secondary encounter with the antigen potentially resulting in clearance before the development of disease (99) Sallusto and Lanzavecchia introduced the concept that memory T cells are heterogeneous (100). Central memory T cells circulate between secondary lymphoid organs, express the LN homing molecules CCR7 and CD62L, and do not exhibit immediate effector functions but can undergo significant recall proliferation upon antigen re-encounter. Effector memory T cells classically lack LN homing molecules and are thus generally deposited in and circulate through peripheral tissues. They exhibit immediate effector function upon antigen recognition.

High infiltrates of memory T cells (CD3/CD45RO) or (CD8/CD45RO) in center of the tumor and invasive margins were highly and significantly associated with very good prognosis, both in terms of disease-free and overall survival (101). Tumors with low memory T or memory-cytotoxic T cells in both zones were associated with very bad clinical outcome. The fact that it is not only the overall quantity or even the functional orientation, but also the location of the immune cells that influences tumor recurrence supports the concept that distinct cells with selective functions located in different tumor regions may play a crucial role in controlling metastasis escape.

5. IMMUNOTHERAPY – FROM EXPERIMENTAL TO COMMERCIAL

Today, a diagnosis of cancer is not necessarily a death sentence: there were nearly 9 million cancer "survivors" living in the United States in 1999 (102) suggesting that current cancer treatments are effective. However, the standard options — surgery, radiotherapy, and chemotherapy — have debilitating and distressing side effects, destroying healthy tissues along with cancer cells. Currently, basic and clinical research is centered on developing so called therapeutic cancer vaccines for patients who already have cancer. Cancer vaccines consisting of antigens of varied composition, identity, and source have been studied clinically. Products might consist of antigens that are recombinant proteins, synthetic peptides, carbohydrates, extracted tumor-derived proteins, or monoclonal antibodies. Alternatively, the product might be DNA encoding the antigen of interest. The identity of the antigen used depends on the type of cancer, although some antigens are associated with multiple types. For example, CEA is the target for several colorectal cancer vaccines, whereas MUC-1 and HER-2 are target antigens for several breast cancer vaccines.

Whole cells displaying cancer-associated antigens can also be used as vaccines. Cells can be derived from two sources: the cancer itself and the immune system. In the first instance, cancer cells are killed (usually by irradiation), then modified either genetically or chemically to increase their immunogenic potential. The identity of the tumor-specific antigens need not be known because the cell itself becomes the vaccine and the immunological key to the destruction of its cancerous relatives. The second method involves producing DCs that directly present the tumor antigen to the immune system. The DCs are loaded with the desired antigen using electroporation and can also

be genetically modified to secrete an additional immune response stimulant such as granulocyte macrophage colony stimulating factor (GM-CSF). Sipuleucel-T is a novel immunotherapeutic consisting of autologous dendritic cells which have been pulsed *ex vivo* with PA2024 as a source of antigen. PA2024 is a recombinant fusion protein consisting of granulocyte-macrophage colony-stimulating factor (GM-CSF) and prostatic acid phosphatase. With the FDA approval of Sipuleucel-T for prostate cancer, active immunization has become an accepted approach for the treatment of established cancer (103).

Also, a wide array of cell based immunotherapies utilizing T cells and NK cells, have been established. One example is the adoptive cell transfer of tumor-infiltrating lymphocytes in combination with lymphodepletion that has proven to be an effective treatment for metastatic melanoma patients, with an objective response rate in 50%-70% of the patients (104) .

In addition to the strategies indicated above, the inhibition of immunosuppressive mechanisms associated with tumor infiltration by the immune system using RNA interference also offers a new approach to vaccine design. For instance, TLR agonists have been shown to boost immune responses toward tumors. Furthermore, a rapidly expanding repertoire of monoclonal antibodies is being developed to treat tumors, and many of the available antibodies have demonstrated impressive clinical responses. One good example is ipilimumab that blocks cytotoxic T lymphocyte antigen 4 (CTLA-4), a key negative regulator of T cell activity and potentiates antitumor responses (105).

Immunotherapy will likely not be able to eliminate tumors by itself, but combination therapies that incorporate immunotherapeutic agents have great potential for providing clinical success in treating cancer in the coming years (106).

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Abbreviations: MCA methylcholantherene, IL Interleukin, TGFb Transforming Growth Factor, IFN-g Interferon gamma, MHC I Major histocompatibility complex, MDSCs Myeloid derived suppressor cells, DAMPs Damage-associated molecular patterns, TLRs Toll like receptors, RAGE Glycosylation and product specific receptor, HMGB1 DNA-binding molecule high mobility group 1, DCs dendritic cells, HSP heat shock proteins, RAE retinoic acid early transcript, NKG2D natural killer group 2, TRAIL TNF related apoptosis inducing ligand, TAM tumor associated macrophages, TDLN tumor draining lymph node, Th T helper, CEA carcino embryonic antigen, GMCSF granulocyte macrophage colony stimulating factor, MUC1 Cell surface associated mucin 1, HER2neu Human epidermal growth factor receptor 2, MSI microsatellite instability, siRNA small interfering RNA, CTLA 4 cytotoxic T cell lymphocyte antigen 4

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