The role of Regulatory cells as Potential target in Vaccine and Immunotherapy in Cancer and Autoimmunity Treatment and Prevention

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Abstract: Regulatory T cells (Tregs) can mediate suppression through their effects on dendritic cells (DCs), such as physical inhibition of interaction between DCs and conventional T cells (Tconv) or deprivation of co-stimulation or soluble factors. Cytotoxic T lymphocyte-associated antigen (CTLA)-4 on Tregs interacts with CD80 and CD86 on DC with high affinity.

Further, peripheral dendritic cells were shown to migrate to the thymus to induce clonal T cell deletion or development of T regulatory (Treg) cells.

Recent sudy suggest that dendritic cells can induce peripheral tolerance through presentation of immunodominant antigens expressed at high levels.

Further, dendritic cells are thought to make a major contribution to peripheral tolerance by facilitating induction and/or maintenance of peripheral Treg cells.

It has been suggested that Tregs display an enhanced capacity for infiltration of, and accumulation within, the tumour in comparison to Teff

In this article, I will describe, Regulatory Cells in Cancer,Innate immunity and Cancer, Adaptive immunity and cancer, Immune Direct Apoptosis of Cancer and regulatory cell -Based Vaccines and Immunotherapy in the treatment and prevention of Cancer and Autoimmunity.

Key Words: Antigens, APC, T cell, innate immunity, Adaptive immunity,Immunotherapy, and Vaccine,

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1. Introduction

Cancer arises as a result of a multi-step process leading from the initial benign transformation of cells through to invasive, metastatic disease(1). It is a deadly (insidious) disease that progresses slowly, originating from mutant DNA sequences that change the direction of crucial pathways regulating homeostasis, cell survival and cell death (2).

Regulatory T cells (Tregs) are crucial in mediating immune homeostasis and promoting the establishment and maintenance of peripheral tolerance. However, in the context of cancer their role is more complex, and they are thought to contribute to the progress of many tumours. As cancer cells express both self- and tumour-associated antigens, Tregs are key to dampening effector cell responses, and therefore represent one of the main obstacles to effective anti-tumour responses. Suppression mechanisms employed by Tregs are thought to contribute significantly to the failure of current therapies that rely on induction or potentiation of anti-tumour responses.

Later in thisreview, we discuss the role of APC in tolerance, regulatory T cells, Innate and Adaptive Immunity and Cancer as well as to demonstrate how development of dendritic cell-basedtherapies for treatment of tissue-specific Cancer and autoimmunity maybecome broadly applicable.

2. Tolerance

An essential part of T cell-mediated immunity is the development of non-responsiveness toward naturally occurring self-Ag, while mounting effective immune responses against "foreign" Ag (3).Breakdown of self-tolerance will result in the development of autoimmune diseases. Self-reactive T cells, both CD4+and CD8+, have been shown to be responsible for initiating and mediating tissue damage in many experimental animal models of organ-specific autoimmunity as well as in human studies. Immunological tolerance is achieved by different mechanisms at different stages. Initially, potential self-reactive T lymphocytes are deleted during T cell development in the thymus. High-affinity interaction of TCR on immature thymocytes with self-Ag on thymic stromal cells results in apoptosis and elimination of such T cells in the process known as negative selection. T cells with TCR of low to moderate affinity to self-Ag escape from the thymus and migrate to the periphery. These T cells are normally "ignorant" to self-Ag or develop tolerance after initial activation. Although the Ag-specific TCRs of T cells do not possess an intrinsic mechanism to distinguish self from non-self- peptides, the activation by self-Ag is different to that by "foreign" Ag, mainly due to the absence of costimulatory signals from nonactivated APC. This is in contrast to activated APC that up-regulate costimulatory molecules during inflammation, infections, or other pathological conditions. Partial activation of T cells in the absence of costimulatory signals leads, instead of activation, to the state of T cell unresponsiveness toward further stimulation, also known as anergy. In most cases, costimulatory molecules will direct T cell response towards either activation or tolerance. Simple absence of costimulatory signals was shown to induce anergy in effector T cells in vivo and in vitro, while naïve T cells may require a negative signal of CTLA-4 engagement to develop anergy and become tolerant. Self-reactive cycling T cells may also undergo programmed cell death after re-exposure to the same Ag in a process called activation-induced cell death (AICD). AICD is mediated by death receptors (FAS/ FAS-ligand interaction of CD4+ T cells and by TNFRII/ TNF interaction of CD8+ T cells) that involve interaction of caspase-dependent, death-inducing signaling complexes (DISC).Peripheral tolerance can also be controlled by immune cytokine divergence and by Treg cells. Both natural and adaptive CD4+ regulatory cells have been implicated in the regulation of the autoimmune response. Thymus-derived CD25+ nTreg cells suppress other types of cell activation by largely unknown mechanisms. They require strong costimulatory signals for induction and maintenance, with Foxp3 expression. Adaptive (Ag-induced) Treg cells are generated in the periphery by sub-optimal antigenic signals and rely on cytokines such as IL-10 and TGF-β for suppression. These cells of varying phenotype often appear under special conditions such as chronic viral infections. Treg present new possibilities for the treatment of autoimmune disorders and for the maintenance of transplanted organs.

Breakdown of Tolerance

The concept of autoimmunity has evolved through several historical steps. Paul Ehrlich, at the beginning of the twentieth century, postulated that an immune-mediated mechanism capable of selectively affecting structures of the self was incompatible with life and defined it as 'horror autotoxicus'(4).He also performed experiments to demonstrate that it was not possible to induce an autoimmune response in healthy animals. These experiments, however, were repeated by others in subsequent decades in other models, with opposing results. See also: Autoimmune disease: animal models; Ehrlich, Paul Today, it is well accepted that autoimmune reactions are part of the physiological functioning of the immune system. Natural self-reactive antibodies are found at low concentration in the serum of normal individuals.
They usually are of IgMisotype, with low avidity for the antigen. Molecular analyses of the heavy- and light-chain variable regions of natural antibodies show unmutatedgermline V gene segments, which means that the B cells producing these antibodies have not undergone the somatic hypermutation events characteristic of a T cell-dependent adaptive immune response. Natural antibodies are probably used by the organism to facilitate the clearance of senescent cells and autoantigens, and thereforeprevent the activation of cognate autoimmune responses. See also: Antibodies; Antibody classes; Somatic hypermutation in antibody evolution; Natural antibodies Autoantibodies involved in the pathogenesis of autoimmune diseases are found at relatively high concentration in patients' sera . They are usually of IgGisotype, with high avidity for the antigen, and with V regions documenting somatic hypermutations. In other words, these autoantibodies are the product of a T-helper cell-dependent activation of B cells, which mature in conditions of prolonged contact with the antigen and undergo clonal selection.
What is the mechanism that drives the immune system to switch from a harmless natural autoimmune response to the production of very dangerous IgG autoantibodies? The answer is probably within the sophisticated mechanisms that regulate the maintenance of tolerance. Several hypotheses have been formulated to explain the breakdown of tolerance. Some of them are well supported by experimental models.
Tolerance may be broken both at the T- and the B-cell levels. Even though a consistent number of autoreactive B-cell clones is purged during ontogenesis, several autoreactive clones might be generated ex novo by somatic hypermutation of V regions during B-cell activation and maturation to plasma cells. Autoantigen-driven B-cell clonal selection, however, cannot take place without the help of cognate CD4+T cells. Therefore, the organism has to ensure that autoreactive T cells are deleted during ontogenesis or induced to tolerance in the periphery. This explains why most of the models of breakdown of tolerance have been studied at the T-cell level.

3. Failure to delete autoreactive lymphocytes

The familial association of autoimmune diseases suggests that the aetiopathogenesis of these diseases may be controlled by genetic factors. In certain individuals there might be a genetically determined inability to delete all autoreactive T- and B-cell clones during ontogenesis(5).Indeed, autoreactive T- and B-cell clones may be detected in the blood of normal individuals. There is no direct evidence, however, that cells directly involved in the pathogenesis of autoimmune diseases originate from these autoreactive clones. The presence of circulating autoreactive lymphocytes in healthy subjects must be considered as physiological. Indeed, tolerance during ontogenesis should not involve the removal of too many self-reactive clones. Due to the frequent molecular similarity between proteins of self and nonself, extensive deletion of potentially autoreactive lymphocytes recognizing autologous antigens would in fact cause a crippling reduction of the T- andB-cell repertoire. See also: Autoimmune disease: genetics;Immunological discrimination: self/nonselfTolerance is ensured by several other peripheral mechanisms,which during a lifetime avoid the activation ofself-reactive lymphocytes. An inherited impairment ofsuppressor mechanisms has been postulated, which allowsescape of newly generated autoreactive clones(6).Although this issue has long been debatedwithin the immunology community, several

pieces ofexperimental evidence are now available which documentthe existence of T cells with immunomodulatory activity(7),(8),(9).

4. Molecular mimicry

The number of amino acids from which proteins are made is relatively small and, even though the possible combinations are hundreds of thousands, identical stretches of sequence (less than 10 amino acids) are found relatively frequently among proteins of the body, as well as between self and nonself proteins. Moreover, several proteins are highly conserved phylogenetically, even among very distant species, probably because of their indispensable function within the organism. An immune response may be mounted against a microbial antigen that is similar or identical to a self-antigen. The result will be an immune attack against the microorganism and the self-tissue. A clinical example of disease caused by molecular mimicry is acute rheumatic fever, in which the antibody response mounted against a group A Streptococcus may cross-react with self-antigens expressed on articular, cutaneous, cardiac and brain tissues(10),leading to the appearance of corresponding clinical manifestations (i.e. polyarthritis, erythema marginatum and subcutaneous nodules, carditis and chorea).

5. Tumour Antigenicity

At thebeginningof the 20thcentury, Paul Ehrlichputforward the tumourimmune-surveillance theory. He had already worked in the role of immune responses to control infections caused by microorganisms. He then applied the same observations to cancer. He proposed that cancer cells spontaneously arise in the organism and that immune responses could effectively eliminate them [9]. This same concept was later refined by Burnet [10]. The fast development of organic chemistry, biochemistry, and molecular biology (and nuclear physics!) that followed in the 20th century provided the tools to systematically study cancer and develop chemotherapeutic agents that could inhibit cancer cell growth [11]. For the first time, drugs could be developed that were effective to at least control (and in some cases cure in combination with surgery and radiotherapy) cancer. Therefore, biomedical research directed its efforts in the development of these newdrugs.The study of anticancer immune responses steadily continued, but it never reached a therapeutic status as achieved by other “conventional” methods. The lack of success of cancer vaccines led to another misconception which still lingers within a relatively large proportion of the scientific community; immune responses did not play a significant role in controlling cancer, unlike “classical” antineoplastic strategies such as radiotherapy and chemotherapy. Interestingly, there is strong recent evidence that classical anticancer treatments heavily rely on the immune system for their effectiveness [12–20]. These treatments include radiotherapy and chemotherapy and depend on cellular stress responses [17].These responses lead to enhanced antitumour activities through the activity of TLR agonists released from necrotic tumour cells and activation of the inflammasome in antigen presenting cells by released ATP [14, 15]. Interestingly, these conventional antineoplastic treatments lose their efficacy when immune-compromised mice are used in the experiments, or when human patients have deleterious mutations on TLR4 [14]. What determines whether cancer vaccines can become a success in human immunotherapy? Exactly the same as required for infectious diseases, cancer has to be immunogenic and activate cytotoxic T cell responses. Consequently, cancer cells have to possess immunogenic antigens susceptible of being targeted by vaccination. Since Ehrlich’s proposal, researchers have been looking fortumour-associated antigens (TAAs) that could be exploited for cancer immunotherapy. And even though early studies found someexperimental evidence towards their existence (particularly from virus-induced tumours), the problem of the immunological tolerance always came back for the counterattack [21–26]. Many of these studies concentrated on immune responses against virus-induced tumours rather than endogenous cancer antigens [24, 27–29]. In fact, at the timetherewas an increasingly accumulating body of evidence supporting the viral aetiology of nearly all human

cancers [30–32]. This resulted in a major change of view for cancer therapy, as it was much easier to target foreign viral antigens expressed by tumour cells thanmutated self-antigens [30, 33–35]. Now we know that only a number of human cancers are caused by viral infections.Nevertheless, the "viral aetiology" theory for human cancer could not explain the immune responses against chemically induced cancers that were also observed. However, in many instances these results could not be reproduced by other research groups [36]. Even so, these early studies provided evidence that immune responses could be raised against tumours of nonviral origin. Spontaneous tumour regressions were also sporadically observed in human patients, in some cases provoked after immunisation towards common pathogens, strongly supporting the existence of TAAs of nonviral origin [20, 37, 38]. A turning point came from the study of oncogenic viruses, especially fromtheRetroviridae family which led to a "shocking" discovery.These viruses induced cancer through the expression of oncogenes, which had their corresponding cellular variants [39–47]. These oncogenes included v-raf, c-my, c-rel, and k-ras among others. All these proteins were largely involved in the regulation of cell proliferation and survival. So after all, transforming oncoviruses had "hijacked" cellular oncogenes for their own advantage. But, in cancers of nonviralaetiology, are the corresponding cellular versions involved in carcinogenesis? That turned out to be the case [48]. Cancerous cells accumulate a series of mutations leading to genetic instability, which results in protein expression changes, increased survival, and uncontrolled proliferation [47–52]. Many of the mutated proteins were transcription factors (c-myc), part of key signalling pathways (human Ras), cell cycle regulators (retinoblastoma protein, Rb), and antioncogenes (p53). As a result of uncontrolled proliferation and defects in DNA repair/apoptosis pathways, further mutations and chromosomal rearrangements appear. "Fortunately," as a direct consequence, these cells express a collection ofmutated self-proteins that confers them with a degree of immunogenicity (quasi-antigens). In some cases, self-proteins can be aberrantly overexpressed in tumours, which would not normally be expressed in the corresponding healthy tissue. This acquired immunogenicity allows the immune system to identify and destroy them.

6. Regulatory T cells in Cancer

The role of the immune system in cancerogenesis and tumor progression has been the subject of much controversy since the 1950s when Burnet and Thomas formulated their concept of "tumor immune-surveillance"; a process through which the immune system recognizes and (ideally) eliminates self-cells that have undergone malignant transformation(11).Numerous observations in clinical and experimental settings have fortified this concept that was further advanced by the model of "immune editing." According to this theory, multiple factors generated by the oncogenic process counteract the immune system cumulatively hampering an efficient immune response and facilitating the "tumor escape"(12).Tregs as regulatory elements have the ability to actively suppress immune responses and represent a predominant tolerance-inducing modality(8).Already in the early days of the discovery of the suppressor cells, observations from tumor mouse models indicated a central (negative) role of Tregs in immune-surveillance; namely hindering an efficient tumor eradication. Tumor cells, in particular methylcholanthrene-induced fibro-sarcomas, elicited measureable T cell responses that were not sufficient to eradicate the tumors due to the development of tumor-induced suppressor T cell activity within the CD4 þ T cell population(13),(14).In the following part of the review, we have focused mainly on the impact of Tregs in patients with solid tumors and hematological malignancies. The underlying biological mechanisms and targeted therapeutic interventions are discussed.

7. Regulatory T Cells in Solid Malignancies

The vast majority of the studies on Tregs in cancer are performed on patients with solidmalignancies. It is obligatory to take into consideration that virtually all of these studies were carried out during the period when the phenotype of Tregs was being refined thereby complicating direct comparisons between studies. Shortly after the publication on the existence of CD4þCD25high Tregs in the PB of healthy individuals(15),the group of Carl June was the first to provide direct evidence that patients with epithelial malignancies, in particular ovarian and non-small-cell lung cancer (NSCLC) displayed increased levels of CD4þCD25high Tregs in the circulation and within the tumor infiltrating lymphocytes (TILs). These cells constitutively expressed CTLA-4 and exhibited suppressive effects by inhibiting the proliferation of conventional T cells and IFN-_ production. The suppressive activity was partly mediated by TGF-_(16),(17).In patients with pancreatic and breast cancer, increased levels of cells with similar phenotype were found in the PB, LNs, and tumor tissue. These cells were positive for IL-10, TGF-_, and CTLA-4(18).Furthermore, results from these initial studies strongly indicated a tropismof Tregs toward tumor sites as their proportion in draining LNs and TILs was higher than that expected theoretically, based on their frequencies in PB. In addition, the first Treg cell lines derived from autologous cocultures of tumor cells and lymphocytes from colorectal cancer patients were generated. These cells displayed tumordependent expansion and suppressed both allogeneic and autologous T cell responses independent of cell-to-cell contact via TGF-β (19).One of the first proposed mechanisms underlying the activation and induction of Tregs was heavy-chain Ferritin (H-Ferritin), which is produced in large amounts by melanoma cells. Melanoma patients exhibited a significant positive correlation between serum levels of H-Ferritin and increased Treg frequencies and activation(20),(21),(22).Several studies on gastro-esophageal cancers also reported that increased fre(16)quencies of IL-10-p(20)roducing CD4 þCD25high Tregs can be found in PB, TILs, draining LNs, and ascites fluid, which were strongly associated to disease stage(23),(24),(25),(26).Importantly, the proportion of Tregs was significantly reduced in patients to almost physiological levels upon curative surgery. Furthermore, the level of Tregs rebounded at the timepoint of postoperative recurrent disease, strongly indicating an interconnection between tumor burden and Treg accumulation(25). It has been shown thatCD4þCD25þ Tregs are capable of suppressingNKcell-mediated cytotoxicity in patients with various types of epithelial tumors including lung, breast, and colorectal cancer(27).Upon identification of FOXP3 as a more reliable marker for Tregs and potentially as a surrogate measure for their suppressive function, an increasing number of subsequent studies included FOXP3 in their staining panels such as the pivotal work carried out by Tyler J. Curiel and colleagues on ovarian cancer patients(28).In this comprehensive study it was convincingly demonstrated that CD4þCD25þFOXP3þ Tregs were present in PB, malignant ascites, tumoral tissue, and drainingLNs. Interestingly, Treg levels in tumor-draining LNswere lower as compared to control LNs and tonsils and decreased with increasing disease stage. One of the proposed mechanisms underlying this phenomenon was the presence of the chemokine CCL22. Secreted by ovarian cancer cells and tumor-associated macrophages (TAMs), a concentration gradient of CCL22, which binds to CCR4 expressed on Tregs, is generated and thereby mediates migration of Tregs away from the draining LNs toward the CCL22- rich tumor microenvironment. It is worth mentioning that physiologically CCL22 facilitates the encounter between DCs and activated antigen-specific T cells suggesting that tumors elegantly capture this process in order to efficiently suppress activated effector cells(29)Similar findings regarding Treg trafficking and redistribution have been largely made in various types ofmalignancies(30),(31),(32),(33),(34),pointing toward the need for examining the distribution of Tregs in multiple tissue compartments since quantification of Tregs in PB alone may not accurately portray Treg frequency or trafficking. Analysis of subset frequency for effector cells such as NK and T cells together with Tregs revealed that a shift of the Treg/effector T cell ratio was often linked to the tumor burden and disease course(35),(36),(37).The global interest in Tregs resultedin several analogous studies on Treg (-subsets) in different types of malignanciesincluding melanoma(22),hepato-cellular carcinoma(HCC)(38),(39).Ewing sarcoma(40),head-and-neck(41),prostate(42),(43),ovarian(44),(45),breast(46),colorectal(47),(48), and pancreatic

cancer(18).Despite the fact that the preponderance of results indicated a negativeimpact of Tregs in carcinogenesis and disease progression, some findingsraised doubts with regard to this "simplification". The presence of Tregs wasin fact correlated to positive prognosis in head-and-neck as well as gastriccancer(49),(50).These prima facie contradictory findings gained further credibility from studies in animal models of colorectal and gastric cancer providing further evidence for the plasticity of Tregs and their rather complex role in immune-regulation(51),(52),(53),(54).It must be emphasized that these anecdotal exceptions do not negate the perception that Tregs hamper "immune surveillance" but rather they present a more holistic view of their functional repertoire. Tregs are per se associated with immunosuppression and anti-inflammatory activity. Consequently, by counteracting inflammatory processes Tregs may mediate an anticarcinogenic effect given that inflammation-initiated carcinogenesis and tumor progression is a well-established model (55),(56).Under certain pro-inflammatory conditions characterized by elevated levels of IL-6, IL-1_, IL-23, and lactic acid, Tregs can convert from anti- to pro-inflammatoryIL-17þ cells. Thus, Treg populations with contradictory functions can coexist at elevated levels in tumor tissue. One speculation is that functionally reversed Tregs may contribute at an early stage to the escalation of cancer-associated inflammation and subsequently during the course of disease inhibitory Tregs suppress tumor-specific responses as implied by most studies.

8. Cancer development and innate immune responses

Innate immune cells have huge capacity to produce cytokines, chemokines, metalloproteinases, ROS, histamine and other bioactive mediators for cell survival which enables them to participate in cancer development(57),(58).Chemokines and their receptors are responsible for infiltration of lymphocytes into the tumour tissue. Due to the ability for matrix metalloproteinases (MMPs) to regulate epithelial cell proliferation, angiogenesis, cancer development, tissue homeostasis and disease, it has been identified as a crucial immune cell-derived mediator(59),(60). During acute inflammation, tumour necrosis factor-alpha (TNF-□) another inflammatory cytokine is mobilized. TNF-□□mediates cancer development by regulating the proliferation and survival of neoplastic cells. They also have an indirect effect on endothelial cells, fibroblast and immune cells present in tumour microenvironments(61). If produced by the tumourmicroenvironments, TNF-β will activate the pro-inflammatory nuclear transcription factor-B (TNF-B) dependent anti-apoptotic pathway during the time at which the foci of pre-malignant hepatocytes develop into tumours. NF-□B has shown susceptibility to inflammation-induced intestinal tumours. These proinflammatory cytokines contribute in a paracrine fashion to neoplastic cell proliferation and increase survival of initiated or damaged epithelial cells(62).
The cytokines released in response to this tissue destruction can induce up-regulation of key genes thought to be necessary for malignant transformation of tissues which are chronically inflamed, thought to inhibit apoptosis, promote angiogenesis, modulate cellular adhesion, and induce pro-inflammatory mediators, in addition to further recruitment of other innate and adaptive cell types(63),(64).Suppression of anti-tumour adaptive immune responses by chronically activated innate immune cells can indirectly contribute to cancer development by allowing tumours to escape from immune surveillance.

9. Adaptive immunity and cancer

The role of adaptive immune cells in cancer development is still debatable. The relative risk (RR) of cancer varies depending on the organ site and cancer origin. In cases of infection by oncogenic viruses, such as hepatitis virus and human T-lymphotropic virus type 1 (HTLV-1), viral antigen presentation by HLA class I and II molecules to T-cells, and subsequent T-cell mediated cytotoxicity and cytokine production, are also key elements in the control of infection(65). The adaptive immune system can also differentially regulate cancer development within the same epithelial microenvironment, as a function of varied initiation. Natural killer T (NKT) cells have also been reported in cancer development. NK cell recognition is mediated by the opposingeffects of two

different types of NK receptors: activation and inhibitory receptors. The activation receptors recognisestressinduced ligands that are expressed on the target cell, and then transmit intracellular signals that initiate cytotoxicity(66).The inhibitory receptors recognise cell-surface MHC class I molecules and generate counter-activating signals that block the induction of cytotoxicity. NK cells can also influence subsequent adaptive immune responses by releasing cytokines and chemokines that induce growth and differentiation of various immune cells(65).They express certain NK cell markers and recognize glycolipid ligands presented by the MHC class I like molecule, cluster of differentiation 1 (CD1d)(67),(68).Ironically, the influence of NKT cells during cancer development is probably a consequence of their inherent capacity to produce both pro-inflammatory Th1 cytokines and anti-inflammatory Th2 cytokines; therefore, the nature and balance of surrounding stimuli might determine which type of NKT cell induced T-helper response dominates and contributes to malignant outcomes. CD4+ and CD8+ T-cells are important modulators of such tissue-damaging B-lymphocyte responses(69),(70). Adaptive immunity has a crucial role in regulating and activating innate immune cells in affected tissues such as immunoglobulin depositionwhich contributes to chronic inflammation and disease pathogenesis(71).

10. Immune Directed Apoptosis of Cancer

T-lymphocytes play a major role in the destruction of tumour cells. The immune system identifies tumour cells as ''non-self'' by several mechanisms, including recruitment of programmed cell death receptors that cause apoptosis of these cells(72). However, tumour cells neutralise the immune system by evading detection and thereby prevent an immune response. The sensitised T-cells can affect killing of tumour cells by means of the lymphokines that they release. When these lymphokines are released, they mobilise and activate B-cells through B-cell growth factors and B-cell differentiation factors(73). Macrophages and NK cells also exert tumour-killing effects through other mechanisms(74). On the other hand cancer cells may stimulate the immune system to express blocking antibodies, which cannot activate complement. This also means that no C3a or C3b is formed. Complement forms part of the innate immune system, it is sometimes recruited and brought to work by the adaptive immune system. As the disease progresses, there is associated decrease
in immunity which results in a progressive fall in response to all foreign antigens(73). Tumour cell death induced by conventional treatments releases a host of tumour associated antigens (TAAs) which induces tumour cell death in order to stimulate an antitumour immune response. Both radiotherapy and chemotherapy have been assumed to antagonise any priming of the immune system, by inhibiting lymphocyte division and inducing lymphocyte death(75). Tumour cell apoptosis induced by these treatments is considered non-immunogenic(76).

Conclusion

When a dynamic state of equilibrium is established upon interaction of the immune system with the developing tumour, strong T cell responses are key to acquiring long-lasting tumour-specific immunity. The mechanisms of establishing tumour-specific tolerance, with a principal contribution from Tregs, are becoming increasingly a focus of research. Based on the data currently available, it is clear that the timing and dose of certain therapeutics is of key importance. One of the major caveats for cancer immunotherapy is the incidence of adverse reactions, such as hypersensitivity and autoimmunity, which arise as a consequence of targeting Tregs. Development of effective therapeutic strategies to target cancer will rely on combining control of Treg function as well as APC, Breg and Treg maintaining Tolerance and Balance Modification One of the best and potential Theraphy for the future of cancer treatment and Prevention.

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