Seminars in Cancer Biology 22 (2012) 307–318

Contents lists available at SciVerse ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

New insights into chronic inflammation-induced immunosuppression

Julia Kanterman[1], Moshe Sade-Feldman[1], Michal Baniyash*

The Lautenberg Center for General and Tumor Immunology, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

ARTICLE INFO

Keywords:
Chronic inflammation
Immunosuppression
Cancer
Immunotherapy
Autoimmune diseases
Transplantation biomarkers

ABSTRACT

Chronic inflammation is a common factor linking various pathologies that differ in their etiology and physiology such as cancer, autoimmune diseases, and infections. At a certain stage of each of these diseases, while the chronic inflammation proceeds, some key players of the immune system become immunosuppressed as natural killer (NK) cells and T cells. The suppressive environment induced during chronic inflammation is governed by a complex processes characterized by the accumulation and activation of immune suppressor cells, pro-inflammatory cytokines, chemokines, growth and angiogenic factors, and by the activation of several inflammatory signaling pathways mediated predominantly by NFκB and STAT3 transcription factors. A substantial body of evidence supports the notion that the development of a suppressive environment during chronic inflammation limits the success of immune-based and conventional therapies, skewing the balance in favor of a developing pathology. Thus, appropriate, well-designed and fine tuned immune interventions that could resolve inflammatory responses and associated immunosuppression could enhance disease regression and reinforce successful responses to a given therapy. This review describes the interrelationship between chronic inflammation and induced immunosuppression, and explains the current evidence linking inflammation and pathological processes, as found in cancer. We further highlight potential strategies, harnessing the immunosuppressive environment in treating autoimmune diseases and facilitating transplantation. In parallel, we emphasize the use of modalities to combat chronic inflammation-induced immunosuppression in cancer, to enhance the success of immune-based therapies leading to tumor regression. In both cases, the urgent necessity of identifying biomarkers for the evaluation of host immune status is discussed, with the goal of developing optimal personalized treatments.

1. Chronic inflammation and induced immunosuppression

An inflammatory process reflects the host's principal immune response aimed at eliminating foreign substances invading the body, or abnormally generated self-compounds produced during tissue injury. The response promotes the optimal restoration of tissue structure and function, but must also rapidly turned off in order to prevent over reaction that could result in irreversible damage [1–3]. In general, the innate immune response is initiated within minutes, and if necessary, it is supported by the adaptive immune arm. Both responses are able to resolve the inflammation within several days. In contrast, failure to clear the endanger elements or inefficient termination of the response, could result in chronic inflammation, possibly leading to increased morbidity due to the induction of immunosuppression [1,4,5].

Indeed, in recent years, numerous studies showed a suppression of innate (NK cells) and adaptive (T cells) immune cells, associated with T-cell antigen receptor (TCR) ζ-chain (CD247) down-regulation over the course of several pathologies such as cancer [4,6], autoimmune disorders [7,8] and chronic infectious diseases [9,10]. Initially, this phenomenon was identified in hosts with developing tumors (mice and humans), and it was explained as one of the modes by which tumors escape immune surveillance [11]. However, the same phenomenon was observed in autoimmune and infectious diseases, which led us to hypothesize that chronic inflammation is a common denominator linking these pathologies and the observed immunosuppression. We were the first to demonstrate that this hypothesis is indeed valid, and over the years it was shown by others and by us, that the immunosuppression observed in all these pathologies is induced by chronic inflammation, and is the normal outcome of the body's defense system to avoid excessive immune stimulation. While the nature of the initial stimulus could vary, and as long as it induces the sustained activation of a variety of responding cells that elicit an inflammatory response, the recurrent consequence is immunosuppression, which starts as local, and at a later stage, becomes systemic.

* Corresponding author at: The Lautenberg Center for General and Tumor Immunology, The Hebrew University-Hadassah Medical School, P.O. Box 12272, Jerusalem 91120, Israel. Tel.: +972 2 6757461; fax: +972 2 643 0834.
E-mail address: baniyash@cc.huji.ac.il (M. Baniyash).
[1] These authors equally contributed to this work.

1044-579X/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.semcancer.2012.02.008

1.1. Stimulators

The specific cause for a persistence chronic inflammation is not completely understood. However, the contribution of several factors has been demonstrated to take central roles in triggering the ongoing inflammation. In assessing the disordered microenvironment of a target tissue it was shown that infiltrating leukocytes and resident tissue-specific cells such as fibroblasts, endothelial cells, and resident macrophages, along with their primary functions, can perpetuate the local inflammatory response [1,12–14]. Since the function of immune as well as stromal cells is not constitutive, their activity requires stimulatory support. Through the production of a complex network of cytokines and chemoattractants, these cell types directly alter the behavior of newly recruited and infiltrating effector cell populations, resulting in continuous stimulation of these populations, and their inappropriate survival and retention [1,15]. Inflammation that becomes chronic can develop due to antigen-specific stimulation of T-helper-1 (Th-1) cells, leading to their persistent activation. Such responses could be directed against a wide range of pathogens from microbial, viral or parasitic infections (for example: *Helicobacter pylori*, Hepatitis B and C, and *Schistosoma mansoni*) [5,16,17], or exposure to allergens and toxic chemicals. Moreover, Th-1-mediated responses can lead to chronic sterile inflammatory conditions due to over-reactive responses directed against endogenous antigens and abnormally exposed cellular compounds, as in autoimmune diseases and cancer. In addition, the innate immune system as well as some adaptive cells can be triggered by Toll Like Receptor (TLR) ligands, typical to various pathogens and endogenous compounds, eliciting pro-inflammatory stimulators and factors, which are also involved in the induction of the infections or sterile pathological conditions as cancer and autoimmune diseases.

TLRs, the archetypal pattern recognition receptors (PRRs), are activated in response to stress and danger signals, stimulating primarily the innate immune system cells as well as, in some cases, adaptive immune cells. They play a crucial role in defending against pathogenic infection and abnormally occurring sterile host stimuli, by inducing an inflammatory response associated with an array of cells, secreted cytokines including type I interferons, and chemokines [18]. Thus, TLR-mediated responses triggered by endogenous ligands, serve in many cases as a possible promoter of inflammation even in the absence of infection. TLR-dependent responses can potentially expand as they can co-stimulate additional innate and adaptive immune cells, thus having an extensive and direct effect on the entire microenvironment. Indeed, our studies demonstrate that chronic exposure of mice to a single TLR ligand could induce chronic inflammation and associated immunosuppression, as observed during various infectious and non-infectious pathologies [9]. Therefore, it is not surprising that prolonged and persistent TLR-dependent triggering results in a constitutively active immune response, which is linked to pathological reactions and disorders, including neoplastic transformation and carcinogenesis [18,19].

1.2. Response

Conditions of chronic inflammation are evident due to continuous triggering by specific or non-specific, self or non-self antigens, as in cases of persistent pathogens or growing tumors that could not be cleared, or as autoantigens permanently existing and trigger a continues response, resulting in high concentrations of secreted pro-inflammatory factors [1,4]. These conditions are harmful to the host immune system, leading to a general immunosuppression as reflected by aberrant signal transduction pathways, activated immune cells and inappropriate balance of secreted immune and non-immune factors, all detrimental to normal immune system function [16,17]. Although under such chronic pathological conditions immunosuppression is evident, the inflammatory response still perpetuates due to compounds secreted by a continuously damaged tissue, as endogenous TLR ligands (heat shock proteins, extracellular matrix components, DNA fragments), which trigger inflammatory responses by various immune and non-immune cells.

Under chronic inflammatory condition, central signaling pathways are activated including the transcription factors NFκB, the STAT family, AP-1 and others [16,20,21]. These pathways have emerged as regulators of pro-inflammatory cytokines, as well as mediators of stem-cell renewal, cell proliferation and survival, all involved in persistent inflammation. For example, following continuous inflammatory stimulation, NFκB is constitutively activated and ensures transcription of target inflammatory genes, such as the tumor necrosis factor α (TNFα), a major pro-inflammatory cytokine with pleiotropic functions [13,21]. TNFα can play a dual role; while destroying tumor vasculature and inducing necrosis, it may also stimulate growth and survival of tumor and various immune cells [5,22]. Studies have shown that mice lacking TNFα are resistant to some carcinogenic processes, and elevated levels of TNFα have been detected in various human pathologies characterized by chronic inflammation, including autoimmune disorders, and different types of malignancies [23–25].

Interleukin-6 (IL-6) is an additional major pro-inflammatory cytokine participating in the induced immunosuppression, secreted at high levels by hallmark immune and non-immune cells. IL-6 modulates the expression of genes involved in cell survival and proliferation, primarily *via* the JAK-STAT signaling pathway [26]. Elevated levels of IL-6 have also been reported in clinical cases of cancer patients and other chronic inflammatory disorders [27].

Another major factor induced under NFκB stimulation is nitric oxide synthase (NOS2), which plays a role in pathological conditions and tissue damage, mainly by controlling levels of nitric oxide (NO). Elevated NO levels affect cellular responses by causing DNA damage, increasing angiogenesis through vascular endothelial growth factor (VEGF) stimulation, and enhancing tumor cell growth and invasive properties [20,28,29]. Moreover, exacerbated over-activated inflammatory pathways are also accompanied by the production of reactive oxygen species (ROS). While ROS are usually essential for an anti-microbial defense, inappropriate production leads to oxidative stress, increased mortality of immune cells, tissue damage, genomic instability and enhanced malignant cell proliferation [20,30].

Cyclooxygenase-2 (COX-2) is another key player linked to inflammatory responses, abundantly produced in several human lesions and cancers. COX-2 mediates prostaglandin synthesis (PGE_2), which in turn promotes cell proliferation, cytokine secretion, and suppresses immune surveillance by mechanisms such as inhibition of the Th-1 activation, IL-2 secretion, and DC suppression through IL-10. This pathway was shown to participate in cases of inflammatory diseases such as Crohn's disease and colon carcinoma [31–33].

Another class of regulatory molecules with a compelling role in inflammatory modulation is the recently discovered microRNAs (miRNAs or miRs). These are small, non-coding RNAs that regulate the post-transcriptional behavior of specific genes, and by a feedback loop, they can be regulated *via* other cellular components such as inflammatory cytokines and chemokines, as well as activated transcription factors. The expression of miRNAs can be induced by many different mechanisms including one involving inflammatory stimuli [17,34,35]. For example, the expression of specific miRNAs such as miR-146 and miR-155 can be activated by inflammatory mediators including NFκB and the STAT family transcription factors, and were shown to be involved in the

maintenance of inflammatory responses [36,37]. Recent studies have demonstrated that TNFα stimulation induces miR-155 expression in monocytes and macrophages, resulting in granulocyte/monocyte expansion and growth during inflammation and cancer, suggesting miR-155 as a potential prognostic biomarker in tumor development [34,38].

Inflammatory stimuli, responding cells and associated factors expand the resulting inflammation by leading to the recruitment and activation of various immune cells, which in turn, produce and release a variety of inflammatory factors, generating an autonomous loop of chronic inflammatory responses. Numerous cell types present at the inflammatory microenvironment and circulation have been identified as key players in modulating the response towards immunosuppressive stages. Mesenchymal stem cells (MSCs), mainly derived from the bone marrow, are stromal cells with a large capacity for self-renewal while maintaining their multipotency and can differentiate into a variety of cell types [15,39]. MSC infiltration into tumor sites interferes with DC and T-cell proliferation and function by several mechanisms including induction of indoleamine 2,3-dioxygenase (IDO), NOS2 and PGE_2, as well as secreting cytokines such as IFNγ, TNFα, and IL-1, all contributing to the generation of a local immunosuppressive microenvironment [40].

Tumor-associated macrophages (TAMs) infiltrate almost in all kinds of tumors. They are derived from monocytic precursors that are stabilized by colony-stimulatory factor (CSF) secreted by tumor and immune cells within the microenvironment [14,15,41]. Naturally, prolonged survival and activation of macrophages can elicit tissue destruction and tumor cell elimination. However, once this population is skewed to M2-like phenotype (through inappropriate cytokine secretion and microenvironment modulation), these cells produce growth and angiogenic factors, promoting degradation of extracellular matrix and invasion of tumor cells, facilitating metastasis [42,43].

Within the myeloid lineage, there are also DCs that participate in immune modulation under chronically inflamed conditions. Even though DCs have a crucial role in activation of a Th-1 antigen-specific immunity, in their immature state, they are involved in the maintenance of tolerance induced under pathological episodes [42,44]. The immature DC phenotype is broadened in the chronic inflammatory microenvironment, supporting growth of stromal and tumor cells, mainly *via* the activation or recruitment of regulatory T-cells (Tregs), joining the immunosuppressive environment [45].

Myeloid-derived suppressor cells (MDSCs) represent an immature cell population that is also present in most cancer patients and tumor-bearing mice. The main property of these cells, which are detrimental in the case of cancer, is their ability to inhibit both the innate and adaptive immune responses, subverting immune surveillance [46,47]. MDSCs are identified based on their unique nuclear morphology and surface marker expression profile. In mice, they are found in two sub-populations, the monocytic ($CD11b^+Ly6G^-Ly6C^{high}$) and granulocytic ($CD11b^+Ly6G^+Ly6C^{low}$) phenotypes, whereas in humans the characterization is more complicated; most human MDSCs have a phenotype of $CD11b^+CD33^+CD34^+CD14^-HLA\text{-}DR^-$, but these cells can vary in expression of additional markers, depending on the inflammatory disease type [48,49]. MDSCs, under normal conditions, appear in small numbers in the circulation (3–5%), while under chronically inflamed conditions, their numbers are markedly increased within the spleen and peripheral blood of mice (up to 70%), as well as in human blood, within the tumor, and inflamed tissues and organs [11,50]. Expansion of MDSCs is associated with decreased numbers of mature myeloid cells, including macrophages and DCs, disrupting the normal homeostasis. Triggering of MDSC recruitment and expansion is driven by a variety of secreted survival and maturation-blocking cytokines. We have previously demonstrated that IFNγ plays a key role in the initial phase of MDSC generation and recruitment [10], and a similar pathway was described in tumor bearing hosts [51]. IFNγ is secreted by numerous immune cells including T and NK cells and acts in an autocrine fashion, affecting the function of T-cells and MDSCs. IFNγ can change the nature and function of MDSCs, promoting arginase 1 (ARG1) and NOS2 generation, which contribute to their immunosuppressive activity [46]. MDSC expansion is also observed in response to high concentrations of GM-CSF produced by activated T-cells, a phenomenon mostly found in autoimmune diseases [52]. Recently, it was also shown that PGE_2 plays a central role in MDSC accumulation triggered by the CXCL12-CXCR4 chemokine pathway [53]. Moreover, we demonstrated that cytokines such as TNFα and IL-6 lead to MDSC differentiation arrest, accumulation and activation (submitted for publication). Since MDSCs have the ability to negatively regulate both the innate and adaptive immune responses, they are considered as the major cause of immune suppression observed in numerous chronic inflammatory diseases, including cancer. Among their various deleterious effects, MDSCs were shown by us and others to suppress NK cell attack, as well as T-cell immune responses by several mechanisms, including the production of ARG1 involved in arginine metabolism critical for immune cell function, and NOS2, which is responsible for the release of NO and ROS, as well as autocrine stimulation *via* secreted pro-inflammatory cytokines such as TNFα [46,47]. MDSCs were also found to have a bystander immunosuppressive effect on both $CD4^+$ and $CD8^+$ effector T-cells by down-regulating CD247, resulting in impaired activation and proliferation, as well as induction of Tregs, mainly by producing IL-10 and TGFβ, which, in turn, down regulate cell-mediated immunity [54–58].

1.3. Consequences

A substantial body of evidence supports the conclusion that defects in endogenous inflammatory pathways predispose the individual to the development of chronic inflammatory diseases that can lead to conditions such as cancer, as demonstrated by the association between chronic inflammatory bowel disease (IBD) and the increased risk of colon carcinoma, and human papillomavirus and Hepatitis B and C virus infections, were found to be associated with liver induced inflammation and consequently, with cervical and hepatocellular carcinoma, respectively [59,60]. Chronic inflammatory diseases can affect every part of the body including internal organ systems, and connective tissues, posing life-threatening conditions. Besides the increased cancer risk and additional disease-related complications found in association with chronic inflammation, there is an additional danger of increased susceptibility to opportunistic infections once the individual's immune response is paralyzed under the immunosuppressive conditions [61]. In general, chronic inflammation-induced immunosuppression predisposes tissue transformation, malignancies and other inflammatory insults in which infiltrating cells and factors together with prolonged secretion of activating signaling compounds allow the inflammatory process to overrule the defined borders within a specific tissue, spreading to the neighboring areas and through the blood stream, reaching distant organs and thereby affecting healthy tissues and organs.

2. Clinical implications utilizing chronic immunosuppression for therapy

There is no doubt that chronic inflammation-induced immunosuppression drives serious complications and consequences in associated pathologies. However, there is another side of the coin

in which the suppression of autoreactive cells and neutralization of the over-activated immune response could serve clinical goals, and even represent the only way to enable recovery. The suppressive function of MDSCs is the normal outcome of exacerbated inflammatory response [46]. These cells serve as key players in attenuating the reaction. If the stimulus is cleared, the inflammatory environment is 'calmed', the cytokine milieu is changed, and MDSCs undergo maturation and lose their suppressive activity [46]. Thus, during cancer, chronic infections or any disease in which chronic inflammation induces complications it would be beneficial to neutralize the immunosuppressive environment in order to facilitate an effective immune response, while in cases of autoimmune disease and transplantation, MDSCs could be used to inhibit the autoreactive cells or the host/donor cells, respectively, at the initial disease state, before tissue damage and complications ensue. Thus, immunosuppressive immune cells, such as MDSCs, while damaging in conditions such as cancer, they could also serve as an attractive tool in therapeutic and immunomodulatory strategies being developed for hosts suffering from autoimmune diseases, as well as minimizing the complications associated with cell and organ transplantation.

2.1. Autoimmune diseases

Autoimmune diseases are characterized by immune cell activity against self-antigens, leading in many cases to tissue damage, organ failure and other fatal consequences. The more commonly studied autoimmune disorders are those characterized by chronic inflammation and ineffective immune tolerance. Rheumatoid arthritis (RA), is characterized by disordered synovial tissues and a strong inflammation within joints, in which infiltration of autoimmune effector T-cells mediating Th-1 and Th-17-depedent pro-inflammatory responses are evident [62,63]. These lead to various inflammation-associated complications of the local tissue surrounding the affected joints as the bones, as well as systemically, resulting in cardiovascular, pulmonary, psychological, and skeletal disorders. A similar array of infiltrating inflammatory cells are also found in Multiple sclerosis (MS) an autoimmune disease attacking the CNS [64], and in Crohn's disease affecting the colon [59]. In the latter, the chronic inflammatory environment predisposes the affected host to cancer development, manifested as colon adenocarcinoma.

Interestingly, in numerous autoimmune diseases such as RA, MS, IBD, autoimmune hepatitis and alopecia areata, although accumulation of MDSCs can be detected, disease progression is still evident. In such cases, MDSCs fail to adequately control the autoimmune T-cell responses *in vivo* [65,66]. The reasons why MDSCs cannot suppress these autoimmune diseases are poorly understood. However, two possibilities that require further investigation, could be envisioned to explain this question: (1) MDSCs do suppress the auto-reactive T-cells but sustained inflammation is still induced by damaged tissue compounds that activate TLRs, leading to a continuous inflammatory response and expanded tissue destruction, and (2) MDSCs under continuous inflammation reach a point at which as their immunosuppressive activity is inactivated, enabling autoreactive cells to continue their damaging effect with no limits. Thus, if an autoimmune disorder is identified early enough, before the damaging inflammatory response is exacerbated, MDSCs might be effective in a therapeutic approach as suppressors of the auto-reactive T-cells to overcome disease progression. Indeed, the efficacy of exogenously applied MDSCs in inhibiting autoimmune disease in certain murine models such as alopecia areata [67] and a model system for type 1 diabetes [68] suggests that they could be harnessed as a cellular therapy for autoimmune disease. Patients with autoimmune disease will be able to provide their own cells, isolated from the bone marrow or peripheral blood, expanded *in vitro* and then administered. Nevertheless, the use of MDSCs as a therapeutic strategy for an autoimmune disease might have detrimental rather than beneficial effects; MDSCs could exacerbate the disease, as was documented in experimental autoimmune encephalomyelitis (EAE) models showing the link between MDSC accumulation within peripheral lymphatic organs and brain, and MS disease severity and CNS damage [65].

Additional studies are required to determine the conditions for optimizing the *in vitro* expanded cells, which must be stabilized and retain their immunosuppressive activity, being suitable for immunotherapy-based adoptive transfer. An exact understanding of the suppressive mechanisms induced upon co-interaction with target cells is required as a prerequisite for clinical trials, taking in account the heterogeneity of the identified suppressive cells. Moreover, induction of tolerance in the above mentioned pathologies must take in consideration the timing of a given treatment. Pre-clinical and clinical trials have shown minimal success with such applications, raising the possibility that the administration of immunosuppressive cells is only effective prior to appearance of the disease, or alternatively at its very early stages. Thus, using MDSC as an effective treatment to reverse the disease course is dependent on early detection of such a chronic inflammatory disorder (see "*biomarkers for sensing immune status*").

Some miRNAs may also be harnessed for therapy of autoimmune diseases. It was shown that enhanced autoimmune responses occurred following deletion of an enzyme playing a key role in the miRNA biogenesis; deletion of dicer in $Foxp3^{+}$ mouse Tregs causes a loss of their suppressive functions [69]. More specifically, a similar phenotype could be also demonstrated by central regulatory miRNAs, such as miR-155, which is expressed in both the innate and adaptive systems and is involved in the development and progression of a pro-inflammatory process in autoimmune disorders [70,71]. These characteristics raised the possibility that such a miRNA could serve as a potential target for suppression in order to achieve inhibition of autoreactive immune cells. However, a deeper understanding is needed to characterize the exact immune response following miRNA interference and their applicative manipulation for therapeutic implementations.

2.2. Transplantation

The concept of generating therapeutic strategies based on using MDSCs as an immunosuppressive tool can also be considered in cases of cell- and organ-transplantations. Although treatment protocols are now available to enable long-term graft survival, preventing acute and chronic rejection is still a severe problem limiting the success of tissue and organ transplants. The use of MDSCs in transplantation was first described in a rat model of kidney allografting, where graft-infiltrating MDSCs inhibited the proliferation of effector T-cells [72]. Moreover, in these studies it was noticed that the MDSCs did not adversely affect Tregs, suggesting a possible combinatorial applications of immunosuppression-induced tolerance preventing T-cell recognition of donor antigens. As mentioned above, suppressive cells as MSCs are also considered as promising candidates. Studies using mouse models showed that MSCs were able to prevent of RA exacerbation, as well as EAE progression following MSC injection, apparently due to inhibition of autoreactive cell proliferation [73].

Following transplantation, immune reaction between donor- and recipient-immune cells can occur and lead not only to tissue or organ rejection, but also to a graft-*versus*-host disease (GVHD), resulting in an attack of the recipient's tissues by donor allogeneic-reactive T-cells [74,75]. These complications also could place the individual under a risk of predisposition to opportunistic infections and even malignancies. Immunoregulatory cells such as MDSCs and Tregs expanded *in vitro* and maintaining immunosuppressive

abilities can play a decisive role in prolonging graft acceptance. Studies demonstrate that clinically infused MDSCs can effectively prevent allogeneic-reactive T-cells responses, resulting in prolonged survival in mice [76]. Moreover, clinical trials evaluating safety and efficiency of Treg treatments of GVHD, also demonstrate potential recovery and prolonged survival [77,78]. In all these cases, correct timing is probably essential for the success of the treatment, taking into account the required time for activating the suppressive features of the delivered cells and the time required to reach the target tissue. Along with such challenges, the immunosuppressive cells must resist combinatorial treatments, which include immunosuppressive drugs, to avoid the possibility of their own suppression and dysfunction. Since the recipient will have to be treated with immunosuppressive drugs for long periods, delivery of cells such as Tregs or MDSCs could induce non-specific immune suppression, which could suppress systemic immunity and could result in constant risk for opportunistic infectious diseases.

3. Clinical implications in targeting immunosuppression

In most cases of chronic inflammation, the resulting milieu is deleterious to the host due to the array of pro-inflammatory cells and soluble factors that lead to immunosuppression, alongside susceptibility to cancer, opportunistic infections and the limited success of immune-based therapies. As opposed to the pathologies described in the previous section where inducing an immunosuppressive environment is suggested as a therapeutic strategy to inhibit autoimmune diseases or transplant rejection, other pathologies require treatments aimed at counteracting the inflammatory and immunosuppressive environment towards rehabilitation of the host's immune status; these include patients suffering from chronic infections and cancer.

3.1. Chronic inflammation and cancer

The linkage between chronic inflammation and cancer was first proposed in the nineteenth century, based on the observations that inflammatory cells infiltrate tumors [79,80]. Growing evidence indicates that tumor development and progression indeed rely not only on the six hallmarks proposed by Hanahan and Weinberg, which are restricted to cancer cells and depend on self sufficient proliferation signals, insensitivity to growth suppressors, inducing angiogenesis, resisting cell death, enabling replicative immortality and activating invasiveness and metastasis [81], but also rely on cancer-related inflammation generated within the tumor microenvironment [82,83]. The interactions between immune system components recruited into the tumor microenvironment are crucial for tumor development and progression, relying on inflammatory factors and cells that contribute to cell transformation, support cancerous cell survival, resist immunological destruction and facilitate invasion and metastasis [40,83,84]. As mentioned above, various studies show that chronic inflammation induced during several inflammatory diseases can increase the risk of developing many types of cancers [84,85].

3.2. The tumor microenvironment and accompanying immunosuppression

3.2.1. Mediators in the tumor microenvironment

In the process of tumor initiation, malignant progression, invasion and metastasis, numerous inflammatory mediators are involved, including:

(a) *Transcription factors*: NFκB is an initiator of many inflammatory responses, shown to be involved in cancer initiation and progression, by being directly activated in cancer cells or indirectly by recruiting and activating inflammatory cells [86]. NFκB in its activated form was detected in many solid tumors, and its inhibition in tumor cell-lines was shown to increase their sensitivity to chemotherapeutic drugs and radiation [87]. NFκB activation is mediated mainly *via* IL-1β, TNFα, ROS, TLRs and genetic alterations in tumor cells [24,88–90], promoting expression of several pro-inflammatory mediators (such as TNFα) inducing expression of anti-apoptotic genes supporting tumor cell survival. A linkage between inflammation and cancer was shown by Karin's group, who demonstrated attenuated formation of inflammation-associated tumors in a mouse model of colitis, due to the specific inactivation of the IKK/NFκB pathway in myeloid cells, known to be involved in development of tumors in the colon [91]. Another major transcription factor that was shown to be involved in cancer is STAT3. Its constitutive activation was shown in tumor cells, and in immune cells situated within the tumor microenvironment. Similar to NFκB, STAT3 was also shown to be crucial for tumor cell proliferation and survival [92]. Activation of STAT3 is mediated mainly by VEGF and IL-10, which are secreted by the tumor or infiltrating immune cells, and inhibit expression of mediators necessary for anti-tumor immune activation, by negatively affecting activity of $CD8^+$ T-cells, NK cells and macrophages. Moreover, prolonged activation of STAT3 results in down regulation of MHC class II and co-stimulatory molecule expression on DCs, resulting in induced immune tolerance [93].

Cytokines: Among the cytokines involved in cancer related inflammation, the most prominent are TNFα, IL-6 and IL-1. TNFα is produced and secreted mainly by tumor and myeloid cells infiltrating into the tumor microenvironment and acts primarily through TNF receptor 1 (TNFR1). When chronically produced in the tumor microenvironment, TNFα is a major mediator of inflammation and is crucial for the development of numerous types of cancers. TNFα was identified as a key mediator for the initiation and progression of murine colon carcinogenesis and as a factor involved in the infiltration of myeloid cells into the inflamed colon [94]. Moreover, various studies have shown that TNFα is indirectly involved in genetic aberrations of malignant cells, enhances malignancy, cell survival and proliferation, increases leukocyte infiltration into the sites of inflammation, contributes to angiogenesis, and also induces resistance to some chemotherapies [24,95].

IL-6 is a pro-proliferative, anti-apoptotic cytokine, and is one of the effector signals of STAT3 [96]. As mentioned above, IL-6 is involved in various inflammatory states, including IBD, RA and cancer. One of the clearest associations between IL-6 and its contribution to inflammation-induced carcinogenesis is observed in colitis-associated-cancer (CAC) and hepatocellular carcinoma (HCC) [97]; treatment with IL-6 receptor (IL-6R) antagonist in a mouse model of CAC resulted in a markedly decelerated tumor growth [98].

IL-1 is another key cytokine abundantly produced by malignant and immune cells situated within the tumor microenvironment. The IL-1 family consists of two major agonistic cytokines, IL-1α and IL-1β. Elevated levels of IL-1 are detected in chronic inflammatory pathologies as well as in cancer. IL-1, as IL-6 and TNFα, has many diverse effects on the malignant processes; on one hand IL-1β was shown to be involved in carcinogenesis, tumor growth, invasion and metastasis in chemical-induced tumors [99]; on the other hand, it can target and activate innate and adaptive immune effector cells that potentially limit tumor growth. Moreover, it was shown that over-expression of IL-1β induces gastric inflammation and cancer that was accompanied by increased recruitment of MDSCs into the site of inflammation [100].

(b) *Inflammatory mediators*: Among the variety of inflammatory proteins and compounds enhanced during chronic inflammatory pathologies such as cancer, are the pro-inflammatory proteins S100A8 and S100A9. These proteins form a functional heterodimer binding TLR4 and the receptor for advanced glycation end products (RAGE); both are expressed on various cancer and immune cells such as neutrophils, macrophages and MDSCs. Robust induction of S100A8/9 is found in epithelial tumors, such as breast, lung, colon and liver cancers [101,102]. Their expression levels are controlled by cytokines such as TNFα [103] and IL-10 [104] as well as by transcription factors STAT3 [105] and NFκB [101]. The S100A8/9 proteins promote tumorogenesis mainly by regulating the accumulation and differentiation of MDSCs within the tumor microenvironment, resulting in suppressed host mediated anti-tumor immune responses [56,106]. Moreover, these proteins have been shown to directly affect proliferation and invasiveness of tumor cells.

(c) *Chemokines*: Tumor-cell invasion, migration, and retention as well as survival depend on another type of inflammatory mediators, chemokines and their receptors. Chemokines are produced and secreted by the tumor and immune cells invading the tumor microenvironment. They have the ability to guide cognate chemokine receptor-expressing tumor cells to specific destinations, leading to invasion and metastatic spread, as shown in various types of cancers [107,108]. The of the main over-expressed chemokine receptors in human tumors is CXCR4, which was shown to correlate with poor prognosis [109] and CCR6, CCR7, CXCR1, CXCR3 and CXCR5 that were shown to be up-regulated by tumor cells in various tissue origins and play a role in organ specific metastasis [110,111]. For example, CXCR4 and CCR7 expressed on breast cancer cells are involved in their tissue specific metastasis, directed through the expression of the cognate ligands SDF1 and CCL21, respectively [107].

(d) *Angiogenic and growth factors*: Upon invading the tissue, tumor cell growth requires establishment of an appropriate vasculature network, which is supported by inflammatory cytokines such as TNFα and IL1that affect the production of angiogenic and growth factors such as VEGF, secreted by the tumor, endothelial cells and TAMs recruited into the tumor site. Chemokines are also involved in angiogenic induction. CCL2 for example stimulates prostate cancer growth through the regulation of macrophage infiltration and enhanced angiogenesis within the tumor [112] and the CXCR4/CXCL12 signaling results in PI3K/Akt-mediated expression of VEGF [113].

3.2.2. Inflammatory immune cells in the tumor microenvironment

The tumor microenvironment is shaped and dominated by the tumor, which forms a unique immunological environment favoring recruitment of various suppressive inflammatory cells that support tumor growth and help the tumor to escape the tight surveillance of the immune system. Such conditions pose a critical obstacle in successful therapies. Within the unique suppressive population of cells generated under the tumor associated inflammatory conditions we will focus on TAMs, MDSCs and Treg:

(a) *TAMs*. TAMs (described in Section 1.2) can be polarized toward M2-like phenotype by supporting factors when reaching the tumor site, enabling them to promote tumor angiogenesis, invasion and metastasis in various types of cancer, as shown in animal models [114]. They promote tumorogenesis by producing inhibitory cytokines (IL-10, TGFβ), growth factors (endothelial growth factor (EGF)), angiogenic factors (VEGF, PDGF and FGF) and matrix-degrading enzymes (MMP2, MMP9) [115]. Moreover, upon their recruitment into the tumor sites, these cells also have the ability to suppress the functions of lymphocytes, *via* inhibitory cytokines, secreted ROS and prostaglandins. Their accumulation in the tumor microenvironment is orchestrated by various chemokines (such as CCL2) or growth factors (CSF1) [116].

(b) *MDSCs*: MDSC recruitment depends on different combinations of chemokines and chemokine receptors (CXCR4-SDF1, CXCR2-CXCL5 and CCR2-CCL2), and as described in Section 1.2, display a suppressive activity; their levels were shown to be increased in cancer patients and in tumor-bearing mice. MDSC accumulation is accompanied by enhanced tumor growth, impairing effector immune functions by various mechanisms as mentioned above. Besides the above-mentioned suppressive mechanistic network underlying MDSC functions, they were shown to limit antigen presentation by APCs, thereby blocking DC maturation, and leading to impaired homing of T-cells into lymph nodes by down regulating CD62L. MDSCs abrogate effector cell function by blocking expression of NKG2D on NK cells, down-regulating the expression of CD247 on T and NK cells and increasing the skewing of M1 phenotype of macrophages to M2 [46,47,117].

(c) *Treg*: Tregs are $CD3^+CD25^+$ T-cells expressing the Foxp3 transcription factor. These cells expand during tumor progression and participate in the induced immunosuppression, promoting tumor immune evasion [118]. It was shown that Treg suppressive activity in cancer is mediated through various mechanisms: (1) production of inhibitory cytokines (IL-10, TGFβ), and consumption of IL-2, perforin and granzyme-B production, which destroy T-cells and antigen presenting cells (APCs); (2) CTLA-4 expression leading to production of the enzyme IDO in APCs, resulting in tryptophan degradation and the consequent suppression of T-cell activation; and (3) induction of B7-H4 expression on APCs, which negatively regulates effector T-cell responses [119–123]. The migration of Tregs into the tumor microenvironment depends on CCR4 expressed on these cells, which binds CCL22, produced by tumor cells and TAMs [124].

3.3. Evading immune surveillance

The suppressive environment generated during tumor growth supports tumor evasion from the immune system. The tumor cells continuously manipulate the host immune system by changing the environment into its own benefit or by modifying its molecular characteristics, resulting in increased tumor survival and growth. The mechanisms supporting tumor escape from immune surveillance could be divided into two main categories: those mediated by changes restricted only to tumor cells, and those generated under chronic inflammatory conditions within the tumor microenvironment.

3.3.1. Mechanisms of evasion involving changes within the tumor cells

The mechanisms restricted to the tumor cells include down-regulation of tumor-associated antigens (TAA) and surface expression of HLA class I molecules [125]. Changes in the HLA class I molecule expression could result due to the effect of pro-inflammatory cytokines and growth factors; as shown for TNFα, that can suppress IFNγ-induced MHC class II expression by retinal pigmented epithelial cells [126] and for EGF, as the inhibition of EGF receptor augments the expression of MHC class I and II genes [127].

The reduction in TAA and HLA class I expression occurs due to changes in the antigen processing machinery (APM), ensuing in poor presentation of antigens by the tumor cells to DC and T-cells [128]. This process could be accompanied by enhanced expression of death receptors (Fas, TRAIL-R) and secretion of inhibitory

cytokines or NO, all resulting in impaired effector function and increased apoptosis of immune cells.

Another mechanism of evading immune surveillance is mediated by the expression of the B7 family of proteins by tumor cells. The physiological functions of co-stimulatory B7 family members (B7-1 and B7-2) are to enhance T-cell proliferation, increase cytokine secretion and prevent apoptosis, thereby stimulating T-cell responses. In contrast, the co-inhibitory molecules (B7H-1, B7H-3, B7H-3, B7DC) provide key negative signals by limiting, terminating and attenuating T-cell responses, thereby preventing T-cell hyperactivation and avoiding tissue and organ damage during immune responses [129]. Pro-inflammatory cytokines such as IFNγ and TNFα can upregulate expression of B7 co-inhibitory molecules on tumor cells, as shown for the B7H-1, thus facilitating immune inhibition and escape from immune surveillance. B7-H1, B7-H3 and B7-H4 expression on tumors and/or tumor-infiltrating leukocytes (TILs) is often associated with poor prognosis and aggressive behavior of tumors. Currently, approaches towards upregulation of co-stimulatory molecules and blockade of co-inhibitory signals on tumor cells, T-cells and other immune cells are being evaluated in preclinical models, as well as in clinical trials [130–132].

3.3.2. Mechanisms of evasion involving the tumor microenvironment

Among various evasion mechanisms developed in the tumor microenvironment, the most profound are the recruitment of suppressive cells such as MDSCs, TAMs, Tregs and MSCs, as discussed earlier (Section 3.2.2). These cells have the ability to suppress both the adaptive and innate arms of the immune system through different mechanisms, all resulting in tumor escape from an anti-tumor immune response [40]. This suppressive milieu also leads to the secretion of various cytokines and growth factors, nourishing the tumor cells and enhancing their ability to escape immune-based elimination. To this end, the ability to block tumor evasion depends on a better understanding of the combined cellular and molecular process evolving within the tumor and the microenvironment it induces.

3.4. Cancer therapy strategies

3.4.1. Targeting the tumor and the suppressive microenvironment

The role of the immune system in eliminating cancer is firmly established. Effective function of the immune system in conjunction with various standard treatments given today to cancer patients such as chemotherapy and radiotherapy is critical, since the immune system has the "responsibility" of eliminating cancer cells that fail to be destroyed by the conventional therapies. As previously proposed, effective therapy against cancer should take in consideration not only the tumor itself but also its unique environment that protects it from complete eradication and should include three important parameters: (a) elimination of the tumor cells, leading to immunogenic death; (b) blockade/destruction of the suppressive cells, and (c) activation of effector immune cells [133]. For example, the chemotherapeutic drug 5-fluorouracil (5-FU), in addition to its primary cytotoxic effect, it leads to immunogenic death of cancerous cells, by enhancing the expression of TAA and MHC-I molecules on the cell surface. A recent report also showed that 5-FU has the ability to eliminate MDSCs, leading to their apoptotic death without affecting numbers of DC, NK, T-cells and B-cells. The elimination of MDSCs by 5-FU also enhances IFNγ production by $CD8^+$ cells, and promotes T-cell-dependant anti-tumor responses in mice [134]. In contrast, results from our group showed that other chemotherapeutic agents induce enhanced accumulation of MDSCs in lymphatic organs and blood, increasing the immunosuppression (unpublished data). A similar increase in MDSCs was shown in the peripheral blood of breast cancer patients treated with combined doxorubicin-cyclophosphamide chemotherapy [135]. Taken together, when providing a treatment, both the tumor and the immune environment have to be monitored and accordingly, malignant cells as well as the immunosuppressive milieu could be targeted.

Along with the traditional treatments against cancer available today, several forms of immunotherapy are being explored at the pre-clinical and clinical levels. Immunotherapy could be divided into four main categories: (1) the use of monoclonal antibodies directed against specific TAA's as shown in cases of non-Hodgkin's lymphoma (Rituximab) [136], or antibodies aimed at enhancing the activity of immune cells, as in cases of melanoma (Ipilimumab) [137]; (2) the use of immune response modifiers such as: cytokines, exemplified by IL-2 administration, and cytokine or chemokine receptor antagonists as Etanercept, a TNFα antagonist, and BKT-140, a CXCR4 antagonist; (3) vaccination [138] and (4) therapy with adoptively-transferred modified specific T and DC cells [139]. Although many immunotherapeutic regimens are being studied and currently applied in the clinic, the success rates are very limited. The immunosuppressive features of tumor cells and the generated microenvironment are major obstacles for cancer immunotherapy. The immunosuppressive environment reported in many cancer patients, depends on the tumor stage and the intensity of the induced suppression and plays a critical role in dictating the success rate of various immunotherapeutic regimens. In all cases where active immunotherapy is used, the expectations are either that the patient's immune system will be activated, or that the administrated DCs or T-cells will operate in an optimal favorable environment, suggesting that the immunosuppressive environment will eventually dictate the response to a given therapy. Thus, prior to a given immune-based therapy the patient's immune status has to be evaluated. This could be implemented by the use of related biomarkers (see Section 4). If an immunosuppressive environment is detected, chronic inflammatory conditions must be neutralized in order to induce immune system rehabilitation that will ensue successful treatment.

3.4.2. Combinatorial treatments

Both conventional therapy and anti-cancer immunotherapy have the ability to eliminate cancer cells by different mechanisms. The success of these treatments also relies on the ability to neutralize the suppressive inflammatory environment generated within the host that contributes to the frequent failure of various treatments given today. Thus, future therapies should focus on strategies combining the two approaches, along with elimination of the suppressive factors from the tumor microenvironment. Neutralization of the suppressive environment and suppressive cells prior to therapy seems to be a promising strategy, as seen in humans and in various mouse models. For example the use of all-trans retinoic acid (ATRA) leads to the reduction of MDSCs in metastatic renal-cell carcinoma patients and improves the antigen specific response of T-cells [140]. Furthermore, in tumor bearing mice, the combination of ATRA and vaccination significantly improved the anti-tumor affect of the treatment and enhanced both $CD4^+$ and $CD8^+$ tumor specific immune response [141]. Another example is the use of sildenafil, which was shown by different groups to decrease the numbers of MDSCs and their function by reducing the expression of both NOS2 and ARG1 and the intensity of the inflammatory environment within the tumor sites, by using various mouse models [11,142]. In addition the combination of sildenafil with doxorubicin in mice bearing prostate cancer resulted in a significant inhibition of tumor growth that was associated with increased apoptotic cell death [143].

Besides choosing the right combination of a given therapy, the kinetics for applying each treatment, including the order, should be

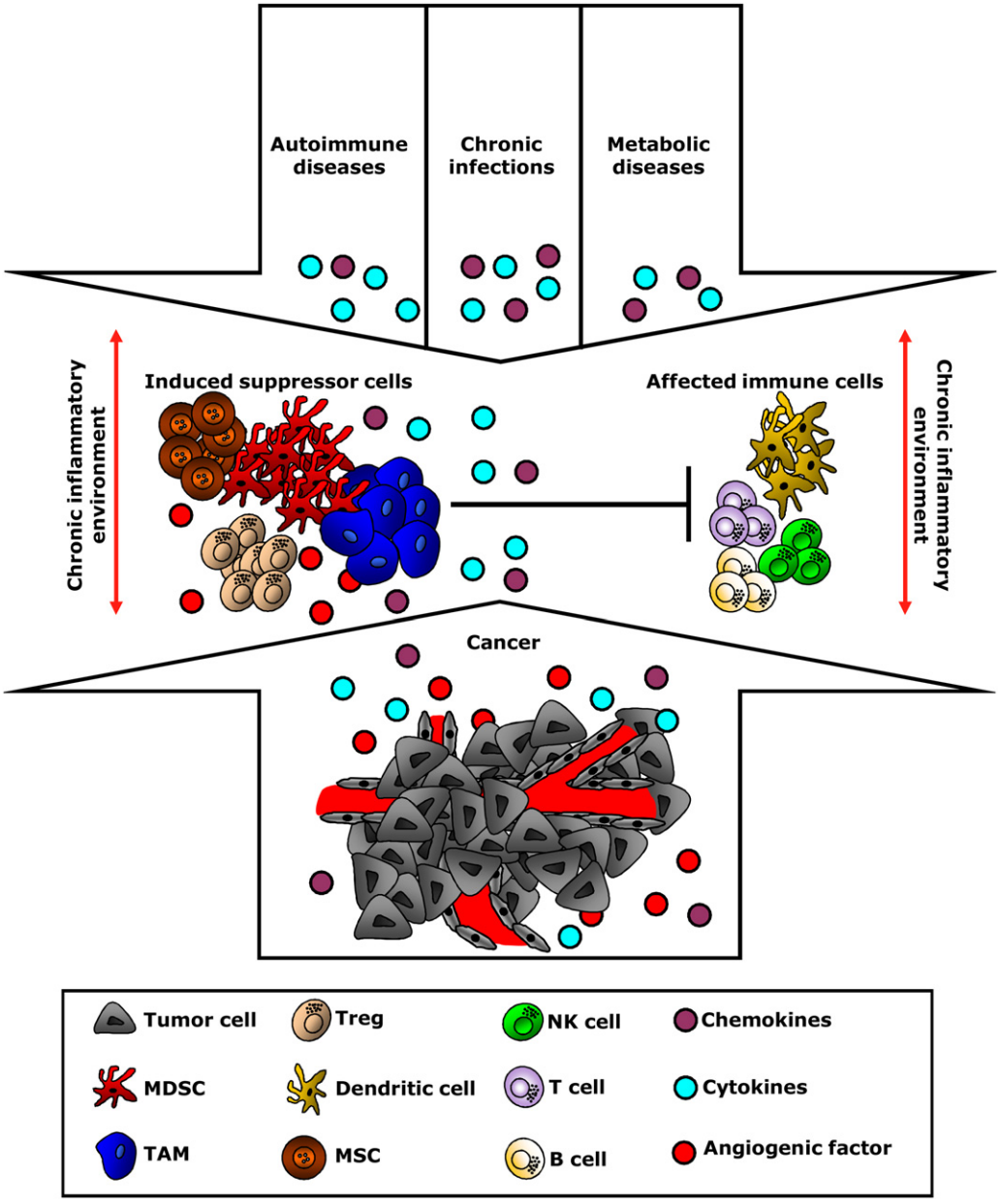

Fig. 1. Functional link between immunosuppression and chronic pathologies. Chronic inflammation developing in various pathologies including cancer, autoimmune disorders, chronic infections and metabolic diseases, promotes the generation of a suppressive environment, which leads to the inhibition of immune cell effector functions. This process involves the induction of suppressive cells and various mediators, such as cytokines, chemokines and angiogenic factors. Consequently, the generated suppressive milieu results in immunosuppression, which impairs the immune response against the disease-causing factors, and enhances its progression.

taken into consideration, since the host immune status and tumor stage are critical determinants for the success of the combined therapy. Other parameters should be taken into an account such as the outcome of the combined therapy, whether it provides a synergistic/additive or antagonistic effect relative to each treatment when given separately, and the toxicity levels generated within the host. An example for combined therapy using chemotherapy followed by adoptively transferred T-cells showed some promising results in patients with metastatic melanoma. In this clinical trial, patients were first treated with lympho-depleting chemotherapy followed by adoptive transfer of *in vitro* expanded tumor specific $CD8^+$ T-cells and high dose of IL-2. This combined treatment yielded strong responses in 18 out of 35 (51%) patients, many with bulky tumors. These responses were accompanied with high levels of tumor specific T-cells in the blood of those patients [144]. In another clinical trial, 29 patients with an advanced stage of small cell lung cancer (SCLC) were vaccinated with autologous DCs infected with adenoviral vectors encoding p53. Although 57% showed p53-specific T-cell responses to vaccination, only one patient showed a clinical response, whereas in the others the disease progressed. However, additional treatment with a second-line of chemotherapy dramatically increased the response rate to 61.5%, and up to 38% patients survived at one year following vaccination, as compared to the historical controls showing less than 6–16% responding to a second-line of chemotherapy given without vaccination [145]. This and other clinical experiments support the notion of effective combined therapy using conventional therapy (chemotherapy) with immunotherapy, and strategies targeting the suppressive tumor environment. Although, the importance of combinatorial therapy is clear and some promising results have already been seen in early

clinical trials, very few studies are being performed with such combinations and almost none are routinely used in the clinic.

4. Biomarkers

Patients suffering from diseases characterized by chronic inflammation including autoimmune disorders, infections and cancer, tend to develop complications due to the sustained inflammation and associated immunosuppression, and in many cases, are subjected to a variety of treatments and drugs that differ in their impact on the immune system.

Currently, diagnostic tests that can distinguish between acute and chronic inflammation, and the ensuing immunosuppression are not available in the clinic, and in most cases, diagnosis of an abnormal immune system is done retrospectively, based on development of complications associated with immune suppression. Thus, there is an urgent need for biomarkers that could be used for frequently monitoring the function of patients' immune system to enable: (1) prediction of complications before they are evident; (2) distinguishing between acute *vs.* chronic inflammation; (3) identifying patients who are likely to respond to immune-based therapies; and (4) determine progression or regression of the disease. In cases of cancer, analyses of the patients' immune status must be performed in conjunction with follow up of biomarkers specific to each cancer type specific for early diagnostic of the disease. Identification of such markers will enable the optimization of treatment for each patient.

Developing monitoring strategies that will allow identification of patients who could benefit from a specific therapy are critical since such tests could provide an objective tool for choosing the appropriate timing of the given treatment, which is critical and could significantly influence the outcome. Biomarkers that could be detected in a simple blood test, without the necessity for surgical interventions or other complex and expensive procedures, could be beneficial. An example of such a biomarker is CD247, which is a key molecule in TCR (T cells) and NCRs (NK cells) expression and effector functions. Its expression levels in the host's peripheral T and NK cells are down regulated during the course of chronic inflammation that develops in various diseases [6]. Our cumulative data indicate that CD247 down regulation is reversible; its expression levels recover to normal upon neutralization of the inflammatory environment by elimination of the stimulus inducing the chronic inflammatory response, treatment with anti-inflammatory drugs, or neutralizing MDSCs. Therefore, CD247 could serve as a prognostic and diagnostic marker predicting whether an individual is likely to respond to a given immune-based therapy as well as for measuring efficacies of given therapies and disease regression or recurrence [6,146]. Indeed, it was recently shown that CD247 is down regulated in T-cells isolated from breast cancer patients by an average of 63%, when testing 65 different cases relative to the controls [147]. This study reveals that CD247 is affected by the suppressive environment generated in the process of breast cancer progression and supports its use as a biomarker for sensing the status of the host's immune system.

Another set of biomarkers could include miRNAs for the detection and staging of various types of cancers. Several miRNAs were shown to be up-regulated or down-regulated in tumors compared to normal tissues, suggesting their dual role in carcinogenesis as onco-miRs or tumor suppressor-miRs [148]. A recent publication by Schooneveld et al. [149] revealed differences in miRNA expression in breast tissues and serum samples taken from cancer patients as compared to controls. Differential expression profile between serum samples from patients and healthy donors revealed expression changes of three miRNAs, miR-452, miR-411 and miR-299-5p. The main difference was observed between healthy donors and metastatic breast cancer patients, suggesting the use of such a set of miRNAs as biomarkers for detection and eventually staging breast cancer progression in patients.

Additional biomarkers that could provide indications of the host's immune status are MDSCs. Based on the direct correlation between increased MDSC levels, chronic inflammation and immunosuppression, monitoring these cells could provide initial indications as to the host's immune status. However, in humans, additional studies are required to pinpoint the exact MDSC population that confers the immunosuppressive activity, and further studies are need to ascertain that these cells maintain their immunosuppressive activity at different stages of the disease and can reflect the immune status of the tested host.

Although many studies are being conducted to identify more sensitive and efficient biomarkers, none of these approaches have reached the clinic. Efforts must be invested in the identification of additional biomarkers that could be used in combination for the evaluation of patients' immune status, type and stage of disease. As new biomarkers are identified, they could be used for cross validation to ascertain the patient's immune and disease status. Thus, in the future, it may be possible to diagnose specific types of cancers at their early stages by using tumor specific markers as well as monitoring the immune status of the patients by using simple biomarker arrays (including proteins, miRNAs and cells) that will enable more specific determination of prognosis and treatment of cancer patients.

5. Concluding remarks

The execution of an acute inflammatory response is critical to protect the body against tissue injury and pathogens, and is supported by structural and functional restoration processes, while unresolved chronic inflammation has harmful effects on the host's systems. In this review, we discussed the ramifications of chronic inflammatory responses shared by different types of chronic pathologies, predisposing the individuals to a developing immunosuppressive environment and accompanying disease progression. The generated immunosuppressive milieu facilitates tumor escape from immune surveillance, supports progression of ongoing infection, as well as tissue destruction during autoimmune diseases. Thus, we described the cumulative data providing an initial understanding of the link between several distinct pathologies, chronic inflammation, induced-immunosuppression, and the ensuing failure of natural mechanisms to protect the human's body (summarized in Fig. 1). Chronic inflammatory processes relay on a large number of endogenous signaling pathways, effector cells and factors, where their combinatorial activation and ongoing stimulation result in tissue destruction and abnormal organ homeostasis, weakening the ability of immune cells to battle against harmful disease progression. In cancer, such harmful conditions are driven by both the immune infiltrates and the tumor, supporting the activity of suppressive cells, targeting surrounding tissues, and creating an overall environment suitable for tumor cell survival and spreading. Numerous studies indicate that mitigating the immunosuppressive environment could limit tumor spread.

Understanding the mechanisms underlying the function of key players in such an intricate environment, could lead to the discovery of attractive therapeutic targets in the inflammatory environment. Therefore, treatment of patients suffering from chronic inflammatory diseases such as diverse types of cancer and autoimmune disorders remains a major challenge in the clinic. The complexity of the immunosuppressive mechanisms is reflected by the different mechanisms occurring in each disease, while many of the consequences are shared by the different chronic pathologies.

Thus, combinatorial treatments accompanied with a detection system for evaluating the host's immune status are needed to reverse these disease related processes.

Today, we are at the earliest stages of designing treatments for the growing list of diseases characterized by chronic inflammation. As our knowledge regarding the involved immune mechanisms increase, new and promising clinical strategies will be developed. Towards the achievement of these goals, major efforts must be invested in the discovery of biomarkers that could be used for monitoring the patient's functional immune status. These are urgently required for predicting appearance of complications, foreseeing patient response to immune-based therapies, determining efficacies of given therapies, and detecting disease recurrence due to re-evolving chronic inflammation. A better understanding of the immunosuppressive environment is still needed, in order to monitor and manipulate the individual's immune status in an appropriate way to achieve optimal treatment towards disease regression.

Conflict of interest statement

The authors, Julia Kanterman, Moshe Sade-Feldman and Michal Baniyash, submitting this manuscript declare that there are no conflicts of interest.

Acknowledgements

We gratefully acknowledge the support of the Society of Research Associates of the Lautenberg Center, the Concern Foundation of Los Angeles and the Harold B. Abramson Chair in Immunology. This study was supported by the US-Israel Binational Science Foundation, The Israel Academy of Sciences and Humanities, The Israeli Ministry of Health, The Israel Cancer Research Foundation (ICRF), The Joint German-Israeli Research Program (DKFZ), and by The Joseph and Matilda Melnick Funds.

References

[1] Lawrence T, Gilroy DW. Chronic inflammation: a failure of resolution. Int J Exp Pathol 2007;88:85–94.
[2] Barreiro O, Martin P, Gonzalez-Amaro R, Sanchez-Madrid F. Molecular cues guiding inflammatory responses. Cardiovasc Res 2010;86:174–82.
[3] Serhan CN. Controlling the resolution of acute inflammation: a new genus of dual anti-inflammatory and proresolving mediators. J Periodontol 2008;79:1520–6.
[4] Baniyash M. Chronic inflammation, immunosuppression and cancer: new insights and outlook. Semin Cancer Biol 2006;16:80–8.
[5] Gonda TA, Tu S, Wang TC. Chronic inflammation, the tumor microenvironment and carcinogenesis. Cell Cycle 2009;8:2005–13.
[6] Baniyash M. TCR zeta-chain downregulation: curtailing an excessive inflammatory immune response. Nat Rev Immunol 2004;4:675–87.
[7] Ciszak L, Pawlak E, Kosmaczewska A, Potoczek S, Frydecka I. Alterations in the expression of signal-transducing CD3 zeta chain in T cells from patients with chronic inflammatory/autoimmune diseases. Arch Immunol Ther Exp (Warsz) 2007;55:373–86.
[8] Hanaoka N, Jabri B, Dai Z, Ciszewski C, Stevens AM, Yee C, et al. NKG2D initiates caspase-mediated CD3zeta degradation and lymphocyte receptor impairments associated with human cancer and autoimmune disease. J Immunol 2010;185:5732–42.
[9] Vaknin I, Blinder L, Wang L, Gazit R, Shapira E, Genina O, et al. A common pathway mediated through Toll-like receptors leads to T- and natural killer-cell immunosuppression. Blood 2008;111:1437–47.
[10] Bronstein-Sitton N, Cohen-Daniel L, Vaknin I, Ezernitchi AV, Leshem B, Halabi A, et al. Sustained exposure to bacterial antigen induces interferon-gamma-dependent T cell receptor zeta down-regulation and impaired T cell function. Nat Immunol 2003;4:957–64.
[11] Meyer C, Sevko A, Ramacher M, Bazhin AV, Falk CS, Osen W, et al. Chronic inflammation promotes myeloid-derived suppressor cell activation blocking antitumor immunity in transgenic mouse melanoma model. Proc Natl Acad Sci USA 2011;108:17111–6.
[12] Liddiard K, Rosas M, Davies LC, Jones SA, Taylor PR. Macrophage heterogeneity and acute inflammation. Eur J Immunol 2011;41:2503–8.
[13] Douglas MR, Morrison KE, Salmon M, Buckley CD. Why does inflammation persist: a dominant role for the stromal microenvironment. Expert Rev Mol Med 2002;4:1–18.
[14] Mantovani A, Sica A. Macrophages, innate immunity and cancer: balance, tolerance, and diversity. Curr Opin Immunol 2010;22:231–7.
[15] Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. Nat Rev Immunol 2011;11:762–74.
[16] He G, Karin M. NF-kappaB and STAT3 – key players in liver inflammation and cancer. Cell Res 2011;21:159–68.
[17] Schetter AJ, Heegaard NH, Harris CC. Inflammation and cancer: interweaving microRNA, free radical, cytokine and p53 pathways. Carcinogenesis 2010;31:37–49.
[18] Tsan MF. Toll-like receptors, inflammation and cancer. Semin Cancer Biol 2006;16:32–7.
[19] Berasain C, Castillo J, Perugorria MJ, Latasa MU, Prieto J, Avila MA. Inflammation and liver cancer: new molecular links. Ann N Y Acad Sci 2009;1155:206–21.
[20] Bartsch H, Nair J. Chronic inflammation and oxidative stress in the genesis and perpetuation of cancer: role of lipid peroxidation, DNA damage, and repair. Langenbecks Arch Surg 2006;391:499–510.
[21] Kim MK, Kim K, Han JY, Lim JM, Song YS. Modulation of inflammatory signaling pathways by phytochemicals in ovarian cancer. Genes Nutr 2011;6:109–15.
[22] Umansky V, Sevko A. Overcoming immunosuppression in the melanoma microenvironment induced by chronic inflammation. Cancer Immunol Immunother 2012;61:275–82.
[23] Rosenblum H, Amital H. Anti-TNF therapy: safety aspects of taking the risk. Autoimmun Rev 2011;10:563–8.
[24] Balkwill F. Tumour necrosis factor and cancer. Nat Rev Cancer 2009;9:361–71.
[25] Kollias G, Kontoyiannis D. Role of TNF/TNFR in autoimmunity: specific TNF receptor blockade may be advantageous to anti-TNF treatments. Cytokine Growth Factor Rev 2002;13:315–21.
[26] Scheller J, Ohnesorge N, Rose-John S. Interleukin-6 trans-signalling in chronic inflammation and cancer. Scand J Immunol 2006;63:321–9.
[27] Heinrich PC, Behrmann I, Haan S, Hermanns HM, Muller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J 2003;374:1–20.
[28] Dolcetti L, Marigo I, Mantelli B, Peranzoni E, Zanovello P, Bronte V. Myeloid-derived suppressor cell role in tumor-related inflammation. Cancer Lett 2008;267:216–25.
[29] Hiraku Y, Kawanishi S, Ichinose T, Murata M. The role of iNOS-mediated DNA damage in infection- and asbestos-induced carcinogenesis. Ann N Y Acad Sci 2010;1203:15–22.
[30] Aguirre J, Rios-Momberg M, Hewitt D, Hansberg W. Reactive oxygen species and development in microbial eukaryotes. Trends Microbiol 2005;13:111–8.
[31] Rizzo MT. Cyclooxygenase-2 in oncogenesis. Clin Chim Acta 2011;412:671–87.
[32] Tabernero A, Reimund JM, Chasserot S, Muller CD, Andriantsitohaina R. Cyclooxygenase-2 expression and role of vasoconstrictor prostanoids in small mesenteric arteries from patients with Crohn's disease. Circulation 2003;107:1407–10.
[33] Thiel A, Mrena J, Ristimaki A. Cyclooxygenase-2 and gastric cancer. Cancer Metastasis Rev 2011;30:387–95.
[34] Okada H, Kohanbash G, Lotze MT. MicroRNAs in immune regulation—opportunities for cancer immunotherapy. Int J Biochem Cell Biol 2010;42:1256–61.
[35] Baltimore D, Boldin MP, O'Connell RM, Rao DS, Taganov KD. MicroRNAs: new regulators of immune cell development and function. Nat Immunol 2008;9:839–45.
[36] Williams AE, Perry MM, Moschos SA, Larner-Svensson HM, Lindsay MA. Role of miRNA-146a in the regulation of the innate immune response and cancer. Biochem Soc Trans 2008;36:1211–5.
[37] Tili E, Michaille JJ, Wernicke D, Alder H, Costinean S, Volinia S, et al. Mutator activity induced by microRNA-155 (miR-155) links inflammation and cancer. Proc Natl Acad Sci USA 2011;108:4908–13.
[38] Iborra M, Bernuzzi F, Invernizzi P, Danese S. MicroRNAs in autoimmunity and inflammatory bowel disease: crucial regulators in immune response. Autoimmun Rev 2010.
[39] Filer A, Pitzalis C, Buckley CD. Targeting the stromal microenvironment in chronic inflammation. Curr Opin Pharmacol 2006;6:393–400.
[40] Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nat Rev Cancer 2009;9:239–52.
[41] Woollard KJ, Geissmann F. Monocytes in atherosclerosis: subsets and functions. Nat Rev Cardiol 2010;7:77–86.
[42] Mantovani A, Sica A, Allavena P, Garlanda C, Locati M. Tumor-associated macrophages and the related myeloid-derived suppressor cells as a paradigm of the diversity of macrophage activation. Hum Immunol 2009;70:325–30.
[43] Mantovani A, Germano G, Marchesi F, Locatelli M, Biswas SK. Cancer-promoting tumor-associated macrophages: new vistas and open questions. Eur J Immunol 2011;41:2522–5.
[44] Lorusso G, Ruegg C. The tumor microenvironment and its contribution to tumor evolution toward metastasis. Histochem Cell Biol 2008;130:1091–103.
[45] Belkaid Y, Oldenhove G. Tuning microenvironments: induction of regulatory T cells by dendritic cells. Immunity 2008;29:362–71.
[46] Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009;9:162–74.

[47] Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. J Immunol 2009;182:4499–506.
[48] Ribechini E, Greifenberg V, Sandwick S, Lutz MB. Subsets, expansion and activation of myeloid-derived suppressor cells. Med Microbiol Immunol 2010;199:273–81.
[49] Bronte V. Myeloid-derived suppressor cells in inflammation: uncovering cell subsets with enhanced immunosuppressive functions. Eur J Immunol 2009;39:2670–2.
[50] Choi J, Suh B, Ahn YO, Kim TM, Lee JO, Lee SH, et al. CD15+/CD16low human granulocytes from terminal cancer patients: granulocytic myeloid-derived suppressor cells that have suppressive function. Tumour Biol 2012;33:121–9.
[51] Guo Q, Lv Z, Fu Q, Jiang C, Liu Y, Lai L, et al. IFN-gamma producing T cells contribute to the increase of myeloid derived suppressor cells in tumor-bearing mice after cyclophosphamide treatment. Int Immunopharmacol 2012.
[52] Serafini P, Carbley R, Noonan KA, Tan G, Bronte V, Borrello I. High-dose granulocyte-macrophage colony-stimulating factor-producing vaccines impair the immune response through the recruitment of myeloid suppressor cells. Cancer Res 2004;64:6337–43.
[53] Obermajer N, Muthuswamy R, Odunsi K, Edwards RP, Kalinski P. PGE(2)-induced CXCL12 production and CXCR4 expression controls the accumulation of human MDSCs in ovarian cancer environment. Cancer Res 2011;71:7463–70.
[54] Ezernitchi AV, Vaknin I, Cohen-Daniel L, Levy O, Manaster E, Halabi A, et al. TCR zeta down-regulation under chronic inflammation is mediated by myeloid suppressor cells differentially distributed between various lymphatic organs. J Immunol 2006;177:4763–72.
[55] Serafini P, Mgebroff S, Noonan K, Borrello I. Myeloid-derived suppressor cells promote cross-tolerance in B-cell lymphoma by expanding regulatory T cells. Cancer Res 2008;68:5439–49.
[56] Sinha P, Okoro C, Foell D, Freeze HH, Ostrand-Rosenberg S, Srikrishna G. Proinflammatory S100 proteins regulate the accumulation of myeloid-derived suppressor cells. J Immunol 2008;181:4666–75.
[57] Foell D, Wittkowski H, Vogl T, Roth J. S100 proteins expressed in phagocytes: a novel group of damage-associated molecular pattern molecules. J Leukoc Biol 2007;81:28–37.
[58] Gebhardt C, Nemeth J, Angel P, Hess J. S100A8 and S100A9 in inflammation and cancer. Biochem Pharmacol 2006;72:1622–31.
[59] Xie J, Itzkowitz SH. Cancer in inflammatory bowel disease. World J Gastroenterol 2008;14:378–89.
[60] De Flora S, Bonanni P. The prevention of infection-associated cancers. Carcinogenesis 2011;32:787–95.
[61] Cuenca AG, Delano MJ, Kelly-Scumpia KM, Moreno C, Scumpia PO, Laface DM, et al. A paradoxical role for myeloid-derived suppressor cells in sepsis and trauma. Mol Med 2011;17:281–92.
[62] Chen G. Immunotherapy of rheumatoid arthritis targeting inflammatory cytokines and autoreactive T cells. Arch Immunol Ther Exp (Warsz) 2010;58:27–36.
[63] Stevens RJ, Douglas KM, Saratzis AN, Kitas GD. Inflammation and atherosclerosis in rheumatoid arthritis. Expert Rev Mol Med 2005;7:1–24.
[64] Centonze D, Muzio L, Rossi S, Furlan R, Bernardi G, Martino G. The link between inflammation, synaptic transmission and neurodegeneration in multiple sclerosis. Cell Death Differ 2010;17:1083–91.
[65] Zhu B, Bando Y, Xiao S, Yang K, Anderson AC, Kuchroo VK, et al. CD11b+Ly-6C(hi) suppressive monocytes in experimental autoimmune encephalomyelitis. J Immunol 2007;179:5228–37.
[66] Haile LA, von Wasielewski R, Gamrekelashvili J, Kruger C, Bachmann O, Westendorf AM, et al. Myeloid-derived suppressor cells in inflammatory bowel disease: a new immunoregulatory pathway. Gastroenterology 2008;135:871–81, 81 e1-5.
[67] Marhaba R, Vitacolonna M, Hildebrand D, Baniyash M, Freyschmidt-Paul P, Zoller M. The importance of myeloid-derived suppressor cells in the regulation of autoimmune effector cells by a chronic contact eczema. J Immunol 2007;179:5071–81.
[68] Yin B, Ma G, Yen CY, Zhou Z, Wang GX, Divino CM, et al. Myeloid-derived suppressor cells prevent type 1 diabetes in murine models. J Immunol 2010;185:5828–34.
[69] Liston A, Lu LF, O'Carroll D, Tarakhovsky A, Rudensky AY. Dicer-dependent microRNA pathway safeguards regulatory T cell function. J Exp Med 2008;205:1993–2004.
[70] Divekar AA, Dubey S, Gangalum PR, Singh RR. Dicer insufficiency and microRNA-155 overexpression in lupus regulatory T cells: an apparent paradox in the setting of an inflammatory milieu. J Immunol 2011;186:924–30.
[71] Lu LF, Thai TH, Calado DP, Chaudhry A, Kubo M, Tanaka K, et al. Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. Immunity 2009;30:80–91.
[72] Dugast AS, Haudebourg T, Coulon F, Heslan M, Haspot F, Poirier N, et al. Myeloid-derived suppressor cells accumulate in kidney allograft tolerance and specifically suppress effector T cell expansion. J Immunol 2008;180:7898–906.
[73] Trento C, Dazzi F. Mesenchymal stem cells and innate tolerance: biology and clinical applications. Swiss Med Wkly 2010;140:w13121.
[74] Ghannam S, Bouffi C, Djouad F, Jorgensen C, Noel D. Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. Stem Cell Res Ther 2010;1:2.
[75] Gulbahce HE, Brown CA, Wick M, Segall M, Jessurun J. Graft-vs-host disease after solid organ transplant. Am J Clin Pathol 2003;119:568–73.
[76] Highfill SL, Rodriguez PC, Zhou Q, Goetz CA, Koehn BH, Veenstra R, et al. Bone marrow myeloid-derived suppressor cells (MDSCs) inhibit graft-versus-host disease (GVHD) via an arginase-1-dependent mechanism that is up-regulated by interleukin-13. Blood 2010;116:5738–47.
[77] Tang Q, Bluestone JA, Kang SM. CD4+Foxp3+ regulatory T cell therapy in transplantation. J Mol Cell Biol 2011.
[78] Adeegbe D, Serafini P, Bronte V, Zoso A, Ricordi C, Inverardi L. In vivo induction of myeloid suppressor cells and CD4(+)Foxp3(+) T regulatory cells prolongs skin allograft survival in mice. Cell Transplant 2011;20:941–54.
[79] Whiteside TL. Tumor-infiltrating lymphocytes in human solid tumors. Immunol Ser 1994;61:137–48.
[80] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.
[81] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57–70.
[82] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
[83] Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 2009;30:1073–81.
[84] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44.
[85] Vakkila J, Lotze MT. Inflammation and necrosis promote tumour growth. Nat Rev Immunol 2004;4:641–8.
[86] Karin M. Nuclear factor-kappaB in cancer development and progression. Nature 2006;441:431–6.
[87] Amit S, Ben-Neriah Y. NF-kappaB activation in cancer: a challenge for ubiquitination- and proteasome-based therapeutic approach. Semin Cancer Biol 2003;13:15–28.
[88] Qin H, Wilson CA, Lee SJ, Zhao X, Benveniste EN. LPS induces CD40 gene expression through the activation of NF-kappaB and STAT-1alpha in macrophages and microglia. Blood 2005;106:3114–22.
[89] Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, et al. NF-kappaB functions as a tumour promoter in inflammation-associated cancer. Nature 2004;431:461–6.
[90] Courtois G, Gilmore TD. Mutations in the NF-kappaB signaling pathway: implications for human disease. Oncogene 2006;25:6831–43.
[91] Greten FR, Eckmann L, Greten TF, Park JM, Li ZW, Egan LJ, et al. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell 2004;118:285–96.
[92] Yu H, Kortylewski M, Pardoll D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. Nat Rev Immunol 2007;7:41–51.
[93] Wang T, Niu G, Kortylewski M, Burdelya L, Shain K, Zhang S, et al. Regulation of the innate and adaptive immune responses by Stat-3 signaling in tumor cells. Nat Med 2004;10:48–54.
[94] Popivanova BK, Kitamura K, Wu Y, Kondo T, Kagaya T, Kaneko S, et al. Blocking TNF-alpha in mice reduces colorectal carcinogenesis associated with chronic colitis. J Clin Invest 2008;118:560–70.
[95] Kulbe H, Thompson R, Wilson JL, Robinson S, Hagemann T, Fatah R, et al. The inflammatory cytokine tumor necrosis factor-alpha generates an autocrine tumor-promoting network in epithelial ovarian cancer cells. Cancer Res 2007;67:585–92.
[96] Haura EB, Turkson J, Jove R. Mechanisms of disease: insights into the emerging role of signal transducers and activators of transcription in cancer. Nat Clin Pract Oncol 2005;2:315–24.
[97] Soresi M, Giannitrapani L, D'Antona F, Florena AM, La Spada E, Terranova A, et al. Interleukin-6 and its soluble receptor in patients with liver cirrhosis and hepatocellular carcinoma. World J Gastroenterol 2006;12:2563–8.
[98] Becker C, Fantini MC, Schramm C, Lehr HA, Wirtz S, Nikolaev A, et al. TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. Immunity 2004;21:491–501.
[99] Krelin Y, Voronov E, Dotan S, Elkabets M, Reich E, Fogel M, et al. Interleukin-1beta-driven inflammation promotes the development and invasiveness of chemical carcinogen-induced tumors. Cancer Res 2007;67:1062–71.
[100] Tu S, Bhagat G, Cui G, Takaishi S, Kurt-Jones EA, Rickman B, et al. Overexpression of interleukin-1beta induces gastric inflammation and cancer and mobilizes myeloid-derived suppressor cells in mice. Cancer Cell 2008;14:408–19.
[101] Nemeth J, Stein I, Haag D, Riehl A, Longerich T, Horwitz E, et al. S100A8 and S100A9 are novel nuclear factor kappa B target genes during malignant progression of murine and human liver carcinogenesis. Hepatology 2009;50:1251–62.
[102] Salama I, Malone PS, Mihaimeed F, Jones JL. A review of the S100 proteins in cancer. Eur J Surg Oncol 2008;34:357–64.
[103] Henke MO, Renner A, Rubin BK, Gyves JI, Lorenz E, Koo JS. Up-regulation of S100A8 and S100A9 protein in bronchial epithelial cells by lipopolysaccharide. Exp Lung Res 2006;32:331–47.
[104] Kumar A, Steinkasserer A, Berchtold S. Interleukin-10 influences the expression of MRP8 and MRP14 in human dendritic cells. Int Arch Allergy Immunol 2003;132:40–7.
[105] Dechow TN, Pedranzini L, Leitch A, Leslie K, Gerald WL, Linkov I, et al. Requirement of matrix metalloproteinase-9 for the transformation of human mammary epithelial cells by Stat3-C. Proc Natl Acad Sci USA 2004;101:10602–7.
[106] Cheng P, Corzo CA, Luetteke N, Yu B, Nagaraj S, Bui MM, et al. Inhibition of dendritic cell differentiation and accumulation of myeloid-derived

suppressor cells in cancer is regulated by S100A9 protein. J Exp Med 2008;205: 2235–49.
[107] Muller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, et al. Involvement of chemokine receptors in breast cancer metastasis. Nature 2001;410:50–6.
[108] Zlotnik A. Chemokines in neoplastic progression. Semin Cancer Biol 2004;14:181–5.
[109] Zlotnik A. New insights on the role of CXCR4 in cancer metastasis. J Pathol 2008;215:211–3.
[110] Shields JD, Fleury ME, Yong C, Tomei AA, Randolph GJ, Swartz MA. Autologous chemotaxis as a mechanism of tumor cell homing to lymphatics via interstitial flow and autocrine CCR7 signaling. Cancer Cell 2007;11:526–38.
[111] Kawada K, Sonoshita M, Sakashita H, Takabayashi A, Yamaoka Y, Manabe T, et al. Pivotal role of CXCR3 in melanoma cell metastasis to lymph nodes. Cancer Res 2004;64:4010–7.
[112] Loberg RD, Ying C, Craig M, Yan L, Snyder LA, Pienta KJ. CCL2 as an important mediator of prostate cancer growth in vivo through the regulation of macrophage infiltration. Neoplasia 2007;9:556–62.
[113] Liang Z, Brooks J, Willard M, Liang K, Yoon Y, Kang S, et al. CXCR4/CXCL12 axis promotes VEGF-mediated tumor angiogenesis through Akt signaling pathway. Biochem Biophys Res Commun 2007;359:716–22.
[114] Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 2006;124:263–6.
[115] Mantovani A, Schioppa T, Porta C, Allavena P, Sica A. Role of tumor-associated macrophages in tumor progression and invasion. Cancer Metastasis Rev 2006;25:315–22.
[116] Goswami S, Sahai E, Wyckoff JB, Cammer M, Cox D, Pixley FJ, et al. Macrophages promote the invasion of breast carcinoma cells via a colony-stimulating factor-1/epidermal growth factor paracrine loop. Cancer Res 2005;65:5278–83.
[117] Serafini P, Borrello I, Bronte V. Myeloid suppressor cells in cancer: recruitment, phenotype, properties, and mechanisms of immune suppression. Semin Cancer Biol 2006;16:53–65.
[118] Zou W. Regulatory T cells, tumour immunity and immunotherapy. Nat Rev Immunol 2006;6:295–307.
[119] Strauss L, Bergmann C, Szczepanski M, Gooding W, Johnson JT, Whiteside TL. A unique subset of CD4+CD25highFoxp3+ T cells secreting interleukin-10 and transforming growth factor-beta1 mediates suppression in the tumor microenvironment. Clin Cancer Res 2007;13:4345–54.
[120] von Boehmer H. Mechanisms of suppression by suppressor T cells. Nat Immunol 2005;6:338–44.
[121] Grossman WJ, Verbsky JW, Barchet W, Colonna M, Atkinson JP, Ley TJ. Human T regulatory cells can use the perforin pathway to cause autologous target cell death. Immunity 2004;21:589–601.
[122] Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. Nat Rev Immunol 2004;4:762–74.
[123] Kryczek I, Wei S, Zou L, Zhu G, Mottram P, Xu H, et al. Cutting edge: induction of B7-H4 on APCs through IL-10: novel suppressive mode for regulatory T cells. J Immunol 2006;177:40–4.
[124] Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 2004;10:942–9.
[125] Ferris RL, Hunt JL, Ferrone S. Human leukocyte antigen (HLA) class I defects in head and neck cancer: molecular mechanisms and clinical significance. Immunol Res 2005;33:113–33.
[126] Makhoul M, Bruyns C, Edimo WE, Relvas LJ, Bazewicz M, Koch P, et al. TNFalpha suppresses IFNgamma-induced MHC class II expression on retinal pigmented epithelial cells cultures. Acta Ophthalmol 2012;90:e38–42.
[127] Pollack BP, Sapkota B, Cartee TV. Epidermal growth factor receptor inhibition augments the expression of MHC class I and II genes. Clin Cancer Res 2011;17:4400–13.
[128] Meissner M, Reichert TE, Kunkel M, Gooding W, Whiteside TL, Ferrone S, et al. Defects in the human leukocyte antigen class I antigen processing machinery in head and neck squamous cell carcinoma: association with clinical outcome. Clin Cancer Res 2005;11:2552–60.
[129] Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008;8:467–77.
[130] Dulos J, Carven GJ, van Boxtel SJ, Evers S, Driessen-Engels LJ, Hobo W, et al. PD-1 blockade augments Th1 and Th17 and suppresses Th2 responses in peripheral blood from patients with prostate and advanced melanoma cancer. J Immunother 2012;35:169–78.
[131] Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol 2012.
[132] Yuan J, Ginsberg B, Page D, Li Y, Rasalan T, Gallardo HF, et al. CTLA-4 blockade increases antigen-specific CD8(+) T cells in prevaccinated patients with melanoma: three cases. Cancer Immunol Immunother 2011;60:1137–46.
[133] Zitvogel L, Apetoh L, Ghiringhelli F, Andre F, Tesniere A, Kroemer G. The anticancer immune response: indispensable for therapeutic success. J Clin Invest 2008;118:1991–2001.
[134] Vincent J, Mignot G, Chalmin F, Ladoire S, Bruchard M, Chevriaux A, et al. 5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer Res 2010;70:3052–61.
[135] Diaz-Montero CM, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. Cancer Immunol Immunother 2009;58:49–59.
[136] Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene 2003;22:7359–68.
[137] Sarnaik AA, Weber JS. Recent advances using anti-CTLA-4 for the treatment of melanoma. Cancer J 2009;15:169–73.
[138] den Brok MH, Nierkens S, Figdor CG, Ruers TJ, Adema GJ. Dendritic cells: tools and targets for antitumor vaccination. Expert Rev Vaccines 2005;4:699–710.
[139] Mansoor W, Gilham DE, Thistlethwaite FC, Hawkins RE. Engineering T cells for cancer therapy. Br J Cancer 2005;93:1085–91.
[140] Mirza N, Fishman M, Fricke I, Dunn M, Neuger AM, Frost TJ, et al. All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. Cancer Res 2006;66:9299–307.
[141] Kusmartsev S, Cheng F, Yu B, Nefedova Y, Sotomayor E, Lush R, et al. All-trans-retinoic acid eliminates immature myeloid cells from tumor-bearing mice and improves the effect of vaccination. Cancer Res 2003;63:4441–9.
[142] Serafini P, Meckel K, Kelso M, Noonan K, Califano J, Koch W, et al. Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function. J Exp Med 2006;203:2691–702.
[143] Das A, Durrant D, Mitchell C, Mayton E, Hoke NN, Salloum FN, et al. Sildenafil increases chemotherapeutic efficacy of doxorubicin in prostate cancer and ameliorates cardiac dysfunction. Proc Natl Acad Sci USA 2010;107:18202–7.
[144] Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23:2346–57.
[145] Antonia SJ, Mirza N, Fricke I, Chiappori A, Thompson P, Williams N, et al. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. Clin Cancer Res 2006;12:878–87.
[146] Whiteside TL. Down-regulation of zeta-chain expression in T cells: a biomarker of prognosis in cancer. Cancer Immunol Immunother 2004;53:865–78.
[147] Yu B, Zhang W. Down-regulation of CD3zeta is a breast cancer biomarker associated with immune suppression. Cell Biol Int 2011;35:165–9.
[148] Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, et al. MicroRNA expression profiles classify human cancers. Nature 2005;435: 834–8.
[149] van Schooneveld E, Wouters MC, Van der Auwera I, Peeters DJ, Wildiers H, Van Dam PA, et al. Expression profiling of cancerous and normal breast tissues identifies microRNAs that are differentially expressed in serum from patients with (metastatic) breast cancer and healthy volunteers. Breast Cancer Res 2012;14:R34.