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Autoimmunity and Cancer, the Paradox Comorbidities Challenging Therapy in the Context of Preexisting Autoimmunity

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Today, improvements in diagnostic and therapeutic options allow patients with autoimmune diseases (ADs) to live longer and have more active lives compared with patients receiving conventional anti-inflammatory therapy just two decades ago. Current therapies for ADs aim to inhibit immune cell activation and effector immune pathways, including those activated by cytokines and cytokine receptors. Understandably, such goals become more complicated in patients with long-term established ADs who develop parallel chronic or comorbid conditions, including life-threatening diseases, such as cancer. Compared with the general population, patients with ADs have an increased risk of developing hematological, lymphoproliferative disorders, and solid tumors. However, the aim of current cancer therapies is to activate the immune system to create autoimmune-like conditions and eliminate tumors. As such, their comorbid presentation creates a paradox on how malignancies must be addressed therapeutically in the context of autoimmunity. Because the physiopathology of malignancies is less understood in the context of autoimmunity than it is in the general population, we undertook this review to highlight the peculiarities and mechanisms governing immune cells in established ADs. Moreover, we examined the role of the autoimmune cytokine milieu in the development of immune-related adverse events during the implementation of conventional or immune-based therapy.

Keywords: immunotherapy, autoimmune diseases, cancer, check point inhibitors, immune-related adverse events

Introduction

Cancer is the second leading cause of mortality in the general population (Noone and others 2018). As tumor cells disable and systematically highjack the mechanisms of tolerance and immune surveillance to avoid immune detection, therapy aims to reverse such behavior and elicit autoimmune-like processes against tumors. Compared with current conventional cancer therapies, such as chemotherapy, radiotherapy, and surgery, biological activation of the immune system with immune therapy drives the activation of immune mechanisms to eradicate tumors. Immunotherapy has been demonstrated to significantly improve relapse-free survival and decrease tumor burden, but only in a subpopulation of patients with melanoma, non-small cell lung cancer, Hodgkin's lymphoma, and cancer of head and neck (Wraith 2017).

Paradoxically, activation of the immune system to fight cancer presents a challenge in the context of autoimmune diseases (ADs). Autoimmunity results from the progressive and continuous breakdown of immune check and balance mechanisms protecting host tissues from destruction (Zhang and Vignali 2016). As a preexisting condition, the autoimmune process starts 2–4 years (around 3.5 years on average) before diagnosis (preclinical stage). Most ADs progress either as an organ-specific (ie, multiple sclerosis [MS] and type 1 diabetes [T1D]) or as a multiorgan disease (ie, systemic lupus erythematous [SLE] or rheumatoid arthritis [RA]). Patients with common autoimmune disorders, such as SLE, RA, and inflammatory bowel disease (IBD) have an increased risk of developing cancers, including hematological disorders and some solid tumors (Franks and Slansky 2012; Liu and others 2014; Yu and others 2016) (Table 1).

Several reports concurred that cancer survival decreases significantly in patients with preexisting AD or chronic inflammatory diseases (Hemminki and others 2012; Criscitiello and others 2016). The decrease in survival has been largely associated with a higher risk of developing immune-related adverse events (IrAEs) in response to anticancer therapy than in the overall population. Generally, IrAEs are unwanted inflammatory events caused by the direct use of disease-modifying antirheumatic drugs alone or in combination with adjuvant biologic therapy (Rosman and others

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Table 1. Most Frequent Associations Between Autoimmune Diseases and Malignancies

Autoimmune disease	*Nonhematological malignancies*	*Hematological malignancies*	*References*
Systemic lupus erythematous	Cervical, lung, breast	Hodgkin and non-Hodgkin lymphoma	Giat and others (2017); Malaguarnera and others (2012)
Rheumatoid arthritis	Lung, breast, ovary	T cell non-Hodgkin lymphoma, lymphoma (follicular or diffuse large B cell)	Giat and others (2017); Malaguarnera and others (2012); Bernatsky and others (2006)
Primary Sjogren syndrome	Oropharynx	Mucosa-associated lymphoid tissue type B cell lymphoma	Malaguarnera and others (2012); Bernatsky and others (2006)
Inflammatory bowel disease	Colorectal cancer	Non-Hodgkin lymphoma	Franks and Slansky(2012); Axelrad and others (2016)
Systemic sclerosis	Lung, skin, esophageal		Malaguarnera and others (2012)
Wagner's granulomatosis	Bladder		Giat and others (2017)

2013). Although any organ system can be affected, IrAEs most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver (Postow and others 2018). IrAEs occur due to therapy-associated cytokine release and T cell-mediated organ infiltration during therapy with immune checkpoint inhibitors (CPIs) (Liu and others 2014).

Hence, cytokines play substantial roles defining the occurrence and severity of IrAEs in a host and disease-specific manner. Because the physiopathology of malignancies is less understood in the context of autoimmunity than it is in the general population, we undertook this review to examine the role of the autoimmune cytokine overlapping milieu or AICOM over the mechanisms defining the biologic response and outcomes of conventional or immune-based therapy in cancer patients with preexisting AD.

The State of Autoimmune Disease When Anticancer Immunotherapy Is Required

Knowing that cancer patients with preexisting ADs are more likely to be female, older, and with established ADs (Khan and others 2016), it is clear that most initial immune mechanisms have already been established when immunotherapy is required as cancer treatment. While explanation of the initial (onset) mechanisms is not the focus of the present review and has been reviewed extensively elsewhere (Goodnow 2007), disease stages are an important prognostic factor both in ADs and every malignancy. Every disease stage relates with the functional status of the immune system and circulating levels of cytokines. For example, higher cytokine levels are more frequently found in advanced stages than in early stages of either AD or cancer (Seruga and others 2008). At this stage, inflammation and cancers exhibit four identifiable and comparable stages. Stage I (early/onset) is characterized by mild-to-moderate inflammation resulting from recruitment of innate immune cells, such as myeloid cells, to sites of inflammation. At this stage, inflammation and most tumors are contained within a target organ or diseased (*in situ*) organs, respectively. At stage II (mild course), there is evidence of an activated adaptive immune system featuring T and B cell proliferation and production of autoantibodies compared with stage I in ADs. On the other hand, tumors are larger than in stage I, but tumor cells remain contained within diseased organs or have started to spread locally into lymph nodes. Likely tumor-secreted cytokines, such as granulocyte–macrophage colony-stimulating factor (GM-CSF), macrophage-CSF or interleukin (IL)-12 have started to be detected in serum. These inflammation- or tumor-derived cytokines are shaping the composition of the cytokine milieu and actively influence the functional status of immune cells in the host.

Stage III (moderate course or active) is characterized by an intermittent or progressive course that could include severe episodes of activity. Stage III features predominant recruitment, activation, and proliferation of leukocytes (neutrophils, eosinophils, and basophils) at sites of inflammation, including single or multiple target organs or tumors. For ADs, many stage III patients exhibit comorbid conditions related to advancement of immunopathology such as muscle atrophy in RA or moderate nephritis in SLE. For cancer, it usually means increased tumor burden and metastatic spread into surrounding tissues and distant lymph nodes. Stage IV (severe course) indicates end-stage disease. It results in constantly abnormal inflammatory processes associated with severe comorbid conditions and organ failures such as kidney failure in SLE or widespread metastasis for cancers.

Adaptation Mechanisms Boosting Response in Established Autoimmunity: Priming and Trained Immunity

Based on retrospective epidemiological studies (Johnson and others 2016; Menzies and others 2017; Abdel-Wahab and others 2018), check point immunotherapy was administered to melanoma patients exhibiting AD and cancer at stages II or III (Fig. 1). At those stages, internal organs and primary tumors have been exposed to multiple waves of cytokines, including transforming growth factor-β (TGF-β) as well as type I and II interferons (IFNs). To withstand these different types of stimuli over time, immune and non-immune cells set in place several adaptation mechanisms or countermeasures, including expression of coinhibitory molecules such as programmed cell death-1 (PD-1), lymphocyte activation gene 3 (LAG-3), natural killer (NK) cell receptor 2B4 (CD244), T cell immunoglobulin and mucin-domain

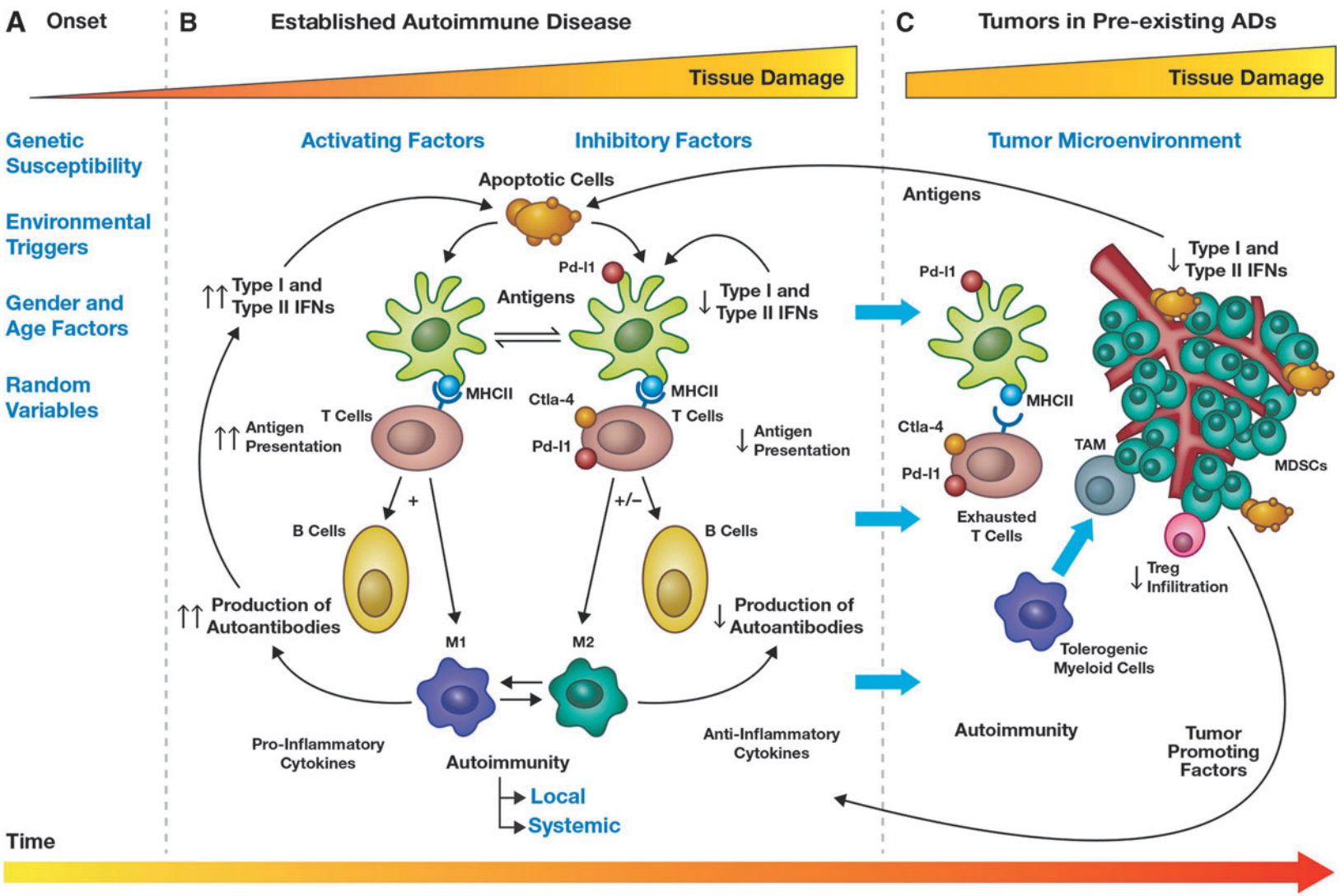

FIG. 1. Preexisting autoimmune mechanisms modulating tumor growth in the context of autoimmunity. The pathogenesis of cancer in ADs can be divided into three distinct stages (**A–C**, *top*) over time of disease (*bottom arrow*). In the first stage or onset (**A**), autoimmunity develops in healthy individuals triggered by unknown environmental, genetic, or random factors. This stage can last for 3 to 4 years before clinical diagnosis. In the second stage (**B**), the AD is diagnosed, and chronic inflammatory mechanisms are established. Based on the balance between activating factors (ie, type I and II IFNs) and inhibitory factors (ie, expression of the coinhibitory molecules such as PD-L1 or CTLA-4) organ or tissue damage ensues. At this stage, responsive feedback loops are established to withstand changes in the AICOM resulting from activation of T cells, B cells, dendritic cells, and macrophages. In the third stage, tumors develop and start gradually modifying the ongoing AICOM through production of tumor-promoting factors to evade immune surveillance. However, immune cells already battling to control ADs showed signs of exhaustion or tolerogenic functional states evidence by the expression of coinhibitory molecules (*arrows* crossing from stage **B, C**). Under conditions different from cancer patients without autoimmunity, immunotherapy is required to contain tumor progression. ADs, autoimmune diseases; AICOM, autoimmune cytokine milieu; CTLA-4, cytotoxic T lymphocyte–associated protein 4; IFNs, interferons; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; PD-L1, programmed cell death-1 ligands; TAM, tumor-associated macrophages.

containing-3 TIM-3, and cytotoxic T lymphocyte–associated protein 4 (CTLA-4) (Blackburn and others 2008). For the purpose of this review, we will focus on the adaptation mechanisms identified on immune cells such as priming, trained immunity, tolerance, or anergy.

Priming represents the response of the adaptive immune system, involving T or B cells, after recognition of specific antigens presented by antigen-presenting cells (APCs) of the innate system, most likely dendritic cells (DCs) and in lesser extend monocytes/macrophages. However, in the context of autoimmunity, monocytes/macrophages aberrantly expressing major histocompatibilty complex II (MHC II) molecules also increase their ability as APCs.

During priming, innate and adaptive immune cells establish cytokine-mediated feedback mechanisms through secretion of IL-1α, IL-6, IL-12, IFN-γ, and tumor necrosis factor-α (TNF-α) (Deng and others 2013; Crowley and others 2017). For example, apart from T cell cross-priming, recent evidence shows that NK cells require IL-18 priming *in vivo* to produce IFN-γ upon subsequent stimulation with IL-12 (Chaix and others 2008). Thus, the orderly action of two cytokines, first IL-18 then IL-12, are necessary to fully produce IFN-γ by NK cells, thereby establishing a temporal and hierarchical activation sequence. As a result, primed immune cells exhibit stronger responses than naive cells based on stimuli thresholds. The concept of cross-priming is the basis of anticancer vaccination and immunotherapy, as well as some chemotherapy options and radiotherapy. For example, immunotherapy based on agonist stimulation of IFN genes (STING) requires STING expression in Batf3-dependent DCs to enhance cross-priming with checkpoint blockade against murine B16F10 melanoma (Barber 2014; Corrales and Gajewski 2015).

Like priming, trained immunity represent the long-lasting capacity to respond more strongly to stimuli through epigenetic reprogramming, which does not involve gene mutation or recombination, by innate immune cells (such as monocytes, macrophages, or NK cells) (Netea and others 2016). Trained immunity is a nonspecific immunologic memory resulting from rewiring the epigenetic program and the functional state of the innate immune system, eventually resulting in protection against secondary infections (Netea and others 2016). An important difference between classical immunological memory and trained immunity is that the latter has a longer duration than the former (Mitroulis and others 2018). Specifically, functional reprogramming of monocytes for either enhanced (training) or decreased (tolerance) cytokine production impacts the outcome of inflammation (Ifrim and others 2014). The functional phenotype of a trained monocyte has been defined with the following characteristics: (1) increased cytokine production, (2) changes in cellular metabolism (mainly increased glycolysis and lactate production), and (3) epigenetic rewiring (Arts and others 2018). Noticeably, training represents epigenetic manifestations of long-term processes for the adaptive and innate immune systems after encountering a stimulus.

Adaptation Mechanisms Limiting Response in Established Autoimmunity: Tolerance, Anergy, and Exhaustion

Opposite to priming and trained immunity, the terms tolerance and anergy have often been used interchangeably, to describe processes that limit immune cell activation. However, these terms are not equivalent, given the existence of significant differences in functional characteristics and underlying molecular programs (Schietinger and Greenberg 2014). Tolerance is a dynamic and active process through which innate and adaptive immune cells limit the immune system activation and prevent tissue damage. For example, tolerance of self-reactive T cells ensues in both a central mode occurring in the thymus, and in a peripheral mode occurring at the site of peripheral lymphoid organs (Singh and others 2013).

Different from central tolerance, peripheral tolerance inactivates self-reactive T cells through induction of an imprinted cell-intrinsic program mediating a state of functional unresponsiveness (Schietinger and Greenberg 2014). Constant exposure to both endogenous cytokines, such as TNF-α and IL-1, and/or exogenous stimuli, such as low levels of lipopolysaccharide can induce a tolerogenic or dysfunctional state on immune cells (Crowley and others 2017). Similarly, the tolerogenic state in macrophages is characterized by low production of cytokines, such as IL-1, IL-6, and TNF-α (Salim and others 2016). Noticeably, additional evidence suggests that mature DCs can limit effector T cell responses and promote immune tolerance in response to signaling triggered by cytokines IL-27 and IL-10 (Mascanfroni and others 2013; Takenaka and Quintana 2017). Recent reports indicate that the cytokine milieu resulting from tolerogenic immune cells could also prime microenvironments to regulate adaptive responses for T helper 17 (Th17) cells over time (Hu and others 2011).

Exhaustion is a state acquired progressively over a period of weeks or months depending on the chronic stimulus, such as sepsis or autoimmunity. Generally, immune cell exhaustion is associated with impaired, rather than lost, cell-specific functions, such as proliferation (T cells), cytokine production (T-, B-, NK-cells, and macrophages), cytotoxicity (NK cells), and phagocytosis (macrophages) (Huang and others 2009; Kardava and others 2011; Bi and Tian 2017). As the high expression of coinhibitory molecules is already in place to limit autoimmune damage (Nishimura and others 1999; Klocke and others 2016), PD-1 expression in combination with reduced proliferation is commonly used to identify exhausted immune cells (Wherry and Kurachi 2015). So far, STAT3, STAT4, and SMAD transcription factors, which are also involved in regulation of chronic inflammation, seem to control expression of most of the inhibitory receptors (Shalapour and Karin 2015). For example, STAT and SMAD molecules are involved in the regulation of coinhibitory receptors through activation of cytokines such as IL-10 and TGF-β, or through prolonged activation of type I IFNs (IFN-α/β) (Shalapour and Karin 2015).

Chronic activation of the above described mechanisms contributes to the maintenance of T cell exhaustion during chronic infections (Schietinger and Greenberg 2014). Noticeably, the strategy to use monoclonal antibodies (mAbs) targeting inhibitory molecules can successfully reinvigorate both tumor- and nontumor-infiltrating immune cells. As a result, the use of blocking mAbs against coinhibitory receptors can elicit both antitumor and autoimmune effects. Indeed, clinical data demonstrated that 40%–60% of cancer patients with preexisting ADs receiving antibodies against CTLA-4 developed some form of IrAEs, and only 20% of cancer patients with ADs exhibited mostly partial antitumor

responses (Johnson and others 2016; Menzies and others 2017). Consequently, therapeutic strategies aiming to reactivate dysfunctional or exhausted immune cells, specifically T cells, need to consider the inflammatory feedback that could exacerbate systemic autoimmunity and induce immune tolerance in the tumor microenvironment (TME).

Different from exhaustion, anergy describes the state by which lymphocytes are functionally unresponsive after antigen encounter, but remain alive for extended periods in a hyporesponsive state (Singh and others 2013). Mostly described for T and B cells, anergy could be established through a generalized inhibition of proliferation (clonal anergy) or through inhibition of effector functions (adaptive tolerance or *in vivo* anergy). Anergic phenotypes have been described in chronic infection and ADs. For example, a significant number of HIV-specific T cells circulate in an anergic state that could be reversed by immune modulator cytokines, such as IL-2, IL-7, and particularly IL-15 (Gu and others 2007). Similarly, in SLE, chronic engagement leads to an eventual reduction in signaling capacity of B cells and T cells (Foster 2007).

As with T cells, B cell anergy results from B cell binding to low avidity or soluble antigens without receiving adequate additional signals to support their activation (Tsubata 2017). Anergic B cells are unable to interact effectively with helper T cells and do not participate in immune responses against their cognate antigen (Mauri and others 2014). Anergic B cells are characterized by a short half-life (<5 days) and low expression of B cell receptor on their cell surface (Andrews and Wilson 2010). Interestingly, it was reported that NK-cells infiltrating MHC class I deficient tumors acquired an anergic state (Ardolino and others 2014). Moreover, the authors reported that cytokine therapy with IL-12 and IL-18 reversed the anergic state in MHC-deficient tumors suggesting that modulating cytokine levels could enhance immune response. Thus, recognizing the training status of immune cells could impact the type of therapeutic intervention and the time before adjustment needed for patients with ADs based on their disease state.

The AICOM

Even at preclinical stages, patients with autoimmune disorders exhibit increased serum levels of certain inflammatory cytokines. For example, SLE patients exhibit increased levels of IFN-γ, IL-5, and IL-6 (Lu and others 2016). The specific set of cytokines present in a nascent autoimmune environment could be called the ''autoimmune cytokine overlapping milieu'' or AICOM. Under AICOM, autoimmunity evolves as a continuously progressive condition reflecting the host-attempted response to balance external and internal stimuli.

It is widely believed that over time a mixture of deregulated pro- and anti-inflammatory set of events characterize human ADs. Most human established ADs exhibit their own mix of local and systemic inflammatory events during disease progression. Consequently, instead of one AICOM, several different and comparable AICOMs are established throughout different body or tissue locations. Generally, systemic engagement of multiple AICOMs result in high systemic cytokine levels and are associated with relapses or active states (also called flares), whereas engagement of local AICOMs result in relatively lower cytokine levels, although high compared with healthy subjects, are associated with remitting or inactive states (Wildner and Kaufmann 2013). Consequently, the group of pro- and anti-inflammatory cytokines in AICOMs are indicators of the immune process. Over time, those cytokines define the temporal and hierarchical establishment of costimulatory and coinhibitory pathways balancing the effects of autoimmunity (Zhang and Vignali 2016).

Similarly, some myeloid leukemias exhibit a consistent history of relapse and remission stages during the course of disease (Sasine and Schiller 2015). In such cases, the inability to resolve chronic inflammation is widely considered one of the primary causes of carcinogenesis and tumor progression (Aggarwal and others 2009). The underlying deregulated cytokine production and aberrant cytokine signaling correspond to the predominance of one or a mixture of cytokines associated with the activation of three main subsets of T cells: T helper 1 (Th1), T helper 2 (Th2), or Th17. Classically, Th1 cytokines are associated with the induction of cytotoxic functions from Th1 cells (ie, IL-2, IFN-γ, and TNF-α) and macrophages (ie, IL-1, IL-6, IL-12, and TNF-α). By contrast, Th2 cytokines are associated with chronic and repair processes carried out by the following cytokines IL-4, IL-5, IL-6, IL-10, IL-13, and IL-25 (Leung and others 2010; Moudgil and Choubey 2011).

More recently, a new subset of T cells called Th17 cells producing mainly IL-17 along with other cytokines, such as IL-6, IL-21, IL-22, and IL-26, have been recognized to play roles in ADs and cancer. The development of Th17 cells is supported by other cytokines, such as IL-6, TGF-β, and IL-23, produced primarily by APC such as DCs and monocytes (Harrington and others 2005; Park and others 2005; Bettelli and others 2006). Nevertheless, heterogeneous rather than homogenous activation patterns featuring increased ratios of blood Th2 and Th17 cells over Th1 cells have been observed in Ads, such as SLE or RA (Ueno and others 2015). Recent evidence using fate mapping experiments found that subsets of Th17 cells also express IFN-γ, which negatively affected the severity of experimental autoimmune encephalomyelitis (EAE) (Hirota and others 2011). Moreover, human Th17 cells can preferentially produce IL-10 and IL-17 to respond against bacterial infection (eg, *Staphylococcus aureus*) or IL-17 and IFN-γ to respond to fungi (eg, *Candida albicans*) (Burkett and others 2015).

IL-17 is known to be produced alternatively by activated $CD8^+$ T cells, $TCR\gamma\delta^+$ T cells, and neutrophils (Stark and others 2005) suggesting that immune cells exhibit increased plasticity to respond against different stimuli. Considering that chronic exposure to IFN-γ is associated with autoimmunity, recent evidence linking increased levels of IL-17 along with IFN-γ to IBD (Harbour and others 2015) suggests that composition of the cytokine milieu involve a variety of immune cells responding to autoimmunity or chronic inflammation. Indeed, AICOMs contain a variety of cytokine activating subsets likely coming from multiple immune cell types, including IFN-α, IFN-β, B cell-activating factor of the TNF family (BAFF/*TNFSF13B*), IL-12p40, and SCF/c-kit ligand (Slight-Webb and others 2016). Under such circumstances, Th17 differentiation is being regulated by some of those cytokines such as IL-12, IFN-γ, or TGF-β plus IL-6 (McGeachy and Cua 2008). Therefore, the ability of immune cells to form heterogeneous populations complicate the traditional approach to targeting unspecific cell types, especially when heterogeneous subsets of

immune cells coproduce cytokines traditionally categorized as Th1, Th2, or Th17.

Targeting Tregs and Th17 Cells in Established ADs and Cancer

Historically, the use of cytokines as adjuvant cancer therapy has been associated with moderate responses and severe adverse events, especially for type I IFN (IFN-α/β), type II IFN, and IL-2 (Gogas and others 2010; Ascierto and others 2013). Different from other cytokines, IFNs are consistently elevated both in preclinical and clinical stages of ADs, such as in RA or in SLE. Paradoxically, IFN-γ-null$^{-/-}$ mice were found to be highly susceptible to multiorgan-specific ADs, including EAE (Willenborg and others 1996). Moreover, blockade of IFN-γ or its signaling pathways exacerbated the severity of disease in murine EAE and collagen type II-induced arthritis (CIA) (Leung and others 2010). Indeed, failure to produce IFN-γ and the resulting deficit in $CD4^+CD25^+$ regulatory T cells (Treg) function during acute inflammation provided evidence that IFN-γ through induction of Forkhead box P3 (FOXP3) is essential in self-regulatory mechanisms (Wang and others 2006). This finding led researchers to investigate the nature of Treg and Th17 cells. Tregs help maintain immune self-tolerance through limiting the activation and expansion of autoreactive immune clones. There are two types of FOXP3-expressing Tregs: one identified as $CD25^+FOXP3^+$ natural or Thymic-derived (nTreg) cells that prevent autoimmunity, and the second is identified as post-thymic-induced Treg (iTreg) cells that maintain a noninflammatory environment in the gut (Leung and others 2010).

Several reports concur that loss of peripheral tolerance due to deficient or dysfunctional Tregs contribute to the development of various ADs such as RA and SLE (Chavele and Ehrenstein 2011). Common gamma chain cytokines such as IL-2, IL-7, and IL-15, are required for FOXP3 expression and Treg cell development in the thymus. By contrast, cytokines that induce other Th cell differentiation fates such as IL-4, IFN-γ, and IL-6 restrain or limit iTreg development (Zhou and others 2009). Although Treg cells exert their suppressive functions in a cell–cell contact manner *in vitro*, it should not be ruled out that Tregs secrete soluble factors (Leung and others 2010). For example, Treg-mediated suppression is mediated by TGF-β and IL-10 in murine models of T1D and EAE, respectively (Leung and others 2010).

The predominance of proinflammatory cytokines (eg, IL-6, IL-1b, and IL-21) in ADs restrain Treg development and support Th17 differentiation (Wang and others 2006). Indeed, expansion of double-negative T cells ($CD4^-$ and $CD8^-$) capable of producing both IFN-γ and IL-17 in patients with SLE, as well as in lupus-prone mice, relates to progressive lupus nephritis and AD (Tsokos and others 2016). Collectively, the persistence of inflammation in lesion sites is significantly associated with reduced levels and impaired function of $CD4^+CD25^+FOXP3^+$ Treg cells induced by proinflammatory cytokines. Thus, biologic therapies in ADs aim to inhibit Th17 and promote Treg cell development to reverse the altered balance between Treg and Th17 cell subsets.

In cancer, it has been shown that $CD4^+CD25^+FOXP3^+$ Treg cells increase in several solid and hematological malignancies (Wang and others 2006). The frequency of Tregs has been associated with mechanisms of tumor immune escape and poor prognosis, as Tregs recruited to tumors are involved in the inhibition of effector functions in both inflammation and cancer (Criscitiello and others 2016). Tumor-recruited Tregs release chemoattractant cytokines (CCL2 and CCL22), immunosuppressive cytokines (TGF-β and IL-10), and upregulate indoleamine-pyrrole 2,3-dioxygenase (IDO) expression leading to T cell anergy (Gyorki and others 2013). In mouse models, Treg depletion can enhance melanoma immunity. By contrast, a significantly greater number of Th17 cells infiltrate tumors at early stages. However, at late stages, the number of intratumoral Th17 cells decreased compared with the density of Th17 cells in the adjacent, nontumor tissue of patients (Takanori and others 2010). This heightened early presence of Th17 cells in tumor tissue holds true for a vast range of malignancies, implying that tumors themselves produce factors that promote Th17 cell trafficking to the diseased site (Bailey and others 2014). Inflammatory Th17 cells and their associated cytokines (ie, IL-17A, IL-17F, IL-21, IL-22, etc.) mediate tumor growth in two distinct ways—by driving angiogenesis and by suppressing antitumor immunity (Bailey and others 2014). The ability of Th17 cells to express several effector cytokines, including IL-2, IL-17, GM-CSF, IFN-γ, and TNF-α define the TME (Zou and Restifo 2010). Nevertheless, tumor-mediated mechanisms exploit the high interconvertible plasticity among Tregs and Th17 cells leading to phenotype changes, including an intermediate phenotype that coexpresses FOXP3 and retinoic acid-related orphan receptor gamma T (RORγT) (Du and others 2008). Different from ADs, cancer therapies aim to increase the antitumor effects of Th17 cells enhancing cytotoxic T cell activity in tumors, while limiting its proangiogenic/protumoral function creating a paradox for treating cancer in the context of autoimmunity.

Chemotherapy in the Treatment of Cancer in Patients with Preexisting ADs

Cancer patients with preexisting ADs are usually excluded from clinical trials with checkpoint inhibitors due to increased risk of toxicity. Consequently, standard cancer therapy options, such as radiation therapy or chemotherapy are the alternative to immunotherapy for these patients. Nevertheless, these interventions have both indirect and direct effects on the immune system depending on the underlying AD. For example, TGF-β is a key mediator of tissue fibrosis and tissue repair in systemic sclerosis (SS) (Lafyatis 2014). SS is associated with increased risk to develop lung, breast, and hematological malignancies (Zeineddine and others 2016). Combined analysis of two studies of women with breast cancer showed that the 8% of women homozygous for the TGF-β1 (-509T) allele, which increases circulating levels of TGF-β1, had a 15-fold increased risk of fibrosis following radiotherapy (Seruga and others 2008). As a result, the use of chemotherapy with agents such as cyclophosphamide is recommended in patients with SS over-radiation therapy, which enhances TGF-β (Meng and others 2016).

Like SS, SLE patients have increased risk for hematological malignancies, such as non-Hodgkin's lymphoma, and some solid tumors in lung, liver, vulvar/vaginal, and

thyroid areas (Goobie and others 2015). However, SLE patients have lower serum TGF-β1 levels than healthy control individuals. The low levels of TGF-β are associated with both increased disease severity and autoreactive lymphocyte subsets (Becker-Merok and others 2010). For cancer patients with SLE, the release of TGF-β as a result of radiation therapy could be beneficial to the underlying SLE. Consequently, the use of radiotherapy in cancer patients with lupus could restrict underlying autoimmunity but the same treatment could pose a risk for patients with SS.

Chemotherapy-induced death of cancer cells can cause the release of immunogenic antigens, and the emission of danger-associated molecular patterns, which result in cell-mediated immune responses to the tumor (Seruga and others 2008). Nevertheless, patients with AD commonly use several chemotherapy drugs as treatment for autoimmunity, such as cyclophosphamide, mercaptopurine, methotrexate, or mitoxantrone (Ben-Ari 2004). In fact, the expression of IFN-related signature genes in autoimmunity, such as levels of CD8a, CD8b, and IFN-γ can improve clinical response to anthracycline chemotherapy (Mattarollo and others 2011). Moreover, when used in the context of breast cancer tumors, anthracyclines activate a type I IFN gene signature, including the rapid secretion of type I IFN and the release of the chemokine CXCL10/IP-10. Eliciting a type I signature through activation of the pattern recognition receptor Toll-like receptor-3 can predict response to anthracycline therapy in breast cancer patients (Sistigu and others 2014). Consequently, the use of anthracyclines could have negative consequences with type I or type II IFN-driven autoimmune conditions, such as RA, SLE, or MS, especially during relapsing states.

On the other hand, cyclophosphamide and methotrexate have specific uses as immune suppressors either in severe or nonsevere stages, respectively. Cyclophosphamide is used in combination with glucocorticoids to preserve organ function in severe lupus nephritis, severe RA, or severe MS. Because of toxicity, the use of cyclophosphamide is limited to severe autoimmune events or to advanced stages of lymphomas, multiple myeloma, ovarian cancer, breast cancer, or sarcomas. Conversely, methotrexate is tolerated at both low and high doses and approved to treat RA, psoriasis, MS, lupus, sarcoidosis, and ectopic pregnancy. It is used at different higher doses and schedules in cancer patients without autoimmunity, but liver toxicity remains the main complication (Emens and Middleton 2015). Also, methotrexate can inhibit cell replication and recruitment of immature and inflammatory monocytes to sites of inflammation. Collectively, there are concerns that chronic immunosuppression from chemotherapies conceivably increase the risk of malignancy, or tumor progression in patients with autoimmunity.

Immune Biological Therapies in ADs and Cancer

Immune biological therapies carry the risk to increase their toxicity or worsen the severity of underlying AD by increasing the occurrence of IrAEs. Specifically, IrAEs grade III or IV are a major cause of concern as a proportion of patients discontinue treatment and fatalities can occur if not promptly treated. The most prominent CPI-blocking strategies with antibodies are those targeting CTLA-4 and PD-1 or its ligand, programmed cell death ligand 1 (PD-L1). For patients receiving combination immunotherapy with anti-PD-1 and anti-CTLA-4, ∼50% developed grade III or IV irAEs compared with patients treated with anti-PD-1 alone (14%) or anti-CTLA-4 (20%–25%) alone (Stucci and others 2017). In fact, just monotherapy with anti-CTLA-4 or anti-PD-1 induced IrAEs or flares in ∼50% of melanoma patients with preexisting ADs. Noticeably, the response rates for anti-CTLA-4 (20%) and anti-PD-1 (33%), were comparable to those reported in melanoma patients without autoimmunity with or without autoimmunity. Thus, the focus of immunotherapy in the context of autoimmunity is to avoid or minimize the occurrence of IrAEs.

Noticeably, genes encoding CTLA-4 (*Ctla4*) and PD-1 (*pdcd1*) have IFN-stimulated response elements making them subject to cytokine regulation, especially for type I and II IFNs (Zhang and Vignali 2016). Recent advances in transcriptional regulation have shown that IFN-stimulated gene factor 3, a complex composed of STAT1, STAT2, and IFN regulatory factor 9 regulates expression of PD-1 (Garcia-Diaz and others 2017). As the loss of IFN production is a hallmark of tumor-infiltrating lymphocytes (TILs), the role of other STAT-activating cytokines, such as IL-10, IL-12, IL-27, and TNF have become centrally important to our understanding of how TILs express coinhibitory molecules as part of the mechanism of response and resistance to immunotherapy (Burkholder and others 2014). Despite their apparent similar regulation, CTLA-4 and PD-1 have distinct roles in the regulation of immunity. CTLA-4 regulates the amplitude of early activation of naive and memory T cells, whereas PD-1 is responsible for the corresponding upregulation of its ligands PD-L1 and PD-L2 that limit the activity of T cells in the periphery during an inflammatory response (Yuan and others 2016).

Similar to their use in cancer, antibodies targeting coinhibitory and costimulatory pathways are used in AD. Most biologic therapies target effector cytokines using antibodies against TNF-α, anti-IL-1, and anti-IL-6 molecules. Historically, the use of antibodies targeting the cytokine TNFSF13B or BAFF have been successful in modifying multiple functions of B cells, such as maturation, proliferation, affinity maturation, and immunoglobulin class switching (Mackay and Mackay 2002). Interestingly, the definition of BAFF cytokine systems provides a major advance in understanding molecular mechanisms of B lymphocyte and tumor cell survival pathways. The results raise additional but addressable questions that could generate a clearer picture of fundamental processes in autoimmunity and cancer, as well as new therapeutic targets (Ware 2000). An alternative to targeting B cell development is to target specific B cell subsets using depleting mAbs, such as anti-CD20 mAbs. CD20 is a transmembrane protein that is expressed on pre-B cells and mature B cells, but not on plasma cells. These anti-CD20 antibodies attenuate humoral autoimmunity and $CD4^+$ T cell autoimmunity by limiting essential ongoing autoantigen presentation by $CD20^+$ B cells, but host defenses can still persist as plasma (effector) cells remain functional (Holdsworth and others 2016). Similarly, anti-CD20 used to target CD20-positive melanoma stem cells, which make up as little as 2% of a tumor, was reported to eradicate melanoma in mice (Schmidt and others 2011). These results provide further evidence for using biological therapies both in autoimmunity and cancer. Considering that these alternative approaches avoid direct T cell targeting, there is a lesson to be learned

Table 2. Preclinical Mouse Models for RA and IBD

Model	*Features*	*Type*	*References*
Collagen type II-induced arthritis (CIA)	Induced by collagen type II emulsified in complete Freund's adjuvant. Incidence and chronicity depend on susceptibility of mouse strain and collagen being used.	Induced	Luross and Williams (2001); Labelle and Hynes (2012)
KBxN arthritis (KBN)	Mice display T and B cell responses to glucose-6-phosphate isomerase on cartilage surface.	Spontaneous	Kyburz and Corr (2003)
SKG arthritis (SKG)	Inflammatory arthritis associated with a point mutation in ZAP-70. Microbiota can affect disease presentation.	Spontaneous	Sakaguchi and others (2003)
IL-1 receptor antagonist$^{-/-}$ arthritis (IL-1ra$^{-/-}$)	Lack of IL-1 receptor antagonist results in spontaneous destructive arthritis. IL-17 dependent.	Spontaneous	Horai and others (2000)
AOM/DSS (IBD)	Chemical induction of DNA damage by AOM combined with repeated epithelial damage by DSS mimic key features of CA-CRC.	Induced	Parang and others (2016)

AOM, azoxymethane; CA-CRC, colitis-associated colorectal cancer; DSS, dextran sodium sulfate; IBD, inflammatory bowel disease; IL, interleukin.

regarding future approaches that combine cancer and autoimmune biological therapies to possibly treat cancer in patients with preexisting ADs.

Mouse Models of ADs

The lack of knowledge about the mechanisms of AD concomitant with cancer make preclinical mouse models necessary for the analysis of anticancer therapies in the context of an autoimmune environment. To the best of our knowledge, there are no murine models of autoimmunity that develop cancer spontaneously or that contain cancer oncogenes. Considering that women represent 80% of all cases of autoimmunity in the United States (Klein and Flanagan 2016), it is imperative to find well-established preclinical mouse models of autoimmunity with female sex bias to examine the efficacy of experimental cancer therapies in the context of autoimmunity. Fortunately, there are trusted experimental mouse models mimicking human ADs (Wagner and others 2002; Webb 2014) that show female gender bias (Hodge and others 2014), although with minor caveats and considerations. In this section, we will overview the most commonly used mouse models of autoimmunity.

Rheumatoid arthritis

In the case of RA, there are several mouse models, but the first animal model for RA was an adjuvant-induced rat model easy to use and highly reproducible (Table 2). The CIA model arose in mouse and replaced the rat model as the standard. The arthritogenic response is generated through immunization with type II collagen emulsified in complete Freund's adjuvant in a DBA/1 mouse. A well-controlled model based on monoclonal anti-collagen type II antibodies has also gained popularity. More recently, transgenic mouse models have been leveraged to study RA. The new models of spontaneous RA include the human T cell leukemia virus (HTLV)-induced arthritis mice that carries the genome of HTLV-1; K/BxN arthritis mice that produces autoantibodies against glucose-6-phosphate isomerase; SKG arthritis mice that possess a point mutation in ZAP-70 and are dependent upon environmental stimuli (Asquith and others 2009; Benson and others 2018). Several other spontaneous models of arthritis involve deficiencies in cytokine signaling pathways, such as mice with deficiency of IL-1 receptor antagonist (IL-1ra$^{-/-}$) causing unopposed excess in IL-1 signaling (Koenders and others 2008); mice with point inactivating mutation at F759 in the gp130 IL-6 receptor subunit causing STAT3-mediated proliferation of CD4^{+} T cells (Sawa and others 2006)or the mice with a double mutation in IFN-1R and DNase II (DNase$^{-/-}$ IFN-1R$^{-/-}$) that impairs macrophage clearance of phagocytosed DNA from apoptotic cells and results in the production of TNF-α (Kawane and others 2006).

Systemic lupus erythematosus

Several mouse models have been developed that mimic variable aspects of SLE (Table 3). Recently, Hodge and others (2014) developed the AU-rich element (ARE) deletion (ARE-Del$^{-/-}$) mouse model of lupus. The deletion in the 3′ untranslated region of the IFN-γ gene increased messenger RNA stability, subsequently increasing the serum levels of IFN-γ. The circulating levels of IFN-γ in the ARE-del model are comparable to levels found in human SLE patients. Moreover, the ARE-del heterozygous mice demonstrate serum levels of IFN-γ that are approximately half the levels observed in the homozygous ARE-del mice. Noticeably, the heterozygous ARE-del mice exhibit moderate renal lesions and elevated blood counts of monocytes and eosinophils. These data suggest a dose-dependent effect

Table 3. Phenotype Comparison of Available Preclinical Mouse Models of Systemic Lupus Erythematous

Phenotype	*SLE patients*	*NZBWF1**	*MRL/MPJ-fas^{lpr}/J**	*ARE-Del$^{-/-}$*	*ARE-Del$^{+/-}$*
Disease onset/severity	Gradual	Severe	Severe	Gradual/moderate	Gradual/mild
IFN signature	Strong[a]/type I and II	Weak[a]/type I	Absent[a]	Strong/type II (≥20 pg/mL)	Moderate/type II (≤20 pg/mL)
Antinuclear antibodies	Yes	Yes	Yes	Yes	Yes
Lymphadenopathy	Yes	Yes	Yes	Yes	Yes
Splenomegaly	Yes	Yes	Yes	Yes	Yes
Glomerulonephritis	Yes	Yes	Yes	Yes	Yes
SLE genes	Yes	Yes	No	Yes	Yes
Gender bias (F/M)	F/M 9:1	Only females	No	Both F/M	Both F/M
Age of onset	16–55 years	29 weeks	10 weeks	10–12 weeks	10–12 weeks
50% survival age	NA	45 weeks	28 weeks	>52 weeks	>52 weeks
50% mortality in females	NA	7–8 months	5 months	>10 months	>10 months
Breeding performance	NA	Fair	Fair	Poor	Fair

*Data obtained from the Jackson Laboratory (2018).
[a]Zhuang et al. (2015).
ARE, AU-rich element; F/M, female/male; IFN, interferon; MRL/lpr, Murphy Roths Large/lymphoproliferative; NA, not applicable; NZBWF1, New Zealand Black × White F_1; SLE, systemic lupus erythematous.

of IFN-γ as a driver of disease progression for SLE. Apart from type I IFNs, IFN-γ is also recognized as a significant contributor to SLE pathogenesis (Harigai and others 2008; Pollard and others 2013). Similar to SLE patients, the ARE-del mice exhibit a female-bias phenotype along with neutrophilia, monocytosis, serum low complement supply, glomerulonephritis, and glomerular complement deposition. Another well-established mouse model of lupus is the Murphy Roths Large/lymphoproliferative (MRL/*lpr*) mouse (Chan and Shlomchik 2000). The MRL/lpr model has a loss-of-function mutation within the gene encoding the Fas protein that bypasses the need for an initiating IFN signature. However, the MRL/lpr model lacks gender bias. Morphologically, the MRL model displays a severe SLE-like disease progression with enlarged lymph nodes, splenomegaly, glomerulonephritis, and in some cases arthritis. SLE morphology and serology can also be seen in the New Zealand Black × White F_1 mice affecting only female mice (Wong and others 2013). However, a male bias in SLE onset can be seen in the C57BL/6 BXSB mouse [a cross of C57BL/6J × SB, followed by selection of the satin, nonbeige phenotype (Staats 1985)]. All lupus models described herein exhibit serum antinuclear antibodies and anti-double-stranded DNA antibodies (Table 3).

Inflammatory bowel disease

Like SLE, IBD is complicated by environmental and genetic contributions leading to different clinical presentations. IBD encompasses both ulcerative colitis, limited to the large intestine and rectum, and Crohn's disease, which can present along the gastrointestinal tract. Patients with IBD are at increased risk for colorectal cancer (CRC) (Danese and Mantovani 2010). There has been a large research effort to investigate ulcerative colitis-associated CRC (CA-CRC) in an animal model. The dextran sodium sulfate (DSS)-induced colitis model is the standard mouse model. The addition of the procarcinogen azoxymethane (AOM/DSS) accelerates onset of tumors in mice and has been at the forefront of exploration of the role of gut AD in tumorigenesis. A recent report indicated the potential for natural products as chemopreventive agents in the AOM/DSS mouse model of CA-CRC (Barker and others 2018). As a dietary supplement, the natural triterpenoid celastrol has been associated with significant suppression of inflammatory cytokines TNF-α, IL-6, and IL-1β, as well as the reduction of inducible nitric oxide synthase and cyclooxygenase-2 (Barker and others 2018).

Summary

With recent clinical focus on immune checkpoint inhibitors in combination with traditional therapeutic approaches to treat cancer, cancer specifically in the context of autoimmunity presents targeting paradoxes that need to be addressed both in AD and host-dependent manners. Indeed, the conditions in which cancer arises in established ADs call for novel therapeutic options somewhat different to the use of checkpoint inhibitors as a first line of attack. We believe that those strategies should be tested thoroughly in preclinical models of autoimmunity and cancer to diminish the already high risk of developing IrAEs facing cancer patients with preexisting ADs.

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