Journal of Carcinogenesis
Covering Genesis to Therapeutics
Journal of Carcinogenesis , ISSN: 1477-3163
2025; Vol 24: Issue 8s, https://carcinogenesis.com/

From Defense to Offense: How Autoimmunity Influences Cancer Progression

Anastasia V. Poznyak [1*], Nikolay Konstantinovich Shakhpazyan[2], Elizaveta Romanovna Korchagina[1], Olga Nikolaevna Maltseva[3], Aleksandra Sergeevna Utkina[4], Alexander N. Orekhov[1]

[1]Institute for Atherosclerosis Research, Osennyaya 4-1-207, 121609 Moscow, Russia

Email ID: tehhy_85@mail.ru

[2]Avtsyn Research Institute of Human Morphology, Petrovsky National Research Centre of Surgery, 3 Tsyurupa Street, 117418 Moscow, Russia

[3]Institute of Experimental Medicine, 12, Academician Pavlov Street Street, 197022, Saint Petersburg, Russia

[4]Department of Commodity Expertise and Customs Business, Plekhanov Russian University of Economics, 36, Stremyanny Lane, 115054 Moscow, Russia

ABSTRACT

Autoimmune disorders represent significant global health challenges, characterized by aberrant immune responses against the body's own tissues, leading to a spectrum of conditions with varying severity. Concurrently, primary immunodeficiencies (PIs) compromise immune tolerance, heightening susceptibility to infections, malignancies, and autoimmune diseases. Notably, there is an emerging recognition of the bidirectional relationship between autoimmunity and cancer, as autoimmune responses may play dual roles: while excessive autoimmunity can promote tissue damage and malignancy, certain immune responses can also exhibit protective effects against tumors. This review meticulously examines the interplay between various immune cells, including T lymphocytes, neutrophils, and macrophages, in both malignancies and autoimmune disorders. It explores how chronic inflammation, driven by autoimmune conditions, can foster an environment conducive to tumor progression, while also considering how immune regulatory mechanisms can become dysfunctional in the face of malignancy. Furthermore, we discuss the implications of recent advancements in cancer immunotherapy which highlight the complexities of using immune checkpoint inhibitors in patients with pre-existing autoimmune conditions. Ultimately, this review posits that a nuanced understanding of the intricate relationships between autoimmunity and cancer could inform novel therapeutic strategies and improve outcomes for affected patients.

1. INTRODUCTION

Autoimmune disorders are major health issues with various occurrence rates and gravity worldwide. Such disorders develop from aberrant immunity responses to healthy tissues and cells. Impairment of immunity tolerance to particular autoantigens leads to progression of such conditions. Primary immunodeficiencies (PI) are chronic conditions which involve increased vulnerability to infections, malignancies and autoimmune diseases [1,2]. Malignancy risk which is approximately from four to twenty-five percent, elevates with ageing. Among the factors accounting for the cancer type are primary immunodeficiencies, infections, ageing. Primary immunodeficiencies are featured by lower resistance to infections and higher rate of cancer [3].

Multiple trials demonstrated connections between cancer and immune system, which should be further investigated. Auto-immune disorders and malignancies coincide more frequently than is typically thought. Lately this phenomenon has been attracting more and more attention. Whereas elevated auto-immunity can be harmful, reduced auto-immunity could be useful. Auto-immune response may be regarded as protection against tumors, and such response might trigger autoantibodies (AAbs) against various self-antigens, such as antigens in tumor cells [4]. Tumor is formed when the immunity is unable to regulate the growth of cells and auto-immunity because of impaired auto-reactive responses. These conditions might be greatly alleviated if the immunity was re-programmed to not need permanent therapy to retain homeostasis. In contrast, inhibition of immunity in order to suppress auto-immunity may enable progression of cancer and increase susceptibility to infections [5,6].

There are various pathological autoimmunity conditions related to the progression of lymphoproliferative disorders (LPD) including SjS, RA and SLE. Furthermore, groups of AAbs were detected in subjects with solid tumors. Subjects with dermatomyositis (DM) were reported to exhibit elevated risk of solid-organ cancer. The connection between auto-immunity and malignancies is yet to be fully explored [7]. In autoimmunity disorders, affected tissues regenerate at the region of auto-immunity that is featured by quick cellular division resulting in progression of malignancies. That is traditional explication of the connection between autoimmune disorders and malignancies. The relationship between auto-immunity and elevated risk of malignancies is linked to cancer. It was hypothesized that in multiple ARDs and malignancies, the connection could be bilateral, and autoimmunity-induced chronic inflammatory processes and tissue injury can result in malignancies while the immunity response to malignant cells leads to auto-immunity [8].

Research in the field of autoimmune responses, T-regs, TLRs and activations of DCs can promote development of novel vaccines which will lead to more beneficial results of treatment. Investigation of potential targets is necessary to engineer novel therapeutic approaches for malignancies. Characteristics of auto-immunity were studied while concentrating on the immunity, apoptotic processes and therapies [9,10].

Table 1. Roles of Immune Cells in Autoimmunity and Cancer

Immune Cell Type	Role in Cancer	Role in Autoimmune Disorders
CD8+ T lymphocytes	Recognize and kill malignant cells via perforin/granzyme and Fas pathway (cancer-protective)	Increased abundance in MS, scleroderma, SLE, T1DM; contribute to tissue injury
Regulatory T cells (Tregs)	Suppress CD8+ and effector T cells; promote tumor progression and immune escape	Dysfunction or deficiency promotes autoimmunity (e.g., IPEX syndrome, polyendocrinopathy)
Th1 cells	Generally cancer-protective; IL-2 supports anti-tumor immunity	Involved in multiple autoimmune diseases; excessive proinflammatory activity
Th2 cells	Mixed role: protective or carcinogenic depending on context	Contribute to allergic disorders, scleroderma, UC; variable role in RA and SLE
Th17 cells	Cancer-protective in some tumors (breast, gastric, prostate); pro-tumor in others (ovarian, RCC, OSCC); effects vary by TME	Elevated in MS, RA, psoriasis, IBD, SLE; strongly proinflammatory
Neutrophils	Tumor-associated neutrophils (N1 = anti-tumor, N2 = pro-tumor); high vs. low density subsets differ in cytotoxicity	In RA and SLE: enhanced NET formation, ROS production, cytokine release → amplify inflammation and autoantibody production
Macrophages	M1 = anti-tumor in early cancer; M2 = pro-tumor in advanced stages	M1 predominant in RA, SLE, T1DM; M2 in fibrotic autoimmunity (scleroderma, IBD)

2. T LYMPHOCYTES

T Lymphocytes in Cancer

CD-8+ T lymphocytes attack malignant cells and represent a part of one of the most important anticancer mechanisms. Via identification of peptide-major histocompatibility complex-I these cells find malignant cells and eliminate them by expressing perforin (PRF) and activating Fac receptor apoptotic pathway [11,12].

Regulatory T cells inhibit the CD-8+ T lymphocyte functioning, facilitating development of malignancies. Moreover, regulatory T cells suppress proliferative processes of effector and memory T cells, e.g., type 1 and 2 helper T cells [13,14]. Type 1 helper T cell cytokine interleukin 2 showed ability to protect against tumours in experimental studies. Interleukin 2 in recombinant form is licensed in some countries for melanoma and renal cell carcinoma (RCC). Although, another type 1 helper T cell cytokine interferon gamma was shown to promote and to suppress tumours [15,16].

Type 1 helper T cell mediated immune processes are typically canceroprotective, whereas type 2 helper T cell mediated immune processes exhibit both canceroprotective and carcinogenic effects [17].

T helper 17 cells can have canceroprotective or carcinogenic in the tumor microenvironment. In blood of subjects with cancer levels of T helper 17 cells are often higher than those of healthy subjects, as was established for different malignancies including RCC, ovary cancer, breast cancer, cervix cancer, endometrium cancer, liver cancer, and OSCC. Although, reduced levels of T helper 17 cells in blood of subjects with cancer were detected in lung carcinoma and pancreas cancer. T helper 17 cells aggregate in tumor microenvironment of breast, stomach and prostate cancer [18,19].

Expanded peripheral blood Tregs of subjects with malignancies were observed in ovary cancer, liver cancer, OSCC, stomach cancer, pancreas cancer, RCC, cervix cancer. Regulatory T cells are more abundant in breast and lung carcinoma. A link between regulatory T cells abundance and development of malignancies was detected in breast and lung carcinoma, liver cancer, OSCC, stomach cancer [20,21].

Aggregation of regulatory T cells in TME together with elevated concentrations of these cells are detected in various malignancies. T helper 17 cells impact on malignancies is typically confined. Interleukin 23 is an important cytokine that drives T helper 17 cells to expand. Interleukin 23 suppression by risankizumab did not lead to an elevation of long-term risks of malignancies [22,23]. Analogously, interleukin 17 A suppressant secukinumab therapy for psoriatic arthritis, psoriasis, Bekhterev's disease subjects showed a long-term reduced risk of cancer. Analyses of other long-term trials on this drug showed similar outcomes. Ixekizumab is another suppressant of interleukin 17 A which has shown a long-term reduced risk of malignancies. Although, other trials on interleukin 23 suppressants show contradicting results with both canceroprotective and carcinogenic impacts. This implies that T helper 17 cells do not exert considerable carcinogenic or canceroprotective effects [24,25].

T-Lymphocytes in Autoimmunity

Autoimmunity disorders are a clear example of proinflammatory chronic disorder. Multiple autoimmune diseases show dysfunction of regulatory T cells. Furthermore, regulatory T cells deficiency promotes autoimmune diseases. Impaired immunity regulation, polyendocrine syndromes, enteropathy, IPEX syndrome are recessive diseases induced by FOX-P3 mutation [26]. This gene is believed to be an important part of regulatory T cells regulation. IPEX syndrome is related to auto-immune enteropathy, T1DM, cutaneous diseased and severe infections. Whereas regulatory T cells dysfunction is present in autoimmunity disorders, CD-4+ T lymphocytes effect is enhanced [27,28]. Specifically, T helper 17 cells and type 1 helper T cells are implicated in the development of many autoimmune diseases. T helper 17 cells abundance and activity are elevated in MS, rheumatoid arthritis, psoriasis, IBD, and systemic lupus erythematosus [29].

Type 2 helper T cells mediate the immunity responses to allergens. They are also involved in pathogenesis of scleroderma and UC. In rheumatoid arthritis, count of type 2 helper T cells was similar to the control group. The results of the studies on type 2 helper T cell cytokines in systemic lupus erythematosus are contradicting. CD-8+ T lymphocytes abundance or activity in blood and organs elevates in multiple sclerosis, scleroderma, aplastic anemia, type 1 diabetes, and systemic lupus erythematosus [30,31].

3. NEUTROPHILS

Neutrophils in Malignancies

Tumour associated neutrophils show plastic characteristics in the tumor microenvironment. With transforming growth factor beta absent, they exhibit proinflammatory and canceroprotective activity (N-1 phenotype), whereas with transforming growth factor beta present they exhibit anti-inflammation and carcinogenic activity (N-2 phenotype). N-1 phenotype generates elevated concentrations of tumor necrosis factor alpha, nitric oxide, and hydrogen peroxide [32,33]. This phenotype is predominant in tumor microenvironment at early stages with low concentrations of transforming growth factor beta. The N-2 phenotype is prevalent at progresses stages when transforming growth factor beta aggregates [34]. In murine model of tumors, neutrophils in blood show 2 groups with different density in PBMC, following density gradient centrifugation. High-density neutrophils are predominant in mice without tumours, whereas low-density neutrophils prevail in mice with tumours. High-density neutrophils showed cytotoxicity to malignant cells in culture, while low-density neutrophils were harmless [35,36]. Analogous to tumor associated neutrophils, HDNs convert into LDNs and the conversion relies on transforming growth factor beta. As expected, subjects with progressed lung carcinoma showed elevated levels of low-density neutrophils in comparison to subjects with early stages and healthy subjects [37].

Neutrophils in Autoimmunity Disorders

Neutrophils show proinflammatory activity in autoimmune diseases. Although, this activity can be different in different disorders. The role of neutrophils in rheumatoid arthritis and systemic lupus erythematosus are reviewed below as typical examples [38].

In subjects with rheumatoid arthritis neutrophils in joints show cytotoxicity and neutrophils in blood are ready to generate reactive oxygen species. Proteases which are expressed from neutrophil granules facilitate rheumatoid arthritis inflammatory process. Myeloperoxidase is an enzyme which shows cytotoxicity and is expressed from neutrophil granules. Myeloperoxidase is observed in circulation, in synovia and in tissues of subjects with rheumatoid arthritis [39]. Myeloperoxidase elevates permeability of the vessels and enables proinflammatory ICs penetration. Moreover, myeloperoxidase recruit neutrophils to the inflamed region. In rheumatoid arthritis synovia neutrophils release

proinflammatory cytokines e.g. BAFF, tumor necrosis factor, RANKL [40,41]. NETs are histone networks and deoxyribonucleic acid fibers which take part in elimination of pathogenic organisms. Citrullinated histones contain approximately seventy percent of all neutrophil extracellular trap proteins. Neutrophil extracellular traps formation is promoted in rheumatoid arthritis. It is considered to cause auto-immunity to citrullinated proteins [42,43].

Analogous to their role in rheumatoid arthritis, in systemic lupus erythematosus neutrophils exhibit proinflammatory activity. They mostly are low-density neutrophils and release type 1 interferon, interferon gamma, interleukin 6, interleukin 8, and tumor necrosis factor alpha. Like rheumatoid arthritis, systemic lupus erythematosus is featured by increased formation of neutrophil extracellular traps. Neutrophil extracellular traps stimulate immunity response in systemic lupus erythematosus via exposure of antigens which are usually protected by plasma membrane, by decreasing T lymphocyte activation threshold and by activating auto-reactive B cells [44].

4. MACROPHAGES

Macrophages in Malignancies

Macrophages may be stratified into two groups: proinflammatory (M-1) and antiinflammatory (M-2). M1 stimulate inflammatory processes by releasing proinflammatory cytokines e.g. tumor necrosis factor alpha, interleukin 1 alpha, interleukin 1 beta, interleukin 6, interleukin 12, interleukin 18 and interleukin 23, as well as by producing reactive oxygen species and RNS [45,46]. M1 macrophages release high amounts of major histocompatibility complex which enables the acquired immunity activation. M2 release high amounts of interleukin 10, prostaglandin E2 and transforming growth factor beta, cytokines involved in protection against inflammation [47,48]. M2 release high amounts of arginine amidinase 1, low amounts of major histocompatibility complex class2, and mannose receptor [49].

Tumor associated macrophages involve both M-1 and M-2. Macrophages were suggested to exert proinflammatory anti-tumour activity (M-1) in early stages of malignancies and antiinflammatory protumor activity (M-2) in advanced stages [50,51].

Macrophages in Autoimmunity Disorders

In multiple autoimmune diseases macrophages exhibit M-1 proinflammatory phenotype, e.g. rheumatoid arthritis, systemic lupus erythematosus, SjS, type 1 diabetes, PBC. Although, M-2 macrophages were observed in fibrotic autoimmune diseases e.g. scleroderma and IBD. In MS, whereas the majority of macrophages in the lesions exhibit M-1 phenotype, a big portion of macrophages exhibit both M-1 and M-2 phenotypes [52].

5. REACTIVE OXYGEN SPECIES

Reactive Oxygen Species in Malignancies

ROS concentrations are high in TME. As tumour progresses, reactive oxygen species aggregate in the tumor microenvironment of solid malignancies, which is caused by excessive generation by tumour Mt and NADPH oxidase. Moreover, reactive oxygen species are expressed to the tumor microenvironment by CAF, tumor associated macrophages and MDSC. The impacts of reactive oxygen species on malignancy proliferation are intricate. They are partially mediated by interplay of reactive oxygen species with regulatory T cells, but there could be more pathways. Examples of such interplay are reviewed below [53,54].

Reactive Oxygen Species Are Required for Regulatory T Cell Function

In mice, Mt RC complex 3 ablation can cause impairment of Mt OXPHOS. In this case, the regulatory T cells lose their ability to inhibit without alterations of their proliferative activity and survival [55].

Reactive Oxygen Species and Regulatory T Cells Mutually Promote Each Other's Function

In vitro and in vivo studies have shown that reactive oxygen species produced my macrophages nicotinamide adenine dinucleotide phosphate complex increase levels and activity of regulatory T cells. Additionally, studies in a rat model of psoriasis demonstrated that reactive oxygen species protect against psoriatic dermatitis caused by imiquimod via stimulation of regulatory T cell activity. At the same time, transforming growth factor beta released by regulatory T cells promoted production of reactive oxygen species by nicotinamide adenine dinucleotide phosphate oxidase. Consistently, immunity inhibition in TME caused by regulatory T cells is mediated by reactive oxygen species produced by regulatory T cells [56,57].

Reactive oxygen species stimulate major histocompatibility complex-I expression in malignant cells (which enhance canceroprotective activity of CD8+ T cells)

Major histocompatibility complex-I expression in malignant cells was proved to elevate OS. This elevated expression of major histocompatibility complex-I enables the recognition of malignant cells by CD-8+ T cells and enhances their attack on tumour cells [58].

Decrease In Reactive Oxygen Species Generation by Dcs Hinders Their Major Histocompatibility Complex-I Machinery and Disrupts Their Role in Cancerоprotective Immunity

Mt ROS are implicated in cross-presentation of major histocompatibility complex-I antigens by plasmacytoid DCs (pDCs). Decrease in Mt production of ROS by pDCs leads to a considerable reduction in these cells' capacity of promoting CD-8+ T cell response after cross-presentation. This phenomenon was observed in normal DCs, where nicotinamide adenine dinucleotide phosphate oxidase isoform NOX-2 was identifies as vital for effective antigen crosspresentation to CD-8+ T cells [59]. NOX-2 is an enzyme which is crucial for production of ROS by Mt. NOX-2 deficiency in dendritic cells leads to cross-presentation impairment. DCs from subjects with CGD with disrupted NOX-2 catalytic unit demonstrated impaired antigen cross-presentation to CD-8+ T cells. Whereas DCs are of great importance in regulation of malignancies by acquired immune system, a decrease in reactive oxygen species generation by DCs is believed to induce cancer [60,61].

Moderately-High Concentrations of Reactive Oxygen Species Stimulate Solid Cancers, While Low Concentrations Are Cytostatic and Elevated Concentrations Are Cytotoxic

Impact of reactive oxygen species on growth of tumours can be mediated by regulatory T cells, although, there could be other pathways for it. At pre-malignant stages reactive oxygen species can trigger cancer by causing OS and mutations of single nucleotide polymorphisms (SNP) in anti-oncogenes e.g. TP-53 [62,63]. As tumour progresses, the elevated concentrations of reactive oxygen species in tumor microenvironment facilitates tumour proliferation by stimulating function of regulatory T cells. Moreover, reactive oxygen species trigger activation of some traditional pathways implicates in tumour development, e.g. nuclear factor kappa B pathway, mitogen-activated protein kinase pathway, and PI-3K/PTEN pathway. ROS can also facilitate the progression of tumour metastases by promoting EMT and by suppressing anoikis, a kind of programmed cellular death triggered by its detachment from ECM [64].

Such pro-tumor effects of elevated concentrations of reactive oxygen species promote tumor development. Although, greatly elevated concentrations of oxidative substances can lead to the injury of tumour tissue. High concentrations of reactive oxygen species promote cellular apoptotic, necrotic and ferroptotic processes. Hereby, moderately-high concentrations of reactive oxygen species in the tumor microenvironment could be optimal for tumour development [65,66]. Hereby, regulation of reactive oxygen species balance is necessary for tumour development. Moderately-high intracellular an extracellular concentrations of reactive oxygen species stimulate solid tumor propagation, tumor metastases as well as angiogenesis, while excessive concentrations trigger tumor cellular death, and low concentrations of reactive oxygen species are cytostatic [67,68].

6. REACTIVE OXYGEN SPECIES IMPACT ON AUTOIMMUNE DISORDERS

Low Concentrations of Reactive Oxygen Species Induce Autoimmune Diseases

CGD is a rare condition which involves genetic disorders. It develops due to impairments of nicotinamide adenine dinucleotide phosphate oxidase units. Elevated rates of various autoimmune disorders were detected in subjects with chronic granulomatous disease. Human and animal experimental studies showed that there might be a connection between reactive oxygen species deficit and autoimmunity disorders, e.g. SLE, RA, GBS, psoriasis [69].

Low Concentrations of Reactive Oxygen Species Disrupt Activity of Regulatory R Cells, Which Leads to Autoimmune Disorders, And Increased Concentrations Alleviate Autoimmune Disorders

Kim and colleagues conducted a study in murine model and discovered that psoriatic dermatitis caused by imiquimod was alleviated by increased concentrations of reactive oxygen species, while reduced concentrations of reactive oxygen species impaired function of regulatory R cells and exacerbated the condition. These findings indicate that regulatory T cells dysfunction under reduced concentrations of reactive oxygen species could facilitate autoimmunity [70].

Excessive concentrations of reactive oxygen species (OS) lie at the core of regulatory T cells damage that facilitates lupus and EAE

Strickland and colleagues discovered that T lymphocytes stimulated with oxidants promoted lupus-like disorders in murine model. Additionally, SLE-relate genes were elevated by reactive oxygen species. This impact was the most significant with an oxidant peroxonitrite. Peroxonitrite anion is in equilibrium with peroxonitrous acid. This acid quickly disintegrates in nonalkaline medium to •NO2 and •OH (approximately 30% yield). The rest of the acid is isomerized rapidly to NO−3

[k=1,2s-1]. The researchers applied 20 μM peroxonitrite solution to treat T lymphocytes. Such oxidative media promoted the disorder [71].

T lymphocyte Mt function impairment was suggested to produce OS in systemic lupus erythematosus. Mt OS and deoxyribonucleic acid damage was observed in regulatory T cells derived from subjects with autoimmune diseases. This Mt OS and deoxyribonucleic acid damage that led to death of regulatory R cells, has also been detected in mice with experimental autoimmune encephalitis. OS was proved to have an impact on the regulatory T cells/T helper 17 cells balance in systemic lupus erythematosus. These discoveries suggest that OS, i.e. excessive concentrations of reactive oxygen species, stimulates autoimmune disorders [72].

Immunity Inhibiting Agents Promote Production of ROS In Kidney Transplant Subjects

Kidney transplant recipients who did not show any adverse effects following the procedure and exhibited stable kidney functioning were administered with several immunity inhibiting compounds prior to the transplant and as a result demonstrated considerable elevation in concentrations of reactive oxygen species [73].

7. MAJOR HISTOCOMPATIBILITY COMPLEX-I

Major Histocompatibility Complex-I In Cancer

Major Histocompatibility Complex-I Promotes the Inhibiting Activity of Regulatory T Cells Which Facilitates Malignancies

Mu and colleagues conducted a study in a murine model and discovered that major histocompatibility complex-I transcription is stimulated by the TF FOX-P3 in T lymphocytes. This elevates expression of major histocompatibility complex-I in CD-4(+)CD-25(+) Tregs more than in traditional CD-4(+)CD-25(-) Tregs. The researchers detected that expression of major histocompatibility complex-I by regulatory T cells partly accounts for their regulation activity. Inhibiting function of regulatory T cells promotes advanced malignancies as well as metastases [74]. The authors mentioned a trial that revealed that CD-8+ T cells interplay with major histocompatibility complex-I on regulatory T cells is necessary for activation of regulatory T cells. T-cell receptors released in peripheral regulatory T cells is able to identify foreign antigens with significant affinity. Regulatory T cells inhibiting effect specific for antigens is due to regulatory T cells-dendritic cells interplay. There has been suggested a mechanism by which dendritic cells are presenting antigens to regulatory T cells as part of major histocompatibility complex-II, by means of regulatory T cell T-cell receptor [75]. This leads to production of tolerogenic dendritic cells specific for antigens. This could imply that such antigens could then be binding to major histocompatibility complex-I to create protein-major histocompatibility complex-I- complex, which could enable CD-8+ T cells to identify regulatory T cells, the same way they identify malignant cells, prior to their direct activation [76].

Transforming Growth Factor Beta Inhibits Expression of Major Histocompatibility Complex-I

A study in transforming growth factor beta 1 null murine model showed an inhibition of major histocompatibility complex-I expression by transforming growth factor beta 1, where increased messenger RNA levels of major histocompatibility complex I and II were observed in comparison to healthy or transforming growth factor beta 1 heterozygous controls. Two incubated human uvea cancer cell lines, with transforming growth factor beta present, produced more than fifty percent reduction in the expression of major histocompatibility complex I antigens [77].

Tumours Escape Immunity Control Via Impairment of Major Histocompatibility Complex-I Antigen Presenting Machinery

Peptide-major histocompatibility complex I complexes mediate CD-8+ T cell attacks on tumours. Several solid tumours show reduced expression of major histocompatibility complex-I antigen presentation, hereby avoiding the immunity control by CD-8+ T cells [78].

8. MAJOR HISTOCOMPATIBILITY COMPLEX-I IN AUTOIMMUNITY

Major Histocompatibility Complex-I Impact on Autoimmune Diseases Is Controversial and Limited to Few Disorders

BXSB-Yaa is a mouse strain which develops sudden lupus-like disorder. It was shown that BXSB-Yaa mice with microglobulin beta 2 (B2M) deficit and major histocompatibility complex I dysfunction exhibit more severe lupus-like disorders than BXSB-Yaa control group. MRL/lpr murine strain is also a model of spontaneous SLE. MRL/lpr mice with beta-2-m deficit demonstrated rapid lupus cutaneous lesions as well as alleviated kidney inflammation [79,80]. Although, other findings were conflicting. Major histocompatibility complex-I mitigated lupus symptoms in lupus mice and caused resistance to experimental SLE inducing in other murine model. Hereby, major histocompatibility complex-I impact on

lupus is not fully known. It was reported that major histocompatibility complex-I alleles are related to only several autoimmune disorders (psoriasis, Bekhterev's disease) while major histocompatibility complex-II alleles are related to larger group of diseases (rheumatoid arthritis, type 1 diabetes, multiple sclerosis, coeliac disease and berylliosis). These findings indicate that major histocompatibility complex-I is not implicated in development of all autoimmune diseases and its impact is unclear [81].

9. MAJOR HISTOCOMPATIBILITY COMPLEX-II

Major Histocompatibility Complex-II In Cancer

Antigen presentation to CD-4+ T cells mediated by major histocompatibility complex-II facilitates immunity response by Th cells and CD-8+ T cells (and CD-4+ cells are necessary for activity of the latter). Whereas major histocompatibility complex-II is released mostly by antigen presenting DCs, macrophages and B cells, as well as by TECs, other types of cells can also release major histocompatibility complex-II, e.g., malignant cells [82]. Besides alterations in expression of major histocompatibility complex-I by malignancies, alterations in the expression of major histocompatibility complex-II by malignant cells were also detected. Levels of major histocompatibility complex-II alleles in subjects with malignancies differ from levels in healthy controls. Such distinctions rely on cancer type. They were proved to be in correlation with the cancer progression risk and with responding to therapy. CD-4+ T cells and expression of major histocompatibility complex-II could be vital in antitumor immune system. Consistently, response to blockade of PD1 in mice with melanoma needed CD-4+ T cells apart from CD-8+ T cells, as well as co-stimulation by DCs and macrophages [83].

Regulatory T Cells Deplete MHC-II From Dcs

Akkaya and colleagues performed a study in a murine model and demonstrated that regulatory T cells deplete peptide-major histocompatibility complex-II complex from dendritic cells, thus inhibiting immunity. As progressed malignancy is a condition with high levels of regulatory T cells, this activity is believed to stimulate immunity escape in progressed stages of cancer [84].

Transforming Growth Factor Beta Decreases Expression Of MHC-II In Macrophages

Delvig and colleagues showed that by decreasing expression of major histocompatibility complex-II on macrophages, transforming growth factor beta suppresses antigen presentation of 2 T cell antigenic determinants. Moreover, transforming growth factor beta decreased the constitutive expression of CIITA, invariant chain and HLADO messenger RNA. These results were validated by another trial, that demonstrated MHC-II transactivator diminution mediated by regulatory T cells. Whereas regulatory T cells are an important source of transforming growth factor beta, these discoveries are in line with the previous evidence of regulatory T cells depleting major histocompatibility complex-II [85].

Expression Of Major Histocompatibility Complex-II Reduces While Cancer Develops

Activity of regulatory T cells and concentrations of transforming growth factor beta elevate in blood and in tumor microenvironment during progression of malignancies. Drawing on the evidence mentioned above, expression of major histocompatibility complex-II is believed to decrease in development of malignancy. Accordingly, expression of major histocompatibility complex-II allele HLADRB1*07 was elevated in lymph nodes of subjects with early NSCLC, in comparison to subjects with progressed cancer [86].

Hereby, expression of major histocompatibility complex-II is vital for efficient antitumor immune activity. Suppression of major histocompatibility complex-II expression mediated by regulatory T cells stimulates tumor immunity escape. [87,88].

Major Histocompatibility Complex-II In Autoimmunity

Genomic trials showed that connections between major histocompatibility complex and autoimmunity are mainly due to major histocompatibility complex-II alleles. Some alleles elevate the risk of progression of several autoimmune diseases (a direct correlation), and other alleles decrease the risk (an inverse correlation) [89,90]. Basedow’s disease, narcolepsy, Hashimoto's disease, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, systemic lupus erythematosus, UC and CD are linked to major histocompatibility complex-II polymorphism. UC and CD are also related to MHC-I, but the connection is not as consistent [91,92].

Pronounced expression of major histocompatibility complex-II in murine retina was detected in a murine model of EAU. Increased endothelial major histocompatibility complex-II expression was detected in subjects with rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, Crohn’s disease and DCM. Peripheral blood mononuclear cells, obtained from patients with homozygosity for auto-immune vitiligo high-risk single nucleotide polymorphism haplotype, were stimulated with pathogens which led to elevated generation of interferon gamma and interleukin 1 beta in comparison to patients with homozygosity for low-risk haplotype [93,94].

Autoimmune diseases are linked to major histocompatibility complex-II polymorphism. Expression of major histocompatibility complex-II is enhanced in autoimmune diseases and it promotes proinflammatory effects [95].

10. THE EMERGENCE OF CANCER IMMUNOTHERAPY EMPHASIZES THE INTRICATE CONNECTION BETWEEN AUTOIMMUNITY AND MALIGNANCIES

In the past ten years, advancements in cancer immunotherapy provided considerable survival advantages to some individuals by enhancing anti-tumour immune response via immunity checkpoint suppression targeting CTLA-4, PD1, PDL1. Although, these novel strategies may cause autoimmunity toxicity even in subjects with no autoimmunity disorders [96]. Moreover, checkpoint blockade immunotherapy in subjects with malignancies and autoimmunity disorders can aggravate autoimmune diseases. Bender and colleagues reported that a retrospective study of immune checkpoint blockade in subjects with malignancies and autoimmunity disorders and in subjects just with malignancies showed that the first group of subjects exhibited considerably higher occurrence of hospital admission and need for immunosuppressive therapy [97,98]. Abdel-Wahab and colleagues reported that both multi-center trial and systematic review revealed that more than seventy percent of subjects with autoimmunity disorders who were treated with checkpoint blockade immunotherapy showed aggravation of these autoimmunity disorders or other detrimental effects associated with immunity [99].

Subjects with autoimmune diseases (ADs) typically receive immunosuppressive therapy. Such individuals are believed to have higher risk of malignancies. For instance, anti-TNF treatment was an advancement for ADs and is considered to alleviate RA, CD, UC, psoriasis, Bekhterev's disease, as was reported by Monaco and colleagues [100]. In the beginning of the twenty first century, anti-TNF treatment for RA was associated with higher risk of cancer and infections. Although, these discoveries were conflicting with findings from recent trials: application of anti-TNF treatment following cancer diagnosis does not affect malignancies (Waljee and colleagues) [101], subjects with IBD who received this treatment show reduced CRC rates. These discoveries indicate that more research is necessary in the field of association between immunity inhibition and risk of malignancies [101].

Intricate associations between auto-immunity and malignancies are further complicated by concept of auto-immunity caused by tumour defense, where immunity response against malignancy consequently attacks healthy cells. This hypothesis was suggested to interpret the relationship between malignancies and auto-immunity at least for dermatomyositis (DM) and thyroid gland [102]. Thyroid auto-immunity and malignancies are closely connected, as was reported by Ferrari and colleagues [103]. It was suggested that tumour antigens that exhibit immunogenicity can be shared with healthy tissues of the thyroid gland, and immunity response to these antigens induce ADs as well [104]. Subjects with DM show higher risk of malignancies, and it was suggested that alterations in key DM genes can generate neo-antigens which are able to induce particular anti-tumour responses, although, via cross-reaction or antigenic determinant spreading such neo-antigens could also target the immunity response at normal tissues [105,106].

Whereas further research is required to elucidate different aspects of the complex associations between ADs and malignancies, this review concentrates on a novel aspect of these associations: auto-immunity could have a major role in promoting development of tumors, as was proposed by epidemiologic tendencies in cancer and ADs and by available research results [107].

Table 2. Molecular Mediators Linking Autoimmunity and Cancer

Mediator	Role in Cancer	Role in Autoimmunity
Reactive Oxygen Species (ROS)	Moderate levels promote tumor growth, angiogenesis, and metastasis; excessive ROS induces tumor cell death	Low ROS impairs Treg function → autoimmunity (CGD, psoriasis, SLE); high ROS damages Tregs and DNA → exacerbates autoimmunity (SLE, EAE)
MHC-I	Downregulation allows tumors to evade CD8+ T cells; Treg expression of MHC-I promotes immune suppression	Limited role; associated with psoriasis, ankylosing spondylitis; controversial in SLE models
MHC-II	Expression by tumor cells and APCs crucial for anti-tumor immunity; suppressed by Tregs and TGF-β in advanced cancer	Strongly linked to genetic susceptibility for ADs (RA, MS, T1DM, SLE, IBD); overexpression contributes to chronic inflammation
Cytokines (IL-2, IL-17, IL-23, IFN-γ, TGF-β, TNF-α)	IL-2 protective; IL-17/23 ambivalent; IFN-γ both suppresses and promotes tumors; TGF-β drives tumor immune evasion	IL-17, IL-23 central in RA, psoriasis, IBD; IFN-γ and TNF-α perpetuate tissue inflammation; TGF-β mediates fibrosis (scleroderma, IBD)
Immune Checkpoints (PD-1, CTLA-4)	Blockade enhances anti-tumor immunity (melanoma, RCC, NSCLC), but increases risk of autoimmunity	ICI therapy frequently worsens pre-existing autoimmune diseases; requires careful management

11. CONCLUSION

The intricate interplay between autoimmune disorders and malignancies underscores the duality of immune responses, where autoimmunity can both contribute to tumor development and provide a protective effect against cancer progression. Our review highlights the complex relationships among various immune cell types and their roles in mediating these processes, suggesting that chronic inflammation and dysregulated immune responses may significantly influence malignancy risk in individuals with autoimmune conditions. Advances in cancer immunotherapy bring additional complexity, as treatments targeting immune checkpoints can exacerbate autoimmune diseases while offering potential benefits against tumors.

Future research is essential to unravel these complex interactions, as understanding the underlying mechanisms could pave the way for more effective therapeutic strategies that harness the beneficial aspects of the immune response while minimizing adverse effects. Ultimately, a refined perspective on the connections between autoimmunity and malignancies may lead to innovative approaches in the prevention, diagnosis, and treatment of these challenging conditions, improving patient outcomes and advancing the field of immunology.

Author Contributions: writing—original draft preparation, A.V.P.; writing—review and editing, A.A.V, E.R.K., O.N.M., A.S.U., A.N.O.
Funding: This research was funded by Russian Science Foundation, grant number 23-15-00140
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Acknowledgments: Not applicable.
Conflicts of Interest: The authors declare no conflicts of interest.

REFERENCES

[1] Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease: A Systematic Review. Ann Intern Med. 2018 Jan 16;168(2):121-130. doi: 10.7326/M17-2073. Epub 2018 Jan 2. PMID: 29297009.
[2] Amano H, Amano E, Moll T, Marinkovic D, Ibnou-Zekri N, Martinez-Soría E, Semac I, Wirth T, Nitschke L, Izui S. The Yaa mutation promoting murine lupus causes defective development of marginal zone B cells. J Immunol. 2003 Mar 1;170(5):2293-301. doi: 10.4049/jimmunol.170.5.2293. PMID: 12594250.
[3] Anjani G, Vignesh P, Joshi V, Shandilya JK, Bhattarai D, Sharma J, Rawat A. Recent advances in chronic granulomatous disease. Genes Dis. 2019 Jul 27;7(1):84-92. doi: 10.1016/j.gendis.2019.07.010. PMID: 32181279; PMCID: PMC7063432.

[4] Attique I, Haider Z, Khan M, Hassan S, Soliman MM, Ibrahim WN, Anjum S. Reactive Oxygen Species: From Tumorigenesis to Therapeutic Strategies in Cancer. Cancer Med. 2025 May;14(10):e70947. doi: 10.1002/cam4.70947. PMID: 40377005; PMCID: PMC12082284.
[5] Barcellini W, Fattizzo B. Autoimmune Complications of Lymphoproliferative Diseases. Hematol Oncol. 2025 Jun;43 Suppl 2(Suppl 2):e70063. doi: 10.1002/hon.70063. PMID: 40517537; PMCID: PMC12167643.
[6] Barzaghi F, Passerini L. IPEX Syndrome: Improved Knowledge of Immune Pathogenesis Empowers Diagnosis. Front Pediatr. 2021 Feb 22;9:612760. doi: 10.3389/fped.2021.612760. PMID: 33692972; PMCID: PMC7937806.
[7] Basak U, Sarkar T, Mukherjee S, Chakraborty S, Dutta A, Dutta S, Nayak D, Kaushik S, Das T, Sa G. Tumor-associated macrophages: an effective player of the tumor microenvironment. Front Immunol. 2023 Nov 16;14:1295257. doi: 10.3389/fimmu.2023.1295257. PMID: 38035101; PMCID: PMC10687432.
[8] Bode K, Hauri-Hohl M, Jaquet V, Weyd H. Unlocking the power of NOX2: A comprehensive review on its role in immune regulation. Redox Biol. 2023 Aug;64:102795. doi: 10.1016/j.redox.2023.102795. Epub 2023 Jun 22. PMID: 37379662; PMCID: PMC10320620.
[9] Bustos NI, Sotomayor CG, Pol RA, Navis GJ, Bakker SJL. Polyphenols and Novel Insights Into Post-kidney Transplant Complications and Cardiovascular Disease: A Narrative Review. Front Cardiovasc Med. 2021 Nov 16;8:751036. doi: 10.3389/fcvm.2021.751036. PMID: 34869655; PMCID: PMC8635050.
[10] Byrne WL, Mills KH, Lederer JA, O'Sullivan GC. Targeting regulatory T cells in cancer. Cancer Res. 2011 Nov 15;71(22):6915-20. doi: 10.1158/0008-5472.CAN-11-1156. Epub 2011 Nov 8. PMID: 22068034; PMCID: PMC4287207.
[11] Canton M, Sánchez-Rodríguez R, Spera I, Venegas FC, Favia M, Viola A, Castegna A. Reactive Oxygen Species in Macrophages: Sources and Targets. Front Immunol. 2021 Sep 30;12:734229. doi: 10.3389/fimmu.2021.734229. PMID: 34659222; PMCID: PMC8515906.
[12] Cavalli G, Hayashi M, Jin Y, Yorgov D, Santorico SA, Holcomb C, Rastrou M, Erlich H, Tengesdal IW, Dagna L, Neff CP, Palmer BE, Spritz RA, Dinarello CA. MHC class II super-enhancer increases surface expression of HLA-DR and HLA-DQ and affects cytokine production in autoimmune vitiligo. Proc Natl Acad Sci U S A. 2016 Feb 2;113(5):1363-8. doi: 10.1073/pnas.1523482113. Epub 2016 Jan 19. PMID: 26787888; PMCID: PMC4747741.
[13] Chaput N, Darrasse-Jèze G, Bergot AS, Cordier C, Ngo-Abdalla S, Klatzmann D, Azogui O. Regulatory T cells prevent CD8 T cell maturation by inhibiting CD4 Th cells at tumor sites. J Immunol. 2007 Oct 15;179(8):4969-78. doi: 10.4049/jimmunol.179.8.4969. PMID: 17911581.
[14] Chaudhary B, Elkord E. Regulatory T Cells in the Tumor Microenvironment and Cancer Progression: Role and Therapeutic Targeting. Vaccines (Basel). 2016 Aug 6;4(3):28. doi: 10.3390/vaccines4030028. PMID: 27509527; PMCID: PMC5041022.
[15] Chen D, Guo Z, Yao L, Sun Y, Dian Y, Zhao D, Ke Y, Zeng F, Zhang C, Deng G, Li L. Targeting oxidative stress-mediated regulated cell death as a vulnerability in cancer. Redox Biol. 2025 Jul;84:103686. doi: 10.1016/j.redox.2025.103686. Epub 2025 May 19. PMID: 40424719; PMCID: PMC12159232.
[16] Chen Y, Yu D, Qian H, Shi Y, Tao Z. $CD8^{+}$T cell-based cancer immunotherapy. J Transl Med. 2024 Apr 29;22(1):394. doi: 10.1186/s12967-024-05134-6. PMID: 38685033; PMCID: PMC11057112.
[17] Cinier J, Hubert M, Besson L, Di Roio A, Rodriguez C, Lombardi V, Caux C, Ménétrier-Caux C. Recruitment and Expansion of Tregs Cells in the Tumor Environment-How to Target Them? Cancers (Basel). 2021 Apr 13;13(8):1850. doi: 10.3390/cancers13081850. PMID: 33924428; PMCID: PMC8069615.
[18] Clement CC, Becerra A, Yin L, Zolla V, Huang L, Merlin S, Follenzi A, Shaffer SA, Stern LJ, Santambrogio L. The Dendritic Cell Major Histocompatibility Complex II (MHC II) Peptidome Derives from a Variety of Processing Pathways and Includes Peptides with a Broad Spectrum of HLA-DM Sensitivity. J Biol Chem. 2016 Mar 11;291(11):5576-5595. doi: 10.1074/jbc.M115.655738. Epub 2016 Jan 6. PMID: 26740625; PMCID: PMC4786700.
[19] Cornel AM, Mimpen IL, Nierkens S. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. Cancers (Basel). 2020 Jul 2;12(7):1760. doi: 10.3390/cancers12071760. PMID: 32630675; PMCID: PMC7409324.
[20] Cruz FM, Orellano LAA, Chan A, Rock KL. Alternate MHC I Antigen Presentation Pathways Allow CD8+ T-cell Recognition and Killing of Cancer Cells in the Absence of β2M or TAP. Cancer Immunol Res. 2025 Jan 9;13(1):98-108. doi: 10.1158/2326-6066.CIR-24-0320. PMID: 39485834; PMCID: PMC11717633.
[21] Cruz-Tapias P, Castiblanco J, Anaya JM. Major histocompatibility complex: Antigen processing and presentation. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, et al., editors. Autoimmunity: From Bench to Bedside [Internet].

Bogota (Colombia): El Rosario University Press; 2013 Jul 18. Chapter 10. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459467/

[22] Eshwar V, Kamath A, Shastry R, Shenoy AK, Kamath P. A Review of the Safety of Interleukin-17A Inhibitor Secukinumab. Pharmaceuticals (Basel). 2022 Nov 7;15(11):1365. doi: 10.3390/ph15111365. PMID: 36355537; PMCID: PMC9695424.

[23] Ferrari SM, Fallahi P, Elia G, Ragusa F, Ruffilli I, Paparo SR, Antonelli A. Thyroid autoimmune disorders and cancer. Semin Cancer Biol. 2020 Aug;64:135-146. doi: 10.1016/j.semcancer.2019.05.019. Epub 2019 May 31. PMID: 31158464.

[24] Frazzei G, van Vollenhoven RF, de Jong BA, Siegelaar SE, van Schaardenburg D. Preclinical Autoimmune Disease: a Comparison of Rheumatoid Arthritis, Systemic Lupus Erythematosus, Multiple Sclerosis and Type 1 Diabetes. Front Immunol. 2022 Jun 30;13:899372. doi: 10.3389/fimmu.2022.899372. PMID: 35844538; PMCID: PMC9281565.

[25] Fresneda Alarcon M, McLaren Z, Wright HL. Neutrophils in the Pathogenesis of Rheumatoid Arthritis and Systemic Lupus Erythematosus: Same Foe Different M.O. Front Immunol. 2021 Mar 4;12:649693. doi: 10.3389/fimmu.2021.649693. PMID: 33746988; PMCID: PMC7969658.

[26] Geiser AG, Letterio JJ, Kulkarni AB, Karlsson S, Roberts AB, Sporn MB. Transforming growth factor beta 1 (TGF-beta 1) controls expression of major histocompatibility genes in the postnatal mouse: aberrant histocompatibility antigen expression in the pathogenesis of the TGF-beta 1 null mouse phenotype. Proc Natl Acad Sci U S A. 1993 Nov 1;90(21):9944-8. doi: 10.1073/pnas.90.21.9944. PMID: 8234339; PMCID: PMC47689.

[27] Giese MA, Hind LE, Huttenlocher A. Neutrophil plasticity in the tumor microenvironment. Blood. 2019 May 16;133(20):2159-2167. doi: 10.1182/blood-2018-11-844548. Epub 2019 Mar 21. PMID: 30898857; PMCID: PMC6524564.

[28] Hagerling C, Werb Z. Neutrophils: Critical components in experimental animal models of cancer. Semin Immunol. 2016 Apr;28(2):197-204. doi: 10.1016/j.smim.2016.02.003. Epub 2016 Mar 11. PMID: 26976824; PMCID: PMC4934898.

[29] Huang R, Kang T, Chen S. The role of tumor-associated macrophages in tumor immune evasion. J Cancer Res Clin Oncol. 2024 May 7;150(5):238. doi: 10.1007/s00432-024-05777-4. PMID: 38713256; PMCID: PMC11076352.

[30] Ibis B, Aliazis K, Cao C, Yenyuwadee S, Boussiotis VA. Immune-related adverse effects of checkpoint immunotherapy and implications for the treatment of patients with cancer and autoimmune diseases. Front Immunol. 2023 Jun 5;14:1197364. doi: 10.3389/fimmu.2023.1197364. PMID: 37342323; PMCID: PMC10277501.

[31] Ishina IA, Zakharova MY, Kurbatskaia IN, Mamedov AE, Belogurov AA Jr, Gabibov AG. MHC Class II Presentation in Autoimmunity. Cells. 2023 Jan 14;12(2):314. doi: 10.3390/cells12020314. PMID: 36672249; PMCID: PMC9856717.

[32] Izui S, Merino R, Fossati L, Iwamoto M. The role of the Yaa gene in lupus syndrome. Int Rev Immunol. 1994;11(3):211-30. doi: 10.3109/08830189409061728. PMID: 7930846.

[33] Jarocki M, Karska J, Kowalski S, Kiełb P, Nowak Ł, Krajewski W, Saczko J, Kulbacka J, Szydełko T, Małkiewicz B. Interleukin 17 and Its Involvement in Renal Cell Carcinoma. J Clin Med. 2022 Aug 24;11(17):4973. doi: 10.3390/jcm11174973. PMID: 36078902; PMCID: PMC9457171.

[34] Jiang T, Zhou C, Ren S. Role of IL-2 in cancer immunotherapy. Oncoimmunology. 2016 Apr 25;5(6):e1163462. doi: 10.1080/2162402X.2016.1163462. PMID: 27471638; PMCID: PMC4938354.

[35] Jou E. Type 1 and type 2 cytokine-mediated immune orchestration in the tumour microenvironment and their therapeutic potential. Explor Target Antitumor Ther. 2023;4(3):474-497. doi: 10.37349/etat.2023.00146. Epub 2023 Jun 30. PMID: 37455828; PMCID: PMC10345208.

[36] Kerneur C, Cano CE, Olive D. Major pathways involved in macrophage polarization in cancer. Front Immunol. 2022 Oct 17;13:1026954. doi: 10.3389/fimmu.2022.1026954. PMID: 36325334; PMCID: PMC9618889.

[37] Khan S, Gerber DE. Autoimmunity, checkpoint inhibitor therapy and immune-related adverse events: A review. Semin Cancer Biol. 2020 Aug;64:93-101. doi: 10.1016/j.semcancer.2019.06.012. Epub 2019 Jul 19. PMID: 31330185; PMCID: PMC6980444.

[38] Khan S, Gerber DE. Autoimmunity, checkpoint inhibitor therapy and immune-related adverse events: A review. Semin Cancer Biol. 2020 Aug;64:93-101. doi: 10.1016/j.semcancer.2019.06.012. Epub 2019 Jul 19. PMID: 31330185; PMCID: PMC6980444.

[39] Kim HR, Lee A, Choi EJ, Hong MP, Kie JH, Lim W, Lee HK, Moon BI, Seoh JY. Reactive oxygen species prevent imiquimod-induced psoriatic dermatitis through enhancing regulatory T cell function. PLoS One. 2014 Mar 7;9(3):e91146. doi: 10.1371/journal.pone.0091146. PMID: 24608112; PMCID: PMC3946742.
[40] Konig MF, Andrade F. A Critical Reappraisal of Neutrophil Extracellular Traps and NETosis Mimics Based on Differential Requirements for Protein Citrullination. Front Immunol. 2016 Nov 4;7:461. doi: 10.3389/fimmu.2016.00461. PMID: 27867381; PMCID: PMC5095114.
[41] Kurup S, Pozun A. Biochemistry, Autoimmunity. [Updated 2022 Dec 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK576418/
[42] Levandowski CB, Mailloux CM, Ferrara TM, Gowan K, Ben S, Jin Y, McFann KK, Holland PJ, Fain PR, Dinarello CA, Spritz RA. NLRP1 haplotypes associated with vitiligo and autoimmunity increase interleukin-1β processing via the NLRP1 inflammasome. Proc Natl Acad Sci U S A. 2013 Feb 19;110(8):2952-6. doi: 10.1073/pnas.1222808110. Epub 2013 Feb 4. PMID: 23382179; PMCID: PMC3581876.
[43] Li K, Deng Z, Lei C, Ding X, Li J, Wang C. The Role of Oxidative Stress in Tumorigenesis and Progression. Cells. 2024 Mar 2;13(5):441. doi: 10.3390/cells13050441. PMID: 38474405; PMCID: PMC10931308.
[44] Li M, Wang M, Wen Y, Zhang H, Zhao GN, Gao Q. Signaling pathways in macrophages: molecular mechanisms and therapeutic targets. MedComm (2020). 2023 Sep 11;4(5):e349. doi: 10.1002/mco2.349. PMID: 37706196; PMCID: PMC10495745.
[45] Li X, You J, Hong L, Liu W, Guo P, Hao X. Neoantigen cancer vaccines: a new star on the horizon. Cancer Biol Med. 2023 Dec 29;21(4):274–311. doi: 10.20892/j.issn.2095-3941.2023.0395. PMID: 38164734; PMCID: PMC11033713.
[46] Liang W, He X, Bi J, Hu T, Sun Y. Role of reactive oxygen species in tumors based on the 'seed and soil' theory: A complex interaction (Review). Oncol Rep. 2021 Sep;46(3):208. doi: 10.3892/or.2021.8159. Epub 2021 Jul 30. PMID: 34328200; PMCID: PMC8329912.
[47] Lin P, Lin Y, Chen X, Zhao X, Cui L. Decoding MHC loss: Molecular mechanisms and implications for immune resistance in cancer. Clin Transl Med. 2025 Jul;15(7):e70403. doi: 10.1002/ctm2.70403. PMID: 40673641; PMCID: PMC12268796.
[48] Lin Y, Song Y, Zhang Y, Li X, Kan L, Han S. New insights on anti-tumor immunity of $CD8^+$ T cells: cancer stem cells, tumor immune microenvironment and immunotherapy. J Transl Med. 2025 Mar 17;23(1):341. doi: 10.1186/s12967-025-06291-y. PMID: 40097979; PMCID: PMC11912710.
[49] Liou GY, Storz P. Reactive oxygen species in cancer. Free Radic Res. 2010 May;44(5):479-96. doi: 10.3109/10715761003667554. PMID: 20370557; PMCID: PMC3880197.
[50] Liu S, Wu W, Du Y, Yin H, Chen Q, Yu W, Wang W, Yu J, Liu L, Lou W, Pu N. The evolution and heterogeneity of neutrophils in cancers: origins, subsets, functions, orchestrations and clinical applications. Mol Cancer. 2023 Sep 7;22(1):148. doi: 10.1186/s12943-023-01843-6. PMID: 37679744; PMCID: PMC10483725.
[51] Llosa NJ, Geis AL, Thiele Orberg E, Housseau F. Interleukin-17 and type 17 helper T cells in cancer management and research. Immunotargets Ther. 2014 Mar 10;3:39-54. doi: 10.2147/ITT.S56529. PMID: 27471699; PMCID: PMC4918233.
[52] Luo M, Zhao F, Cheng H, Su M, Wang Y. Macrophage polarization: an important role in inflammatory diseases. Front Immunol. 2024 Apr 10;15:1352946. doi: 10.3389/fimmu.2024.1352946. PMID: 38660308; PMCID: PMC11039887.
[53] Macy AM, Herrmann LM, Adams AC, Hastings KT. Major histocompatibility complex class II in the tumor microenvironment: functions of nonprofessional antigen-presenting cells. Curr Opin Immunol. 2023 Aug;83:102330. doi: 10.1016/j.coi.2023.102330. Epub 2023 Apr 30. PMID: 37130456; PMCID: PMC10524529.
[54] Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. Int Immunol. 2015 Jan;27(1):55-62. doi: 10.1093/intimm/dxu102. Epub 2014 Nov 19. PMID: 25411043; PMCID: PMC4279876.
[55] Moorman CD, Sohn SJ, Phee H. Emerging Therapeutics for Immune Tolerance: Tolerogenic Vaccines, T cell Therapy, and IL-2 Therapy. Front Immunol. 2021 Mar 29;12:657768. doi: 10.3389/fimmu.2021.657768. PMID: 33854514; PMCID: PMC8039385.
[56] Mozes E, Kohn LD, Hakim F, Singer DS. Resistance of MHC class I-deficient mice to experimental systemic lupus erythematosus. Science. 1993 Jul 2;261(5117):91-3. doi: 10.1126/science.8316860. PMID: 8316860.
[57] Mu J, Tai X, Iyer SS, Weissman JD, Singer A, Singer DS. Regulation of MHC class I expression by Foxp3 and its effect on regulatory T cell function. J Immunol. 2014 Mar 15;192(6):2892-903. doi: 10.4049/jimmunol.1302847. Epub 2014 Feb 12. PMID: 24523508; PMCID: PMC3952169.

[58] Műzes G, Sipos F. Autoimmunity and Carcinogenesis: Their Relationship under the Umbrella of Autophagy. Biomedicines. 2023 Apr 8;11(4):1130. doi: 10.3390/biomedicines11041130. PMID: 37189748; PMCID: PMC10135912.

[59] Nakamura H, Takada K. Reactive oxygen species in cancer: Current findings and future directions. Cancer Sci. 2021 Oct;112(10):3945-3952. doi: 10.1111/cas.15068. Epub 2021 Aug 2. PMID: 34286881; PMCID: PMC8486193.

[60] Nishikawa H, Koyama S. Mechanisms of regulatory T cell infiltration in tumors: implications for innovative immune precision therapies. J Immunother Cancer. 2021 Jul;9(7):e002591. doi: 10.1136/jitc-2021-002591. Erratum in: J Immunother Cancer. 2021 Sep;9(9):e002591corr1. doi: 10.1136/jitc-2021-002591corr1. PMID: 34330764; PMCID: PMC8327843.

[61] Oberkampf M, Guillerey C, Mouriès J, Rosenbaum P, Fayolle C, Bobard A, Savina A, Ogier-Denis E, Enninga J, Amigorena S, Leclerc C, Dadaglio G. Mitochondrial reactive oxygen species regulate the induction of $CD8^+$ T cells by plasmacytoid dendritic cells. Nat Commun. 2018 Jun 8;9(1):2241. doi: 10.1038/s41467-018-04686-8. PMID: 29884826; PMCID: PMC5993805.

[62] Ogulur I, Mitamura Y, Yazici D, Pat Y, Ardicli S, Li M, D'Avino P, Beha C, Babayev H, Zhao B, Zeyneloglu C, Giannelli Viscardi O, Ardicli O, Kiykim A, Garcia-Sanchez A, Lopez JF, Shi LL, Yang M, Schneider SR, Skolnick S, Dhir R, Radzikowska U, Kulkarni AJ, Imam MB, Veen WV, Sokolowska M, Martin-Fontecha M, Palomares O, Nadeau KC, Akdis M, Akdis CA. Type 2 immunity in allergic diseases. Cell Mol Immunol. 2025 Mar;22(3):211-242. doi: 10.1038/s41423-025-01261-2. Epub 2025 Feb 17. PMID: 39962262; PMCID: PMC11868591.

[63] Parvez A, Choudhary F, Mudgal P, Khan R, Qureshi KA, Farooqi H, Aspatwar A. PD-1 and PD-L1: architects of immune symphony and immunotherapy breakthroughs in cancer treatment. Front Immunol. 2023 Dec 1;14:1296341. doi: 10.3389/fimmu.2023.1296341. PMID: 38106415; PMCID: PMC10722272.

[64] Passeri L, Marta F, Bassi V, Gregori S. Tolerogenic Dendritic Cell-Based Approaches in Autoimmunity. Int J Mol Sci. 2021 Aug 5;22(16):8415. doi: 10.3390/ijms22168415. PMID: 34445143; PMCID: PMC8395087.

[65] Peltanova B, Raudenska M, Masarik M. Effect of tumor microenvironment on pathogenesis of the head and neck squamous cell carcinoma: a systematic review. Mol Cancer. 2019 Mar 30;18(1):63. doi: 10.1186/s12943-019-0983-5. PMID: 30927923; PMCID: PMC6441173.

[66] Pisetsky DS. Pathogenesis of autoimmune disease. Nat Rev Nephrol. 2023 Aug;19(8):509-524. doi: 10.1038/s41581-023-00720-1. Epub 2023 May 10. PMID: 37165096; PMCID: PMC10171171.

[67] Pol JG, Caudana P, Paillet J, Piaggio E, Kroemer G. Effects of interleukin-2 in immunostimulation and immunosuppression. J Exp Med. 2020 Jan 6;217(1):e20191247. doi: 10.1084/jem.20191247. PMID: 31611250; PMCID: PMC7037245.

[68] Poznyak AV, Orekhov NA, Churov AV, Starodubtseva IA, Beloyartsev DF, Kovyanova TI, Sukhorukov VN, Orekhov AN. Mitochondrial Dysfunction in Systemic Lupus Erythematosus: Insights and Therapeutic Potential. Diseases. 2024 Sep 23;12(9):226. doi: 10.3390/diseases12090226. PMID: 39329895; PMCID: PMC11430897.

[69] Purhonen J, Banerjee R, Wanne V, Sipari N, Mörgelin M, Fellman V, Kallijärvi J. Mitochondrial complex III deficiency drives c-MYC overexpression and illicit cell cycle entry leading to senescence and segmental progeria. Nat Commun. 2023 Apr 24;14(1):2356. doi: 10.1038/s41467-023-38027-1. PMID: 37095097; PMCID: PMC10126100.

[70] Qu N, Xu M, Mizoguchi I, Furusawa J, Kaneko K, Watanabe K, Mizuguchi J, Itoh M, Kawakami Y, Yoshimoto T. Pivotal roles of T-helper 17-related cytokines, IL-17, IL-22, and IL-23, in inflammatory diseases. Clin Dev Immunol. 2013;2013:968549. doi: 10.1155/2013/968549. Epub 2013 Jul 14. PMID: 23956763; PMCID: PMC3728507.

[71] Rastogi I, Jeon D, Moseman JE, Muralidhar A, Potluri HK, McNeel DG. Role of B cells as antigen presenting cells. Front Immunol. 2022 Sep 8;13:954936. doi: 10.3389/fimmu.2022.954936. PMID: 36159874; PMCID: PMC9493130.

[72] Relle M, Schwarting A. Role of MHC-linked susceptibility genes in the pathogenesis of human and murine lupus. Clin Dev Immunol. 2012;2012:584374. doi: 10.1155/2012/584374. Epub 2012 Jun 19. PMID: 22761632; PMCID: PMC3385965.

[73] Richard-Miceli C, Criswell LA. Emerging patterns of genetic overlap across autoimmune disorders. Genome Med. 2012 Jan 27;4(1):6. doi: 10.1186/gm305. PMID: 22284131; PMCID: PMC3334554.

[74] Rizo-Téllez SA, Sekheri M, Filep JG. Myeloperoxidase: Regulation of Neutrophil Function and Target for Therapy. Antioxidants (Basel). 2022 Nov 21;11(11):2302. doi: 10.3390/antiox11112302. PMID: 36421487; PMCID: PMC9687284.
[75] Rőszer T. Understanding the Mysterious M2 Macrophage through Activation Markers and Effector Mechanisms. Mediators Inflamm. 2015;2015:816460. doi: 10.1155/2015/816460. Epub 2015 May 18. PMID: 26089604; PMCID: PMC4452191.
[76] Sakowska J, Arcimowicz Ł, Jankowiak M, Papak I, Markiewicz A, Dziubek K, Kurkowiak M, Kote S, Kaźmierczak-Siedlecka K, Połom K, Marek-Trzonkowska N, Trzonkowski P. Autoimmunity and Cancer-Two Sides of the Same Coin. Front Immunol. 2022 May 13;13:793234. doi: 10.3389/fimmu.2022.793234. PMID: 35634292; PMCID: PMC9140757.
[77] Santocki M, Kolaczkowska E. On Neutrophil Extracellular Trap (NET) Removal: What We Know Thus Far and Why So Little. Cells. 2020 Sep 11;9(9):2079. doi: 10.3390/cells9092079. PMID: 32932841; PMCID: PMC7565917.
[78] Shu P, Liang H, Zhang J, Lin Y, Chen W, Zhang D. Reactive oxygen species formation and its effect on $CD4^+$ T cell-mediated inflammation. Front Immunol. 2023 May 25;14:1199233. doi: 10.3389/fimmu.2023.1199233. PMID: 37304262; PMCID: PMC10249013.
[79] Strickland FM, Li Y, Johnson K, Sun Z, Richardson BC. CD4(+) T cells epigenetically modified by oxidative stress cause lupus-like autoimmunity in mice. J Autoimmun. 2015 Aug;62:75-80. doi: 10.1016/j.jaut.2015.06.004. Epub 2015 Jul 9. PMID: 26165613; PMCID: PMC4529773.
[80] Strizova Z, Benesova I, Bartolini R, Novysedlak R, Cecrdlova E, Foley LK, Striz I. M1/M2 macrophages and their overlaps - myth or reality? Clin Sci (Lond). 2023 Aug 14;137(15):1067-1093. doi: 10.1042/CS20220531. PMID: 37530555; PMCID: PMC10407193.
[81] Sun S, Liu L, Zhang J, Sun L, Shu W, Yang Z, Yao H, Zhang Z. The role of neoantigens and tumor mutational burden in cancer immunotherapy: advances, mechanisms, and perspectives. J Hematol Oncol. 2025 Sep 2;18(1):84. doi: 10.1186/s13045-025-01732-z. PMID: 40898324; PMCID: PMC12406617.
[82] Tan QKG, Louie RJ, Sleasman JW. IPEX Syndrome. 2004 Oct 19 [Updated 2024 Feb 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1118/
[83] Tavakol M, Delavari S, Salami F, Ansari S, Rasouli SE, Chavoshzadeh Z, Sherkat R, Ahanchian H, Aleyasin S, Esmaeilzadeh H, Moazzen N, Shafiei A, Abolnezhadian F, Iranparast S, Ebrahimi SS, Moeini Shad T, Pashangzadeh S, Nazari F, Rezaei A, Saeedi-Boroujeni A, Nabavi M, Arshi S, Fallahpour M, Bemanian MH, Sharafian S, Shokri S, Eshaghi S, Nazari S, Shamsian BS, Dargahi Mal-Amir M, Khazaei R, Ashkevari P, Khavandegar A, Haghi S, Esmaeili M, Abolhassani H, Rezaei N. Diversity of malignancies in patients with different types of inborn errors of immunity. Allergy Asthma Clin Immunol. 2022 Dec 12;18(1):106. doi: 10.1186/s13223-022-00747-2. PMID: 36510326; PMCID: PMC9743521.
[84] Taylor JP, Tse HM. The role of NADPH oxidases in infectious and inflammatory diseases. Redox Biol. 2021 Dec;48:102159. doi: 10.1016/j.redox.2021.102159. Epub 2021 Oct 4. PMID: 34627721; PMCID: PMC8487856.
[85] Trowsdale J, Knight JC. Major histocompatibility complex genomics and human disease. Annu Rev Genomics Hum Genet. 2013;14:301-23. doi: 10.1146/annurev-genom-091212-153455. Epub 2013 Jul 15. PMID: 23875801; PMCID: PMC4426292.
[86] Valencia JC, Egbukichi N, Erwin-Cohen RA. Autoimmunity and Cancer, the Paradox Comorbidities Challenging Therapy in the Context of Preexisting Autoimmunity. J Interferon Cytokine Res. 2019 Jan;39(1):72-84. doi: 10.1089/jir.2018.0060. Epub 2018 Dec 18. PMID: 30562133; PMCID: PMC6350415.
[87] Vargas-Uricoechea H. Molecular Mechanisms in Autoimmune Thyroid Disease. Cells. 2023 Mar 16;12(6):918. doi: 10.3390/cells12060918. PMID: 36980259; PMCID: PMC10047067.
[88] Waljee AK, Higgins PDR, Jensen CB, Villumsen M, Cohen-Mekelburg SA, Wallace BI, Berinstein JA, Allin KH, Jess T. Anti-tumour necrosis factor-α therapy and recurrent or new primary cancers in patients with inflammatory bowel disease, rheumatoid arthritis, or psoriasis and previous cancer in Denmark: a nationwide, population-based cohort study. Lancet Gastroenterol Hepatol. 2020 Mar;5(3):276-284. doi: 10.1016/S2468-1253(19)30362-0. Epub 2019 Dec 10. PMID: 31836320; PMCID: PMC12177892.
[89] Wang J, Wang C, Liu L, Hong S, Ru Y, Sun X, Chen J, Zhang M, Lin N, Li B, Li X. Adverse events associated with anti-IL-17 agents for psoriasis and psoriatic arthritis: a systematic scoping review. Front Immunol. 2023 Jan 31;14:993057. doi: 10.3389/fimmu.2023.993057. PMID: 36817423; PMCID: PMC9928578.

[90] Wang X, Qiu L, Li Z, Wang XY, Yi H. Understanding the Multifaceted Role of Neutrophils in Cancer and Autoimmune Diseases. Front Immunol. 2018 Nov 9;9:2456. doi: 10.3389/fimmu.2018.02456. PMID: 30473691; PMCID: PMC6237929.

[91] Wang X, Wen B, Duan X, Zhang Y, Hu Y, Li H, Shang H, Jing Y. Recent Advances of Type I Interferon on the Regulation of Immune Cells and the Treatment of Systemic Lupus Erythematosus. J Inflamm Res. 2025 Mar 30;18:4533-4549. doi: 10.2147/JIR.S516195. PMID: 40182060; PMCID: PMC11967359.

[92] Wang Y, Kim M, Su S, Halwatura L, You S, Kim HL. Using major histocompatibility complex (MHC) II expression to predict antitumor response to CD4 + lymphocyte depletion. Sci Rep. 2025 Feb 14;15(1):5469. doi: 10.1038/s41598-025-88972-8. PMID: 39953106; PMCID: PMC11828847.

[93] Wang Y, Li J, Nakahata S, Iha H. Complex Role of Regulatory T Cells (Tregs) in the Tumor Microenvironment: Their Molecular Mechanisms and Bidirectional Effects on Cancer Progression. Int J Mol Sci. 2024 Jul 4;25(13):7346. doi: 10.3390/ijms25137346. PMID: 39000453; PMCID: PMC11242872.

[94] Weinberg F, Ramnath N, Nagrath D. Reactive Oxygen Species in the Tumor Microenvironment: An Overview. Cancers (Basel). 2019 Aug 16;11(8):1191. doi: 10.3390/cancers11081191. PMID: 31426364; PMCID: PMC6721577.

[95] Wilke CM, Kryczek I, Wei S, Zhao E, Wu K, Wang G, Zou W. Th17 cells in cancer: help or hindrance? Carcinogenesis. 2011 May;32(5):643-9. doi: 10.1093/carcin/bgr019. Epub 2011 Feb 8. PMID: 21304053; PMCID: PMC3086699.

[96] Xiang Y, Zhang M, Jiang D, Su Q, Shi J. The role of inflammation in autoimmune disease: a therapeutic target. Front Immunol. 2023 Oct 4;14:1267091. doi: 10.3389/fimmu.2023.1267091. PMID: 37859999; PMCID: PMC10584158.

[97] Xie Q, Ding J, Chen Y. Role of $CD8^+$ T lymphocyte cells: Interplay with stromal cells in tumor microenvironment. Acta Pharm Sin B. 2021 Jun;11(6):1365-1378. doi: 10.1016/j.apsb.2021.03.027. Epub 2021 Apr 24. PMID: 34221857; PMCID: PMC8245853.

[98] Yang S, Zhao M, Jia S. Macrophage: Key player in the pathogenesis of autoimmune diseases. Front Immunol. 2023 Feb 14;14:1080310. doi: 10.3389/fimmu.2023.1080310. PMID: 36865559; PMCID: PMC9974150.

[99] Yasmeen F, Pirzada RH, Ahmad B, Choi B, Choi S. Understanding Autoimmunity: Mechanisms, Predisposing Factors, and Cytokine Therapies. Int J Mol Sci. 2024 Jul 12;25(14):7666. doi: 10.3390/ijms25147666. PMID: 39062908; PMCID: PMC11277571.

[100] Yu H, Liu Y, Wang M, Restrepo RJ, Wang D, Kalogeris TJ, Neumann WL, Ford DA, Korthuis RJ. Myeloperoxidase instigates proinflammatory responses in a cecal ligation and puncture rat model of sepsis. Am J Physiol Heart Circ Physiol. 2020 Sep 1;319(3):H705-H721. doi: 10.1152/ajpheart.00440.2020. Epub 2020 Aug 7. PMID: 32762560; PMCID: PMC7509276.

[101] Yu Y, Ma X, Gong R, Zhu J, Wei L, Yao J. Recent advances in $CD8^+$ regulatory T cell research. Oncol Lett. 2018 Jun;15(6):8187-8194. doi: 10.3892/ol.2018.8378. Epub 2018 Mar 29. PMID: 29805553; PMCID: PMC5950136.

[102] Zhang L, Yuan Y, Xu Q, Jiang Z, Chu CQ. Contribution of neutrophils in the pathogenesis of rheumatoid arthritis. J Biomed Res. 2019 Oct 24;34(2):86-93. doi: 10.7555/JBR.33.20190075. PMID: 32305962; PMCID: PMC7183296.

[103] Zhang XM, Liu CY, Shao ZH. Advances in the role of helper T cells in autoimmune diseases. Chin Med J (Engl). 2020 Apr 20;133(8):968-974. doi: 10.1097/CM9.0000000000000748. PMID: 32187054; PMCID: PMC7176439.

[104] Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, Li Y. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther. 2021 Jul 12;6(1):263. doi: 10.1038/s41392-021-00658-5. PMID: 34248142; PMCID: PMC8273155.

[105] Zhao Y, Ye X, Xiong Z, Ihsan A, Ares I, Martínez M, Lopez-Torres B, Martínez-Larrañaga MR, Anadón A, Wang X, Martínez MA. Cancer Metabolism: The Role of ROS in DNA Damage and Induction of Apoptosis in Cancer Cells. Metabolites. 2023 Jun 27;13(7):796. doi: 10.3390/metabo13070796. PMID: 37512503; PMCID: PMC10383295.

[106] Zhou D, Shao L, Spitz DR. Reactive oxygen species in normal and tumor stem cells. Adv Cancer Res. 2014;122:1-67. doi: 10.1016/B978-0-12-420117-0.00001-3. PMID: 24974178; PMCID: PMC4207279.

[107] Zhou Y, Shen G, Zhou X, Li J. Therapeutic potential of tumor-associated neutrophils: dual role and phenotypic plasticity. Signal Transduct Target Ther. 2025 Jun 4;10(1):178. doi: 10.1038/s41392-025-02242-7. PMID: 40461514; PMCID: PMC12134342.