

From Immunosuppression to Immunomodulation: Current Principles and Future Strategies

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Abstract

Over the last few decades, tremendous progress has been made in understanding the mechanisms of immune responses. This progress has also led to a more detailed knowledge of the processes leading to the loss of self-tolerance and the destruction of self-tissue in the case of autoimmune diseases, the effector mechanism involved in transplant allograft rejection as well as the driving factors in exacerbated inflammatory disorders. Despite this progress, the challenge still remains to selectively interfere with immune responses responsible for autoimmunity or transplant rejection while keeping an intact response to infectious agents. To date, such a selective interference is still difficult to achieve, as highlighted by the fact that an overall increased risk for infections and malignancy continues to be the most frequent side effect of the currently used immunosuppressive principles. Nevertheless, although discovered several decades ago, many of the 'first-generation' immunosuppressive principles such as steroids, methotrexate and cyclosporin A are still in clinical use, demonstrating the therapeutic value of these drugs for the patients that are in need. In this review,

the author describes the mode of action of the currently most used immunosuppressive agents (not attempting to cover all principles that are available) and expands on recent activities in the discovery and development of novel immunomodulatory principles.

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Components of Immunity That Represent Targets for Interference

Productive immune responses are a result of a complex interplay of various cell types with either direct or indirect effector functions. The interaction between the individual cell types is mediated either by cell-to-cell contacts (between ligands and receptors) or by soluble factors (such as cytokines, chemokines and growth factors). Immunosuppression may thus be achieved directly by interfering with the activation, differentiation or survival of the respective 'helper' or 'effector' immune cells or indirectly by the blockade of the cell-to-cell interactions and/or by the neutralization of soluble factors. Both innate immune cells (e.g. monocytes/macrophages, dendritic cells and NK cells) and adaptive immune cells (e.g. T and B lymphocytes) represent target populations for immunosuppressive agents.

Interestingly, most of the first-generation immunosuppressive agents seem to interfere with the immune responses at multiple levels. For example, steroids not only interfere with proinflammatory cytokine production [interleukin (IL)-6, IL-2 and interferon (IFN)-gamma] which stimulate the cells of the adaptive and innate immune systems, but also inhibit the production of proinflammatory prostaglandins [1]. Unfortunately, steroids affect not only inflammatory signaling but also other physiological stimuli, resulting in inherent side effects such as hypertension, osteoporosis, diabetes and impaired wound healing.

Interference with Cell Cycle, Proliferation and Cell Survival

The two classic antiproliferative drugs methotrexate and azathioprine have been widely used for many years for the treatment of autoimmune disorders. Methotrexate (Trexal[®]) has been used successfully for more than 20 years for treating rheumatoid arthritis (RA). Apart from its major antiproliferative effect on lymphocytes, based on the inhibition of dihydrofolate reductase in the de novo purine and pyrimidine synthesis, a multiple of other mechanisms are discussed which likely mediate the anti-inflammatory effects [2]. Thus, in analogy to the steroids described above, a multitude of different effects on immune cells may account for the efficacy of this treatment, particularly of rheumatic diseases. However, hepatotoxicity remains the major adverse side effect requiring rationalization. Other prominent side effects such as ulcerative stomatitis, leukopenia, nausea and abdominal distress are also associated with methotrexate therapy.

Azathioprine (Imuran[®]) is an analog of 6-mercaptopurine that acts by inhibiting purine metabolism so as to block the division of immune cells. Imuran is approved by the FDA for the prevention of rejection in renal transplantation and for the management of RA. In renal transplantation, it is being replaced more and more by treatment with mycophenolic acid (MPA) which includes mycophenolate mofetil (MMF, CellCept[®]) and enteric coated mycophenolate sodium (Myfortic[®]). In the purine metabolism, MPA inhibits type 2 inosine monophosphate dehydrogenase (IMPDH), an enzyme in the de novo purine nucleotide synthesis pathway. In the presence of MPA, cells remain in the S phase of the cell cycle and its powerful cytostatic effect affects T and B lymphocytes (including antibody production) equally. MPA, however, does not directly affect the production of pro-

inflammatory cytokines; several mechanisms have been proposed for why MPA has a more potent cytostatic effect on lymphocytes than on other cell types [3]. Leukopenia and neutropenia seem to be the major hematological side effects of MPA treatment, but gastrointestinal and vascular side effects also occur. Apart from organ transplantation, MPA is currently used for the treatment of graft-versus-host disease and several autoimmune conditions, e.g. systemic lupus erythematosus, pemphigus vulgaris and Behçet's disease.

To inhibit or reduce the proliferation of immune cells, cytokine or growth factor starvation has been successful. After initial activation, T lymphocytes, in particular, require the cytokine IL-2 for expansion, differentiation and survival. Antibodies directed to the IL-2 receptor alpha chain, e.g. CD25 [basiliximab (Simulect[®]) and daclizumab (Zenapax[®])], are in use to reduce the risk for episodes of acute rejection after renal transplantation without an increase in the overall incidence for infection and malignancy being apparent [4, 5]. Their excellent tolerability and safety profile make IL-2 receptor alpha chain blocking antibodies an attractive regimen for such an induction therapy that is maintained only during the first couple of weeks after transplantation. However, comedication with other immunosuppressive agents such as calcineurin inhibitors (CNI), MMF or steroids is essential to keep alloreactivity under control [6]. Interestingly, more recent discoveries on particular T cell subsets have led to a reevaluation on the role of IL-2 in immunity. IL-2 is not only a growth factor for pathogenic T effector cells but also promotes the generation of T regulatory cells that have the capacity to downmodulate immune reactivity. Based on this, low-dose administration of recombinant IL-2 not only reversed steroid-refractory chronic graft-versus-host disease in patients who underwent allogeneic hematopoietic stem cell transplantation but also improved autoimmune vasculitis, presumably by significantly increasing the T regulatory:T effector cell ratio in these patients [7]. Thus, in contrast to the administration of high doses of recombinant IL-2 (Proleukin[®]) which leads to immunostimulation used for the treatment of renal cell carcinoma and metastatic melanoma, the delivery of the same cytokine at a low dose seems rather to dampen immune responses.

The mammalian target of rapamycin (mTOR) kinase is a central node in the intracellular signal transduction pathway downstream of not only the IL-2 receptor but also of many other cytokine and growth factor receptors as well as G protein-coupled receptors. It regulates various cellular functions including metabolism, growth and

survival by mediating protein synthesis [8]. Two small molecule inhibitors of mTOR, everolimus (Certican[®]) and sirolimus (Rapamune[®]), are indicated for the prophylaxis of organ rejection in adult patients receiving renal or cardiac transplants in comedication with CNI and steroids. The mTOR inhibition prevents the cell cycle from the G1 to the S phase and thus prevents T and B cell proliferation in response to cytokine and growth factor stimulation and consequently also reduces antibody production by B cells. The most common side effects of mTOR inhibition are hyperlipidemia and cytopenia, which occur dose-dependently, impaired wound healing and thrombocytopenia. mTOR inhibitors are also tested in a variety of oncological settings for tumor indications.

Inhibition of Proinflammatory Cytokines and Growth Factors

Cytokines are important regulators of hematopoiesis and also mediate immune responsiveness and inflammation. This concept is the basis for many approaches of downmodulating immune cells by the neutralization of cytokines and growth factors. Indeed, blockade of cytokine(s) or growth factors or their signaling pathways shows a significant clinical impact.

Anticytokine therapies are successful, particularly in autoimmune diseases with strong inflammatory components. Blockade of the important inflammatory mediator TNF-alpha provides beneficial effects in RA, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis. Several biologics are available to either neutralize TNF-alpha or to block its receptor [etanercept (Embrele[®])/infliximab (Remicade[®])/adalimumab (Humira[®])/certolizumab pegol (Cimiza[®])/golimumab (Simpioni[®])]. TNF-alpha is an autocrine and paracrine stimulator of immune cells and a potent inducer of other proinflammatory cytokines and adhesion molecules (see below). The use of TNF-alpha antagonists is associated with opportunistic infections (upper respiratory tract), lymphomas and sometimes also autoimmune syndromes [9]. Similar to TNF-alpha, IL-1 is a potent activator of monocytes, tissue macrophages and synovial fibroblasts. To inhibit this important mediator, several biologics are available. Canakinumab (Ilaris[®]) is an IL-1 beta-blocker indicated for the treatment of cryopyrin-associated periodic syndromes including familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Similarly, anakinra (Kineret[®]) is approved for juvenile arthritis and RA, and rilonacept (Arcalyst[®]) (also known as IL-1 Trap

is used for cryopyrin-associated periodic syndromes, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease.

The soluble activation products of monocytes/macrophages and synovial fibroblasts contribute significantly to the pathogenesis of autoimmune disease by further fueling the inflammatory cascade, but also by direct destruction of tissue. Amongst others, IL-6 seems to be a central proinflammatory player. This is pharmacologically demonstrated by the fact that IL-6 neutralization by a monoclonal antibody (mAb), tocilizumab (Actemra[®]), is able to significantly reduce disease activity in RA, juvenile arthritis and Castleman's disease. IL-6 contributes not only to T cell activation but also acts as a B cell differentiation factor. IL-12 is also released by activated monocytes/macrophages and dendritic cells and mediates the differentiation of T cells towards the proinflammatory T 'helper' type 1 (Th1) and Th17 subsets (as opposed to the Th2 subset that is important in providing 'help' to the B lymphocytes to produce antibodies). IL-12 blockade by a mAb that neutralizes the p40 subunit of the IL-12 (and the IL-23) cytokine heterodimer ustekinumab (Stelara[®]) has shown efficacy in the treatment of psoriasis. Other mAbs blocking IL-12 are in late-stage clinical trials and will probably soon be available for clinical use. IL-23 also belongs to the IL-12 cytokine family together with IL-27 and IL-35 [10]; it is also produced by antigen-presenting cells (APC) and stabilizes the Th17 cell subpopulation (secreting the effector cytokine IL-17) which normally controls Gram-negative bacteria but which may substantially contribute to the pathogenesis of a number of autoimmune manifestations. Indeed, results from recent proof-of-concept trials indicated that neutralization of IL-17 (as in the case of the anti-IL-17 mAb secukinumab) may represent a new option to treat patients suffering from psoriasis, autoimmune uveitis and RA [11]. Similar activities can be expected from the anti-IL-17 mAb ixekizumab and from the anti-IL-17 receptor mAb brodalumab [12]. Th17 cells not only produce IL-17, but also a series of other cytokines which may contribute to autoimmunity, among them IL-21, an important growth and differentiation factor for B cells. Blockade of IL-21 by using mAbs is currently under clinical investigation.

Neutralization of a single cytokine or soluble mediator does, however, not always lead to the expected immunomodulatory effects in patients. For example, blockade of IL-4 and IL-9 did not show a significant benefit for asthma patients, and IL-15 neutralization is not efficacious in the treatment of RA and psoriasis. Although there may be numerous explanations for the clinical failures described

above, redundancies occurring in the complex cytokine networks still represent a major hurdle to be overcome with anticytokine therapies.

Inhibition of the signaling pathways downstream of the cytokine and growth factor receptors therefore represents attractive targets for immune intervention. To this end, small molecule inhibitors acting on the Janus kinase (JAK) family were recently discovered. The three JAKs (JAK1, JAK2 and JAK3) transmit signals from more than 30 cytokines and growth factors by using the signal transducer and activator of transcription phosphorylation pathway and subsequent upregulation of transcription factors resulting in the expression of pro-survival and anti-apoptotic genes and factors. The inhibition of JAK3 and JAK1, in particular, seems attractive for interference with activation, growth and survival of immune cells. The kinases transmit the signals of many pro-inflammatory interleukins and interferons [13]. One of the most advanced JAK inhibitors, tofacitinib (Xeljanz[®]), has just been approved by the FDA for the treatment of moderate-to-severe RA in nonresponders to methotrexate therapy. Unlike many other kinase inhibitors that inhibit a broad range of different kinases, Xeljanz seems to have good specificity for the JAK kinase family and reports describe a more potent inhibition of JAK1 and JAK3 (which transmit signals of a variety of pro-inflammatory cytokines and interferons) compared to JAK2 (which transmits signals of a multitude of hematopoietic factors including IL-3, EPO and GM-CSF).

Kinase inhibition is not only considered for the JAK family, but also for a series of other kinases that are involved in the activation pathways of immune cells, such as the serine-threonine kinase p38 mitogen-activated protein kinases (p38 MAPK), the spleen tyrosine kinase (SYK) and the phosphatidylinositol 3-kinases (PI3K), nicely reviewed by Kyttaris [14]. P38 MAPKs transmit cytokine, stress, heat and osmotic signals and are involved in cell differentiation and apoptosis. SYK is involved in many signaling pathways including those for the B cell receptor, T cell receptor, Fc-gamma receptors and integrins. The expression of SYK in myeloid-derived cells like osteoclasts makes this molecule an attractive target for RA for its putative effect and bone erosion. The PI3K family of kinases is composed of several classes and isoforms but the class I PI3K, particularly, seem to regulate the growth, proliferation and differentiation of immune cells [15]. A large series of small molecule compounds inhibiting the above kinases are currently in preclinical and clinical testing for autoimmune or hematological indications.

T Cell Activation and Costimulation

Evidently, T cells play a central role not only in transplant rejection but also in many autoimmune diseases as well as in numerous inflammatory disorders. The approval of the CNI CsA (Neoral[®]/Sandimmune[®]) for transplantation in 1983 was a milestone for immunosuppression and, still today, CN inhibition with either CsA or tacrolimus (Prograf[®]) is part of almost all maintenance regimens in organ transplantation and is also used in the prophylaxis of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Neoral is also approved for psoriasis, atopic dermatitis, RA and nephrotic syndrome. Calcineurin, a calcium-dependent phosphatase, is important in the phosphorylation of a variety of transcription factors including NF-AT which controls transcription of the pro-inflammatory cytokines IL-2, IL-3, IL-4, GM-CSF, IFN-gamma and TNF-alpha in T cells. Unfortunately, CNI seems to be inherently linked to nephrotoxicity [16]. Other common side effects include cardiovascular complications, neurotoxicity, lipid abnormalities, gingival hyperplasia and hirsutism.

Inhibition of early activation steps in T cells (as well as in B cells) would be prudent and would lead to a more efficient intervention in immune responses to self-antigens and alloantigens. The protein kinase C (PKC) family molecules could be such an early and important activation node close to the T/B cell receptor and maybe other activating receptors as well, as has been demonstrated by the discovery of sotrastaurin, a novel oral PKC inhibitor with immunomodulatory properties [17]. In this context, the classic isoforms of PKC, particularly, seem to be important to deliver the activation signals leading to AP-1 and NFκB activation and IL-2 production. Costimulatory molecules expressed by APC such as dendritic cells and monocytes/macrophages deliver an additional activation signal to the T cells that is required to proceed to a productive response. Naïve T cells, particularly, are highly dependent on such costimulatory signals, whereas memory T cells seem to be more dependent on cytokine signaling. Antibodies directed against these cell surface molecules may thus be a means to efficiently reduce T cell activation. The interaction between CD28 (on T cells) and CD80/CD86 (on APC) results in very powerful costimulation and is likely the best-studied costimulatory pathway to date. CTLA4-Ig abatacept (Orenica[®]) is a fusion product between the extracellular part of CTLA-4, a negative regulator expressed on the surface of T cells, and the Fc portion of immunoglobulin. It binds to CD80/CD86 and consequently prevents the delivery of the costimu-

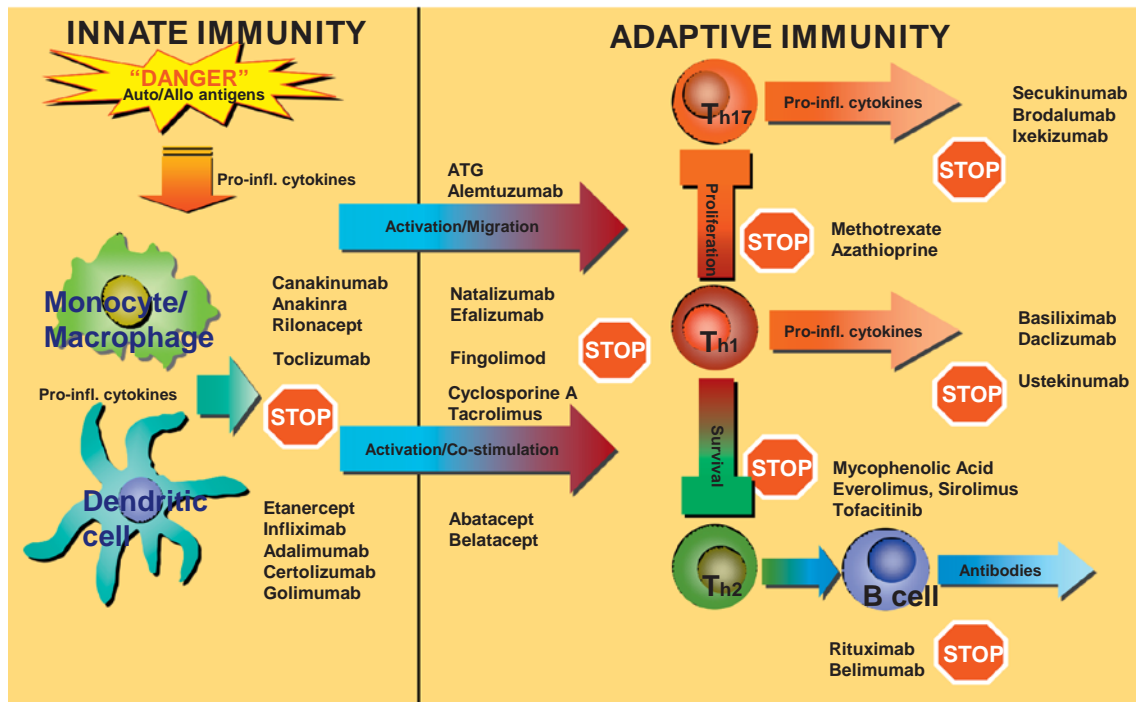


Fig. 1. Points of interference of therapeutic principles for autoimmune/inflammatory diseases and transplant rejection.

latory signal to CD28-expressing T cells. Orenica is approved for RA and juvenile arthritis and the most common side effects are cardiovascular (increased blood pressure) and infections. Recently, LEA29Y belatacept has been introduced to renal transplant patients. It has a 4× higher binding affinity to CD80/CD86 and an approximately 10-fold higher in vitro potency compared to Orenica [18, 19]. Other costimulatory molecules that are under investigation are CD40, OX40, 4-1BB, CD30, BTLA, LIGHT, HVEM, ICOS and many others.

In some disease conditions, the elimination of T cells or multiple immune-cell subsets may represent a therapeutic benefit for the patients. Antithymocyte globulins, e.g. Thymoglobulin[®], are polyclonal antibodies (generated in rabbits) directed against multiple T cell antigens, such as CD2, CD3, CD8, CD28 as well as antigens expressed on B cells, NK cells and macrophages. Thymoglobulin infusion leads to depletion of peripheral lymphocytes by antibody-mediated and complement-mediated lysis, apoptosis and receptor internalization. It is approved for use in organ and bone marrow transplantation; however, leukopenia/thrombocytopenia are major hematological side effects. Similarly, alemtuzumab (Cam-

path[®]), a mAb directed to CD52 which is expressed on T and B cells as well as on monocytes, macrophages and NK cells, induces a profound depletion of peripheral and lymph node lymphocytes [20]. Campath is considered for the treatment of multiple sclerosis (MS) and adverse effects include immune thrombocytopenic purpura, thyroid dysfunction and mild-to-moderate infections.

B Cells as Targets

Although not approved for autoimmune indications, the depletion of CD20-expressing B cells in the periphery by the mAb rituximab (Rituxan[®] or Mabthera[®]) was reported to show therapeutic benefit in subpopulations of RA and MS patients. These results indicated that B cells may significantly contribute to pathophysiology in certain autoimmune diseases and maybe even in (chronic) allograft rejection. Rituximab depletes mature B cells as well as B cell precursors from the pre-B cell stage onwards but not (auto) antibody producing plasmablasts that do not express CD20 [21]. A series of mAbs binding to various surface molecules expressed on B cells (CD19 and

CD22) are currently in late-stage development for autoimmune disease indications [22, 23]. However, selective inhibition of B cell function or survival rather than the relatively long-lasting depletion of B cells may have considerable safety advantages. Such an inhibition may be achieved by neutralizing the B cell-activating factor of the TNF family (BAFF or Blys), an important B cell stimulation factor. The anti-BAFF mAb belimumab (Benlysta[®]) has recently been successfully tested for the reduction of disease activity in systemic lupus erythematosus patients and is now licensed by the FDA. BAFFR, the receptor for BAFF, can bind another two ligands, namely TACI and APRIL which are also taken into consideration as potential targets for B cell inhibition [24]. Future B cell-directed therapies may likely also consist of small molecule inhibitors acting on intracellular activation pathways preferentially used by B cells. Particularly, inhibitors of the tyrosine kinase, Brunton's kinase (BTK) which is associated with the B cell receptor signalosome, and inhibitors of the SYK kinase (see above) are competitively explored for their putative efficacy in treating autoimmune diseases [25].

Leukocyte Adhesion and Cell Trafficking and Immune Cell Distribution

Until recently, interference with immune cell adhesion and trafficking was a field dominated by mAbs directed to cell surface integrins. Natalizumab (Tysabri[®]), a mAb directed to $\alpha 4\beta 7$ integrin (expressed on all leukocytes), blocks the interaction with vascular cell adhesion molecule 1 (VCAM-1) expressed on endothelial cells. This results in impaired adhesion and migration of leukocytes through the blood-brain barrier into the central nervous system. Tysabri is approved for the treatment of severe forms of relapsing remitting MS [26]; however, its use is limited due to its association with increased risk for the

development of JC virus-induced progressive multifocal leukoencephalopathy. The leukocyte function-associated antigen 1 (LFA-1 or CD11a), another adhesion molecule expressed on leukocytes, is the target receptor of efalizumab (Raptiva[®]). This mAb blocks the interaction with intracellular adhesion molecule 1 (ICAM-1) expressed on endothelial cells and interferes with the activation of lymphocytes in lymph nodes, the extravasation of circulating lymphocytes as well as with the T cell reactivation by cutaneous APC [27]. Raptiva is used to treat moderate-to-severe psoriasis.

More lately, a small molecule compound was discovered that modulates the redistribution of T cells in secondary lymphoid organs. The sphingosine 1 phosphate receptor agonist fingolimod (Gilenya[®]) selectively prevents the exit of T cells from secondary lymphoid organs such as lymph nodes, and leads to a profound reduction of the lymphocyte counts in circulation [28]. In addition to the cell trapping effects, various other mechanisms are postulated to account for the therapeutic efficacy of Gilenya in relapsing remitting MS. Gilenya, the first oral drug approved for MS, induces a negative chronotropic effect after first dosing that requires monitoring.

It has become evident that, although reactivity to pathogens and autoimmunity/transplant rejection have similar mechanisms and effector principles, preferential response patterns do exist which may facilitate the development of more specific immunomodulatory principles. A series of such principles has recently been discovered or is currently in late-stage clinical development (fig. 1). These agents may offer additional and improved therapeutic options for patients suffering from autoimmune manifestations, transplant rejection and inflammatory conditions if they achieve on both, safety and efficacy. To substantiate this hope, more long-term investigations on these novel principles will have to be conducted in the coming years.

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