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Challenges, Progress, and Prospects of Developing Therapies to Treat Autoimmune Diseases

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Autoimmune diseases are a result of the immune system being misdirected toward its host and have major and increasing unmet clinical needs. In general, present therapies are broadly acting and non-disease specific; consequently, they are associated with numerous side effects. Precise and early intervention strategies are urgently needed. We highlight the challenges, progress, and prospects in achieving these goals.

The human immune system is a multi-faceted network of functionally diverse cells expressing a broad array of receptors that collectively function to respond to infection, eliminate pre-cancerous cells, and maintain metabolic health. Breakdown of this delicately poised immune response is typically life limiting; however, even subtle changes in its ability to distinguish an invading pathogen from the host can give rise to a spectrum of autoimmune diseases. Indeed, autoimmune diseases affect approximately 5%–8% of the world population and cause tremendous suffering to patients while also representing a major global socioeconomic issue.

Presently, more than 80 autoimmune diseases have been described. They can be systemic, such as systemic lupus erythematosus, which can affect the skin, joints, kidneys, and CNS, or organ specific, such as type 1 diabetes, which primarily affects the pancreas. Loss of B cell or T cell tolerance is frequently implicated in autoimmunity, and indeed, the human leukocyte antigen (HLA) locus is commonly associated with increased risk of autoimmune disease susceptibility (Table 1). Although detailed molecular, immunological, genetic, and clinical studies have provided an increasingly sophisticated understanding of the mechanisms that underpin some autoimmune diseases, the drivers of human autoimmune diseases, including environmental triggers, and the ensuing pathogenesis remain poorly understood.

In general, current immune-modulatory drugs used in the treatment of autoimmune diseases are broadly acting, non-disease specific, and, consequently, associated with side effects such as infection and malignant disease. Furthermore, it is clear that the majority of patients are not responding optimally, if at all, to these therapies (Table 2). Thus, there is a pressing need for development of new drugs or repositioning of drugs based on a molecular and clinical understanding of the specific autoimmune diseases in individual patients in combination with high-throughput analysis of integrated datasets. Such personalized medicines may go hand in hand with inclusion of new diagnostics, leading to a better disease understanding and more patient-centric clinical trials that also consider ethnic diversity and patient-reported outcome measures. Prevention should also be part of future early intervention. This perspective will highlight the different types of current therapies and showcase how future basic studies, new technologies, and clinical trials could dynamically and reciprocally inform each other, leading to a better understanding of disease mechanisms and, hence, more refined treatments.

Biologic and Synthetic Drugs

Treatment of autoimmune diseases has drastically changed over the last 20 years with development and routine clinical use of synthetic or biologic drugs that block various pathways and components of the immune system, such as cytokines, cell adhesion molecules, and co-stimulatory molecules, or delete entire immune cell populations (Table 2). Presently, synthetic drugs approved for treatment of autoimmune diseases are dominated by Janus kinase (JAK) inhibitors (Schwartz et al., 2017). JAK1, JAK2, JAK3, and the non-receptor tyrosine-protein kinase TYK2 are intracellular tyrosine kinases that act in concert with seven different signal transducer and activator of transcription (STAT) transcription factors in mediating the signaling of more than 50 distinct cytokines, as well as hormones and growth factors. Upon cytokine-receptor binding at the cell membrane and phosphorylation by JAKs, the recruited STAT translocates to

Table 1. Examples of Autoimmune Diseases Affecting Different Organs

Primary Target Organ(s)	Disease	Prevalence[a]	Typical First Symptoms	Mechanism
Skin and Hair				
Skin	psoriasis	~2%–3%	skin redness, thickening, and scales	abnormal keratinocyte proliferation in the dermis and epidermis
Skin and oral mucosa	pemphigus vulgaris	~0.01%	blisters and erosions	loss of cell adhesion in stratified squamous epithelia
Skin	vitiligo	~0.5%–1%	milky white skin patches	destruction of melanocytes
Hair follicles	alopecia areata	~0.1%	patchy hair loss on the scalp	weakness in the hair shaft leading to hair shaft breaking
CNS				
Optic nerve, brain, spinal cord	multiple sclerosis	~0.1%	visual loss, numbness, tingling, paresis, and spasticity	destruction of myelin
Hypothalamus	narcolepsy	~0.03%	excessive daytime sleepiness, sleep attacks, sudden loss of muscular control	destruction of orexin-producing neurons
Optic nerve, spinal cord	neuromyelitis optica	~0.004%	resembles MS, but attacks are more severe	destruction of myelin, autoantibodies against aquaporin-4
Endocrine and Exocrine Glands				
Pancreas	type 1 diabetes	~0.4%	increased thirst, frequent urination, weight loss,	destruction of insulin- producing β cells
Thyroid gland	Graves disease (hyperthyroidism)	~0.5%	anxiety, irritability, hand tremors, weight loss, enlarged thyroid gland, bulging eyes, palpitations	autoantibodies against the thyrotropin receptor on thyroid follicular cells leading to increased synthesis of thyroid hormone
Thyroid gland	Hashimoto's disease (hypothyroidism)	~0.1%	many, changeable and unspecific, including fatigue, sensitivity to cold, puffy face, constipation, pale and dry skin	fibrosis and atrophy of thyrocytes leading to decreased synthesis of thyroid hormone
Tear and salivary glands	Sjögren's syndrome	~0.2%–1%	dry eyes and mouth	loss of function of exocrine glands
Gastrointestinal System				
Entire gastrointestinal tract, but especially the ileum, patchy lesions	Crohn's disease	~0.2%–0.3%	diarrhea, abdominal pain, bloody stool, fever, fatigue	transmural inflammation
Rectum and sometimes also the colon, uninterrupted lesions	ulcerative colitis	~0.2%–0.4%	abdominal pain, rectal pain and bleeding, urgency but inability to defecate, fever, fatigue	mucosal inflammation
Small intestine	celiac disease	~0.7%	loose stools, abdominal discomfort	flattening of villi and elongation of crypts
Stomach	autoimmune gastritis	uncertain	anemia, gastritis, vitamin B12 deficiency, and impaired food protein degradation	destruction of acid-producing parietal cells
Liver	primary biliary cholangitis	~0.03%	tiredness, itching	destruction of small bile ducts
Liver	autoimmune hepatitis	~0.02%	nonspecific, mild fatigue, often no symptoms of liver disease but elevation of liver enzymes in peripheral blood	destruction of hepatocytes

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Table 1. ***Continued***

Primary Target Organ(s)	Disease	Prevalence[a]	Typical First Symptoms	Mechanism
Kidneys				
Kidneys, CNS	lupus nephritis	~0.008%–0.2%	blood in the urine, foamy urine, swelling in the legs, and high blood pressure	inflammatory response to endogenous chromatin
Kidneys and lungs	Goodpasture syndrome	~0.0001%–0.001%	blood in the urine, foamy urine, swelling in the legs, high blood pressure, coughing, bleeding from the lungs	autoantibodies to the α3 chain of collagen IV in the basement membrane in the lungs and kidneys
Joints				
Proximal small joints of the hands and feet in a symmetrical distribution	rheumatoid arthritis	~0.5%–1%	joint swelling, morning stiffness, and tenderness	synovial hyperplasia leading to invasion and damage of cartilage and bone
Distal joints in an asymmetrical distribution, tendons or ligaments at bone insertions	psoriatic arthritis	~0.06%–0.25%	joint swelling, morning stiffness, and tenderness	synovial hyperplasia leading to invasion and damage of cartilage and bone
Sacroiliac joints	axial spondyloarthritis	~0.3%	unexplained chronic back pain and stiffness	erosion, bone growth, and fusion of vertebrae
Muscles				
Muscles	myasthenia gravis	~0.02%	muscle weakness, drooping of the upper eyelid, double vision	blockade of acetylcholine receptors and muscle-specific kinases in the postsynaptic muscle membrane
Muscles	polymyositis	~0.007%	weakness of muscles around the neck, shoulders, upper arms, hips, thighs	$CD8^+$ T cell invasion of muscle fibers
Reproductive Organs				
Ovaries	autoimmune oophoritis	uncertain	amenorrhea, infertility, hot flushes, vaginal atrophy	inflammation of theca cells of growing follicles
Testes	autoimmune orchitis	uncertain	infertility	apoptosis of spermatocytes and spermatids by anti-sperm antibodies

[a]Prevalence varies according to, e.g., diagnostic criteria, ethnicity, and race; in this context, meant to give a rough indication.

Table 2. Examples of Synthetic and Biologic Drugs for Treating Autoimmune Diseases

Target	Drug	Function	Examples of Clinical Use
JAKs			
	tofacitinib	inhibits JAK1, JAK2, JAK3	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis
	baricitinib	inhibits JAK1, JAK2	rheumatoid arthritis
Cytokines			
TNF	infliximab	inhibits TNF	Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis
Il-17a	secukinumab	inhibits IL-17A	psoriasis, ankylosing spondylitis, and psoriatic arthritis
IL-12/23p40	ustekinumab	inhibits IL-12 and IL-23	psoriasis
IL-23p19	guselkumab	inhibits IL23	psoriasis
IL-6R	tocilizumab	inhibits IL-6R	rheumatoid arthritis, juvenile idiopathic arthritis, neuromyelitis optica
B Cells			
	rituxan	depletes $CD20^+$ B cells	multiple sclerosis, rheumatoid arthritis
	belimumab	inhibits BAFF	systemic lupus erythematosus
Integrins			
	natalizumab	blocks $\alpha4\beta1$ and $\alpha4\beta7$	multiple sclerosis
	vedolizumab	blocks a4b7	ulcerative colitis, Crohn's disease
Co-stimulatory Molecules			
	abatacept	blocks CD80 and CD86	rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis

the nucleus, where it exerts its effect on gene transcription. Different cytokine receptors associate with different JAK complexes. For example, interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21 signaling is mediated by the JAK1-JAK3 complex; IL-6 signaling is mediated by JAK1, JAK2, and TYK2; and signaling of IL-10, IL-20, IL-22, and IL-28 is mediated by JAK1 and TYK2. Notably, signaling of some cytokines, such as tumor necrosis factor (TNF), IL-1, and IL-17, does not depend on JAKs. Pharmacological inhibition of cytokine signaling by blocking the JAK-STAT pathway is increasingly used to treat autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, psoriasis, inflammatory bowel disease, and alopecia areata. The first generation of JAK inhibitors, or jakinibs, are orally administered small-molecule drugs that bind to a kinase domain that is, however, highly similar across the different JAKs. For instance, tofacitinib, which is approved for treatment of rheumatoid arthritis, primarily inhibits JAK3 and JAK1 but also blocks JAK2 to a certain extent. This lack of selectivity and, thus, inhibition of a variety of cytokines may cause side effects such as bacterial, fungal, mycobacterial, and viral infection and, in particularly, herpes zoster infection. Assessment of malignancy risk requires longer-term observational studies. A novel generation of more selective JAK inhibitors is under development with the aim of diminishing side effects without losing efficacy. A novel oral selective TYK2 small-molecule inhibitor has recently shown good effects and tolerability in a clinical trial with psoriasis patients (Papp et al., 2018).

Biologic drugs are typically monoclonal antibodies, and their clinical use has provided a better understanding of their efficacy and side effects and revealed new layers of the complexity of autoimmune diseases. Currently, biologic drugs that bind immune molecules are a mainstay in the treatment of autoimmune diseases and have been extensively reviewed. Here we discuss a few of these examples to exhibit the breadth of the field and the challenges associated with drugs that are in clinical trials or already approved for use. Further, the wealth of structural information gleaned from structural studies of cytokine-receptor complexes (Spangler et al., 2015) is now providing a rational basis for developing cytokines and/or their receptors with enhanced specificity. For example, although pleiotropy is a basic mechanism underpinning many cytokine-receptor interactions, this property makes targeting this axis for any therapy problematic. However, sophisticated strategies and protein engineering approaches, which include altering cytokine-receptor docking topology and increased IL-2 selectivity, have overcome such issues and offer great promise to treat autoimmune diseases (Sockolosky et al., 2018; Trotta et al., 2018)

TNF

The first group of biologic drugs was TNF inhibitors, which radically changed the therapeutic landscape, and they are now routinely used to treat patients with rheumatic diseases, psoriasis, and inflammatory bowel disease. Their development and clinical use have been intensively reviewed over the last decades, and it will suffice to say, in this context, that their clinical use was met with skepticism, as it was argued that blocking a single cytokine would be futile in the context of a network of cytokines with overlapping biological effects (Monaco et al., 2015). Having established a key role for TNF in this network of

cytokines, the concern was that serious side effects would be associated with TNF inhibition. However, serious side effects, such as tuberculosis and demyelinating disease, are rare. Importantly, a significant number of patients do not respond or show loss of clinical response over time to TNF inhibitors. With an improved molecular understanding of this unresponsiveness, new treatment options targeting other pathways central to regulation of tissue inflammation are now emerging. It has been shown recently for inflammatory bowel disease that disturbances in an intestinal microbial network that produce short-chain fatty acids as a carbon source for intestinal epithelial cells and induction of regulatory T cells are linked to poor responsiveness to TNF inhibitors (Yilmaz et al., 2019). An overexpressed IL-7 receptor (IL-7R) signaling pathway in the colon has also been associated with non-responsiveness to anti-TNF therapy in inflammatory bowel disease, which might be explained by findings in a mouse model showing that this pathway is important for T cell homing to the gut and colonic inflammation (Belarif et al., 2019). More recently, expansion of apoptosis-resistant intestinal $TNFR2^{+}IL\text{-}23R^{+}$ T cells was associated with resistance to anti-TNF therapy in Crohn's disease (Schmitt et al., 2019), and single-cell analysis of inflamed tissues from Crohn's patients has identified a unique cellular module associated with failure to respond to TNF inhibitors (Martin et al., 2019). Taken together, these studies are beginning to provide cellular and molecular bases for resistance to TNF blockade.

IL-23/IL-17

Patients who are not responding to anti-TNF therapy may respond to biologic drugs targeting the IL-23/IL-17 axis, which plays a central role in regulation of tissue inflammation. These cytokine inhibitors have, however, very different effects on autoimmune diseases. Increased IL-23 and IL-17 levels have been found in the colon of inflammatory bowel disease patients, but IL-17 inhibitors led to disease exacerbation. In contrast, initial clinical trials with antibodies binding the p40 unit shared between IL-12 and IL-23 and subsequent clinical trials with antibodies targeting the IL-23-specific p19 unit showed efficacy in patients with inflammatory bowel disease. The efficacy of IL-12/IL-23 dual inhibitors and of IL-23-selective inhibitors suggests that the disease is primarily mediated by IL-23 and not IL-12 (Feagan et al., 2017; Neurath, 2019). However, a recent study in a mouse model of inflammatory bowel disease suggests that, early in disease, IL-12 is the dominant cytokine rather than IL-23 and, thus, indicates temporally distinct roles for these two cytokines in driving inflammation. Likewise, preclinical studies might also explain why IL-17 inhibitors led to exacerbation of disease in patients with Crohn's disease because it has been shown that IL-17 may control intestinal barrier integrity in mice and that inhibition of IL-17A or its receptor leads to weakening of barrier function and exacerbation of experimental colitis (Eftychi et al., 2019; Neurath, 2019).

In psoriasis skin lesions, dysregulated IL-17 levels are associated with neutrophil influx and keratinocyte hyperproliferation, which are disease drivers. Biologic drugs that block IL-17 have shown good efficacy in psoriasis patients but are also associated with *Candida* infection. Furthermore, selective inhibition of IL-23 is superior over IL-17 inhibition and is not associated with *Candida* infection (Reich et al., 2019). This indicates that targeting a cytokine upstream of the IL-17 axis is more efficacious but with fewer side effects because of IL-23-independent IL-17 production being seemingly sufficient for local antimicrobial responses (Zwicky et al., 2020).

Despite some preclinical evidence, targeting the IL-23/IL-17 axis in non-barrier-associated autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, has no or little clinical effect. The molecular explanation for this lack of efficacy is unclear but might indicate that targeting this axis is preferential in barrier-associated autoimmune diseases (Zeggini et al., 2019).

IL-1 Family

Members of the IL-1 family, such as IL-1, IL-18, and IL-36, have been associated with a broad spectrum of diseases, including autoimmune diseases, through their role in innate immunity and basal inflammation. Anti-IL-1b antibodies are not commonly prescribed for rheumatoid arthritis patients as a first-line biologic drug choice but can be used for patients not responding to TNF inhibitors. Cardiovascular disease is one of the comorbidities in rheumatoid arthritis patients, and because anti-IL-1b antibodies have shown efficacy in an atherosclerotic disease clinical trial, it has been suggested that this drug might be beneficial in the later stages of rheumatoid arthritis, exemplifying how different biologic drugs can be used at different stages of an autoimmune disease when the original target organ, the joint, is no longer the major therapeutic challenge (Mantovani et al., 2019).

Different lines of evidence implicate IL-18 in the pathogenesis of inflammatory bowel disease. A Mendelian form of severe enterocolitis is due to an activating NLRC4 inflammasome mutation and leads to upregulation of the IL-18 signaling pathway, and pharmacologic inhibition of IL-18 reverse this enterocolitis. Intestinal biopsies from inflammatory bowel disease patients show increased IL-18 expression in epithelial cells, which seems to promote goblet cell dysfunction, impairing intestinal barrier function in experimental colitis. Clinical trials with IL-18 in Crohn's disease are underway and will give a better understanding of its role in inflammatory bowel disease (Neurath, 2019).

IL-36 cytokines are mainly expressed on the barrier sites of the body. Generalized pustular psoriasis is a rare, life-threatening disease, and even though it is sometimes seen in the context of psoriasis, clinical, histologic, and genetic differences suggest that the two diseases have distinct pathogenic mechanisms. This is supported by the observation that TNF inhibitors have less efficacy in generalized pustular psoriasis than in psoriasis. IL-36 has been implicated in the pathogenesis of generalized pustular psoriasis because the lesions have heightened IL-36 cytokine activity, their neutrophilic environment activates IL-36, and missense mutations in the IL-36 receptor are associated with generalized postular psoriasis. In line with this, a phase 1 proof-of concept clinical trial has shown that a monoclonal antibody against IL-36 has efficacy in generalized pustular psoriasis lesions (Bachelez et al., 2019).

IL-6

In line with the original observation that IL-6 knockout mice are protected in an arthritis model, it has been shown that an anti-IL-6R monoclonal antibody has efficacy in rheumatoid arthritis. However, anti-IL-6 treatment is associated with bacterial infection and induces psoriasis in patients with no history of psoriasis and intestinal perforation, reflecting the multi-functional role of

IL-6. Although the risk of bacterial infection is likely to reflect its role in the immune system, induction of psoriasis and intestinal perforations may not. For example, RNA transcriptomic studies of skin from a mouse model of psoriasis compared with human psoriasis skin have shown that, in the absence of IL-6, keratinocytes increase production of numerous additional proinflammatory cytokines, which might explain the molecular basis for this particular side effect (Fritz et al., 2017). Anti-IL-6-associated intestinal perforation, observed in patients with rheumatoid arthritis and anti-IL-6-treated patients with inflammatory bowel disease, is likely to be associated with a role of IL-6 in intestinal epithelial proliferation and repair after injury (Danese et al., 2019). Anti-IL-6R inhibition has efficacy in neuromyelitis optica and in models of systemic lupus erythematosus, which are characterized by signature autoantibodies, indicating that IL-6 in these diseases is exerting its effect via B cells (Kang et al., 2019).

Co-stimulatory Molecules

Co-stimulatory molecules are also potential biological targets in autoimmune diseases. The CD40/CD40L axis plays a key role in generation of humoral immune responses; CD40 is expressed on antigen-presenting cells, including B cells, and interacts with CD40L on activated T cells, resulting in maturation of functional T and B cells and antibody isotype switching. Clinical trials with anti-CD40L antibodies for autoimmune diseases were halted because of thrombotic complications because the antibodies also co-bound platelet CD40L and an Fc receptor on adjacent platelets. To avoid this side effect, a non-antibody CD40L binding protein lacking an Fc domain, VIB4920, has been developed and trialed in a proof-of-concept study in patients with rheumatoid arthritis. VIB4920 significantly decreased disease activity, and, importantly, no thrombotic complications were reported (Karnell et al., 2019).

Interactions between the costimulatory molecules CD80 and CD86 on antigen-presenting cells and their ligand CD28 on T cells are important for activation of effector T cells. A CTLA4-IgG1 Fc fusion protein that binds with a higher affinity to CD80 and CD86 than CD28 can block T cell stimulation, which is considered its dominant mode of action. However, it is also known to act in a less well-defined manner in other cell populations, including regulatory T cells, B cells, monocytes, macrophages, and osteoclasts. The CTLA4-IgG1 Fc fusion protein has shown a good effect in rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis but has not had any efficacy in other autoimmune diseases, such as inflammatory bowel disease, multiple sclerosis, or lupus nephritis. The basis of this differential efficacy is not understood and might indicate, for instance, that blocking this co-stimulatory pathway is disease- and organ-specific or that this drug's effect on osteoclasts might at least partly explain the preferential effect on rheumatic diseases. Monoclonal antibodies against CD28 are also being developed but should be tested with caution because a very-high-affinity anti-CD28 antibody led to T cell stimulation and rapid induction of proinflammatory cytokines in a phase 1 clinical trial where healthy participants became critically ill (Schwarz et al., 2018).

B Cells

Anti-CD20 monoclonal antibodies deplete the majority of B cells, excluding plasma cells. An anti-CD20 monoclonal antibody, originally shown to be effective in patients with B cell malignancies, was subsequently repositioned to treat patients with rheumatoid arthritis. This had positive outcomes, on the foundation that B cells play a pathogenic role in this disease, and was later also extended to treat patients with systemic lupus erythematosus, where there is also evidence that B cells play a role. Primarily based on studies in an animal model of multiple sclerosis, anti-CD20 antibodies were then trialed in multiple sclerosis patients and had an effect that was superior to any other approved therapy for multiple sclerosis (Hauser et al., 2017). However, despite evidence that anti-CD20 antibodies may, in part, play an immunomodulatory role by deleting auto-aggressive or auto-antigen-presenting B cells or reducing B cell-secreted pro-inflammatory cytokines, the basis of its clinical efficacy is overall unclear.

Other B cell-based biologic drugs target two related cytokines belonging to the TNF superfamily, BAFF and APRIL, which are important in survival and differentiation of B cells at distinct developmental stages. Basic studies have shown that BAFF plays a role in maturation and activation of autoreactive B cells, and inhibition of its function delays lupus-like disease in mouse models with clear B cell involvement. A monoclonal antibody inhibiting BAFF is approved for treatment of a subgroup of patients with systemic lupus erythematosus, where it has shown modest effects but without obvious infectious disease side effects, probably because the plasma cell compartment is only partially depleted (Jackson and Davidson, 2019).

A recombinant fusion protein, Atacicept, which binds BAFF and APRIL, was trialed in patients with multiple sclerosis because it had been effective in an animal model of multiple sclerosis and because of the effect of BAFF and APRIL on B cells. However, against expectations, it was found to exacerbate disease. Although the basis of this side effect is unclear, it has been suggested to be a result of depleted regulatory B cells or that APRIL mediates an anti-inflammatory response from astrocytes in multiple sclerosis lesions that are not shared with BAFF (Kappos et al., 2014).

Integrins

Monoclonal antibodies targeting integrins, which are upregulated by proinflammatory cytokines and mediate adhesion and trans-barrier migration of leukocytes into organs, have shown good efficacy in multiple sclerosis and inflammatory bowel disease patients, and their development was predicted by preclinical studies (Yednock et al., 1992). The $\alpha4\beta1$ integrin binds vascular cell adhesion molecule 1 (VCAM1), expressed on inflamed endothelial cells, and the $\alpha4\beta7$ integrin binds to mucosal vascular addressin cell adhesion molecule 1 (MAd-CAM-1), specifically expressed on endothelial cells in the gut. Antibodies targeting the shared $\alpha4$ subunit of the $\alpha4\beta1$ and the $\alpha4\beta7$ integrins had a good effect in animal models of multiple sclerosis and inflammatory bowel disease by preventing leukocytes to migrate across the blood-brain barrier and blood-gut barrier, respectively. In line with this, a monoclonal antibody, natalizumab, against $\alpha4$-containing integrins has shown good efficacy in multiple sclerosis and inflammatory bowel disease. However, an unforeseen side effect was that a minority of patients with multiple sclerosis and inflammatory bowel disease developed progressive multifocal leukoencephalopathy (PML), a potentially fatal

central nervous system (CNS) disease caused by a common polyomavirus that infects and destroys oligodendrocytes (Ley et al., 2016). Consequently, a monoclonal antibody against the gut-specific $\alpha4\beta7$ integrin complex, vedolizumab, was developed and has shown good efficacy in inflammatory bowel disease. This has subsequently replaced natalizumab for treatment of Crohn's disease and is also being used to treat patients with ulcerative colitis. Importantly and expectedly, PML has not been observed in vedolizumab-treated patients and exemplifies informed dynamic drug development integrating a basic understanding of integrins with the outcome of clinical trials (Sandborn et al., 2013).

Cellular Therapies

Regulatory T cells (Tregs) are a population of T cells that can suppress various autoimmune diseases in animal models, and mutations in their transcription factor Foxp3 lead to severe autoimmune and inflammatory conditions. These observations point to Tregs as promising candidates for restoring immune tolerance in autoimmune diseases. Importantly, Tregs can adaptively change function or undergo apoptosis in response to changes in the cellular milieu and, furthermore, accumulate near the inflammation site and function locally, likely causing fewer side effects than systemically acting drugs. A major safety concern is the stability of Tregs because, under particular inflammatory conditions, they can switch from immunosuppressive to effector function (Komatsu et al., 2014). Thus, strategies to maintain Treg stability remain a high research priority. Preclinical studies suggest that antigen-specific Tregs have higher suppressive potential and a lower risk of side effects compared with polyclonal Tregs, on which current clinical data are based (Bluestone et al., 2015). However, the very low frequency of Tregs in peripheral blood makes them difficult to isolate. Thus, engineered T cell receptor (TCR) and chimeric antigenic receptor (CAR) Tregs have rapidly gained ground. For instance, the capability of Tregs to exert bystander suppression has been exploited in the development of CAR-modified Tregs that target extracellular citrullinated vimentin protein, found in inflamed joints of patients with rheumatoid arthritis. *In vitro* culturing of these engineered cells with synovial fluid from inflamed joints led to activation and expansion of CAR Tregs, and studies are ongoing to assess their suppressive capacity (Raffin et al., 2020). Although CAR technologies show clear benefits in terms of availability, flexibility, less dependence on IL-2, and no HLA restriction, they still rely on the laborious and expensive phases of identifying and characterizing the target antigens and producing target-specific antibodies. Interestingly, a method developed to identify neoantigens for cancer therapy by CRISPR genome editing may find use in identifying hidden self-antigens in autoimmune diseases (Manguso et al., 2017). Moreover, CRISPR technology offers an approach to reprogram human T cell function and specificity without the need for CAR-encoding viral vectors for transduction of Tregs (Roth et al., 2018). Although it is unquestionable that gene editing and gene delivery technologies may benefit the development of novel cellular therapies, ethical and, potentially, legal issues need to be addressed before translating these technologies into the clinic. Furthermore, because these technologies are still in their infancy, robust data regarding efficacy and risk assessment in humans are not currently available. A variant of the CAR approach that employs chimeric autoantibody receptors (CAARs) specifically targeting pathogenic autoantibody-producing B lymphocytes has shown promising results in a preclinical model for pemphigus vulgaris. This approach may be extended to other autoimmune diseases with a pathogenic and specific B cell component (Ellebrecht et al., 2016).

Natural killer (NK) cells have been suggested as an alternative to T cells in CAAR and CAR T cell therapy. For example, a novel CAAR-modified and IL-2-independent NK cell line has been demonstrated *in vitro* to selectively kill B cells expressing autoreactive anti-La-SBB B cell receptors, found in patients with Sjögren's syndrome and systemic lupus erythematosus (Meng et al., 2018).

Although much can be learned from the clinical experience with CAR T effectors in cancer therapy, it is important to keep in mind the fundamental differences in the biology of Tregs and effector T cells, including, but not limited to, responses to TCR stimulation, co-receptor ligation, and cytokines. Further, it is well known that treatments with anti-tumor CAR T cells may cause serious side effects, such as cytokine storm, macrophage stimulation syndrome, and neuronal cytotoxicity, but it is presently unknown whether this would be the case for CAR Tregs as well.

Regulatory B cells (Bregs) constitute a highly heterogeneous subset of B cells producing IL-10 and, frequently, transforming growth factor β (TGF-β) and IL-35, but many phenotypes exist in mice and humans. The prevailing hypothesis is that any B cell can potentially differentiate into a Breg in response to the right inflammatory or environmental stimulus. Notably, the same stimuli are often involved in the pathogeneses of autoimmune disorders. For instance, using a mouse model of rheumatoid arthritis (Rosser et al., 2014), it has been shown that IL-1b and IL-6 promote Th17 differentiation and arthritis progression but also induce IL-10-producing Bregs to curb excessive inflammation induced by the gut flora and disease. Likewise, although IL-21 upregulation has been reported in multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease, splenic IL-21-producing $CD4^+$ T cells are also responsible for Breg induction in a mouse model of multiple sclerosis (Yoshizaki et al., 2012). Thus, understanding the generation of Bregs and how to balance pleiotropic cytokine effects is critical for developing therapeutic strategies.

In a mouse model of multiple sclerosis, commensal-reactive immunoglobulin A (IgA)-expressing cells from the intestinal *lamina propria* have been reported to migrate to the inflamed CNS during experimental autoimmune encephalomyelitis (EAE), where they suppressed disease locally by IL-10 production. Remarkably, the corresponding decrease in gut IgA^+ plasma cells was mirrored by findings of reduced IgA-bound fecal bacteria in multiple sclerosis patients during relapses. These data demonstrated that plasmablasts and/or plasma cells mobilized from the gut suppress neuroinflammation and suggest that manipulation of the microbiota could be a therapeutic approach to improve B cell-mediated immune regulation (Rojas et al., 2019). Although the role of Bregs in autoimmune diseases is increasingly recognized, our current understanding of their

biology, specificity, and dysregulation in specific conditions and how to culture and regulate these cells *ex vivo* needs to be improved before exploiting them therapeutically.

A combination of cellular therapies in specific therapeutic windows might be a future option for specific autoimmune diseases, possibly in a setting of adjunctive therapy. Such cell-based therapies might include antigen-specific dendritic cells to re-establish tolerance or mesenchymal stromal cells (MSCs), which, in addition to their tolerogenic phenotype, possess regenerative capacity. Further, MSCs derived from umbilical cords are modifiable and can be screened and selected for high performance while circumventing the need to stimulate the bone marrow for production as well as to collect them from the hip bone or fat. NK cells, whose activity is regulated by a variety of surface receptors, are increasingly considered major players in several autoimmune diseases and, thus, are targets for immunotherapy (Gianchecchi et al., 2018). Moreover, in addition to targeting HLA-restricted T cells implicated in autoimmune diseases, the large family of unconventional T cells (e.g., γδT cells, MR1-restricted mucosal-associated invariant T [MAIT] cells, and CD1-restricted T cells) are often restricted to monomorphic antigen-presenting molecules (Godfrey et al., 2015); thus, any future therapies targeting these immune cell types are, in theory, applicable to the entire human population. Indeed, given the emerging role of such unconventional T cells in mediating autoimmunity (Toubal et al., 2019), this could represent a promising area of therapeutic development.

Targeting Metabolic Pathways

Immune cells are metabolically plastic and use different nutrients as well as metabolic and redox signaling pathways, depending on differentiation state and function. For instance, memory T cells typically favor oxidative phosphorylation and consume fatty acids, whereas effector T cells favor glycolysis (akin to the Warburg effect) to meet their higher energy and biosynthesis demands. This metabolic reprogramming offers a therapeutic opportunity to modulate the immune system by targeting specific metabolic pathways utilized by differential immune cell subsets, including, but not limited to, separating effector from regulatory functions and reprogramming memory capacity. A key concept is that a given drug, even without intrinsic specificity, can exert specific effects according to the metabolic demands of the specific cells to be modulated. The safety of a metabolic therapy thus depends on the sensitivity of the target cell compared with non-target cells at the time of treatment as well as specifically delivering the drug to the target site. Compared with cancer, autoimmune diseases may require lower doses and shorter treatment to reach the outcome of modulating cellular function rather than killing cells, lowering the risk of side effects. Moreover, a more profound understanding of drugs' mechanisms of action provides an opportunity for repositioning of well-known metabolic drugs with approved long-term safety profiles to autoimmune diseases.

For instance, several studies have established that pathogenic $CD4^+$ T cells in systemic lupus erythematosus exhibit elevated glycolysis, mitochondrial oxidative metabolism, and mechanistic target of rapamycin (mTOR) activity in mice and humans (Yin et al., 2015; Figure 1). Dual inhibition of the glycolysis and mitochondrial oxidative metabolism pathways by 2-deoxy-D-glucose and the common antidiabetic drug metformin, respectively, reduces interferon-γ and systemic lupus erythematosus markers in disease models while not affecting $CD4^+$ T cells from control mice. 2-deoxy-D-glucose alone has been shown to limit expansion of T follicular helper (Tfh) cells, germinal center B cells, and production of anti-double-stranded DNA (dsDNA) antibodies without impairing the humoral response to exogenous or influenza virus-mediated induction of antigen-specific Tfh cells (Choi et al., 2018).

Targeting glucose uptake may also be of therapeutic benefit; a novel glucose transporter inhibitor, CG-5, has shown effects comparable with those of glycolysis inhibitors in systemic lupus erythematosus models (Li et al., 2019). In rheumatoid arthritis, $CD4^+$ T cells exhibit decreased glycolysis, shunting glucose into the pentose phosphate pathway and reducing the level of reactive oxygen species (ROS). This metabolic shift leads to a hyperproliferating and proinflammatory T cell phenotype (Yang et al., 2016) that can be normalized by oxidative agents, restoring intracellular ROS (Figure 1).

The mTOR signaling pathway is central in many autoimmune diseases, and the first clinical trial with the mTOR inhibitor sirolimus has shown reduced disease activity and acceptable safety in patients with refractory lupus (Lai et al., 2018). Moreover, the mTOR complex 2 and glycolysis pathways are involved in skewing Treg cells toward an effector T cell-like phenotype in the case of Foxp3 deficiency, which is frequently associated with autoimmune diseases. Inhibition of these pathways has been reported to restore Treg function and attenuate intestinal inflammation in a mouse model (Charbonnier et al., 2019).

Dimethyl fumarate, whose first medical use was described 60 years ago, is now a first-line drug for multiple sclerosis and psoriasis, but its mode of action has only been established recently. By inactivating the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH), it leads to downregulation of aerobic glycolysis in activated myeloid and lymphoid cells (Kornberg et al., 2018) and, thus, exemplifies by serendipity how targeting cellular metabolisms may have therapeutic value in autoimmune diseases.

We have described a few paradigmatic examples of a rapidly evolving field. Importantly, a variety of other druggable pathways, such as amino acid and glutamine metabolism, fatty acid oxidation, and lipid synthesis, contain many potential targets. Because most metabolic pathways are intertwined and overlapping, a better understanding of the mechanisms across cell types, in both homeostasis and cases of dysregulation and autoimmune disease, is, however, required for translating the potential targets into safe therapies, whether with new or repositioned drugs. More research is needed to explore whether abnormalities in metabolism and redox states can be modulated through nutritional interventions, such as nutritional supplements, diets, and fasting regimens.

Targeting the Microbiome

Experimental and clinical studies have demonstrated links between dysbiotic microbiomes and autoimmune diseases such as systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, and atopic dermatitis. Translocation of

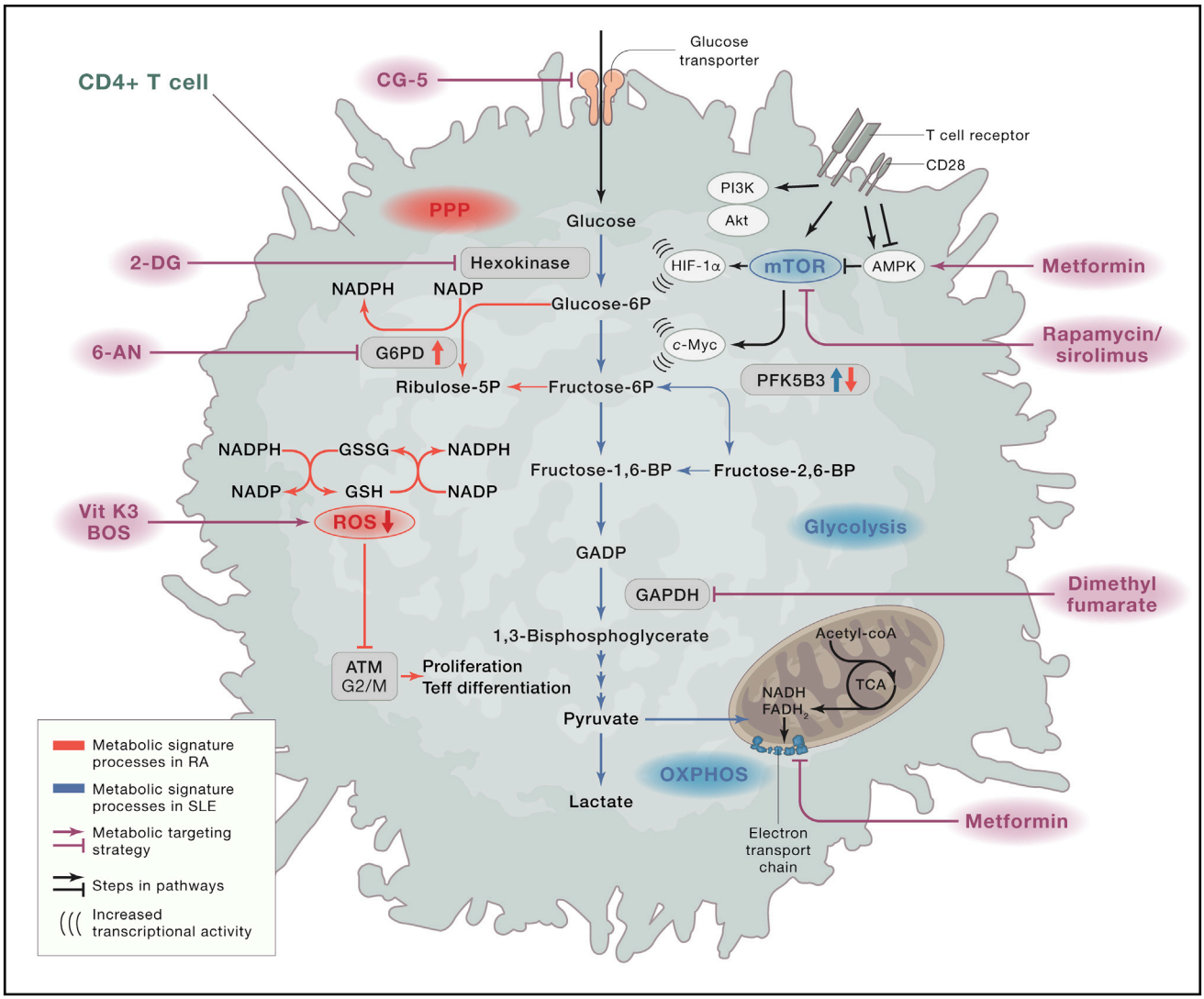

Figure 1. Examples of Abnormal Metabolic Pathways and Potential Targeting Strategies

The metabolic signature of CD4+ T cells in systemic lupus erythematosus (SLE) is elevated glycolysis, oxidative phosphorylation (OXPHOS), and enhanced mTOR activity (blue). Dual inhibition of OXPHOS by metformin and hexokinase/glycolysis by 2-deoxyglucose (2-DG) or inhibiting the glucose transporter by CG-5 inhibitor reverses SLE markers *in vitro* and *in vivo* (Yin et al., 2015). Metformin is also suggested to reduce mTOR overactivity through activation of 5' adenosine monophosphate-activated protein kinase (AMPK). Sirolimus, targeting mTOR, has shown clinical effects in SLE patients (Lai et al., 2018), and dimethyl fumarate, used to treat multiple sclerosis and psoriasis, has been shown recently to exert its effect through suppression of GADPH, leading to downregulation of aerobic glycolysis (Kornberg et al., 2018). In rheumatoid arthritis, CD4+ T cells show decreased 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK5B3) but enhanced glucose-6-phosphate dehydrogenase (G6PD) enzyme activity in addition to increased NADPH and glutathione (GSG), reflecting that glucose is diverted from glycolysis into the pentose phosphate pathway (PPP; red). Increased NADPH and GSG levels cause ROS depletion, which is linked to cell cycle regulation via the enzyme ataxia telangiectasia mutated (ATM) protein kinase, responsible for cell cycle arrest at the G2/M checkpoint. Thus, lack of ATM activity, as observed in rheumatoid arthritis T cells, can lead to hyperproliferation and maldifferentiation (Yang et al., 2016). Inhibition of G6PD with 6-aminonicotinamide (6-AN) rebalances glucose utilization, normalizes ROS levels, and reduces cell proliferation. Furthermore, replenishing ROS levels with oxidative agents such as vitamin K3 or buthionine sulfoximine (BOS) restores ATM activity and suppresses synovial inflammation in a mouse model. Notably, the rheumatoid arthritis and SLE CD4+ T cells in these examples were characterized at early disease stages, suggesting strategies for early disease intervention.

individual taxa of commensal gut bacteria, such as *Enterococcus gallinarum* (Manfredo Vieira et al., 2018) and *Lactobacillus reuteri* (Zegarra-Ruiz et al., 2019), from the gut to secondary lymphoid organs has been linked to systemic lupus erythematosus-like disease in mice. This disease could be prevented by vaccination against *E. gallinarum* or by feeding *L. reuteri* with dietary resistant starch that induced expansion of *Clostriales*, which is known for its capacity to produce short-chain fatty acids (SCFAs) by fermentation of dietary fiber. SCFAs are increasingly being recognized as important metabolites in intestinal immune homeostasis, and numerous studies have established divergent host effects, such as reducing intestinal permeability, inducing Tregs (Arpaia et al., 2013; Atarashi et al., 2013; Smith et al., 2013), and promoting long-term survival of

$CD8^+$ T cells as memory T cells (Bachem et al., 2019). Intriguingly, *L. reuteri* has been reported to be enriched in fecal samples, and *E. gallinarum* has been detected in liver biopsies in a subset of systemic lupus erythematosus patients but not in healthy controls, although the significance of these finding needs further investigation.

Individual microbial taxa are, however, not always identifiable as being responsible for disease phenotypes. For instance, microbiotas from inflammatory bowel disease patients induce colitis by altering the balance of gut Th17 and $ROR\gamma t^+$ Tregs when transferred to mice (Britton et al., 2019). Notably, no major differences in microbiome composition between healthy and inflammatory bowel disease donor guts have been found, suggesting that the functional dysbiosis is due to the unique compositions in these individuals. These findings are in line with a longitudinal study (Lloyd-Price et al., 2019) showing that inflammatory bowel disease microbiomes are less stable over time than those from healthy individuals. The phases of dysbiosis correlating with disease activity are characterized by a variety of shifts in microbial composition and host factors, such as bile acids, which are modified by gut bacteria and used as immune signaling molecules, among which two distinct derivatives of deoxycholic acid have been demonstrated to modulate the balance of Th17 and Treg cells in mice (Hang et al., 2019). Furthermore, gut microbes works in concert with diet to modify bile acids, which, in turn, can influence the level of $ROR\gamma t^+$ Tregs and affect the risk of inflammatory bowel disease in mouse models (Song et al., 2020).

Transfer of an entire microbial community has shown short-term safety and clinical responses in ulcerative colitis (Paramsothy et al., 2017). Further studies are, however, needed to characterize the mechanisms underlying the effects of such fecal microbial transplantation. In multiple sclerosis, transfer of gut microbiota from patients to mouse models has been reported to influence adaptive autoimmune responses, but the effect of single bacterial taxa and how manipulation of the gut microbiota may affect disease course remain unclear (Berer et al., 2017; Cekanaviciute et al., 2017).

The skin microbiota has also been shown to play a role in the pathogenesis of atopic dermatitis, which has an autoimmune component. Patients with atopic dermatitis have reduced diversity in the skin biota, with a low abundance of coagulase-negative staphylococci (CoNSs) and a high frequency of *Staphylococcus aureus* that has been correlated with the severity of lesions (Kobayashi et al., 2015). Identification of novel antimicrobial peptides produced by CoNS species that selectively eliminate *S. aureus* suggests that treatment with moisturizers supplemented with common coagulase-negative *Staphylococcus* species can selectively outcompete *S. aureus* (Nakatsuji et al., 2017) and is currently being tested in a clinical trial. A similar approach of topical *Roseomonas* mucosa transplantation has shown positive results in a phase I/II safety and activity trial for atopic dermatitis (Myles et al., 2018).

It is increasingly recognized that microbial effects may mediate the link between diet and autoimmune disease. For instance, a high-salt diet exacerbates EAE disease in mice by depletion of *Lactobacillus murinus* (Wilck et al., 2017), whereas omission of tryptophan from the diet impairs encephalitogenic T cell responses and changes the composition of the gut microbiota in EAE mice housed conventionally but not under germ-free conditions (Sonner et al., 2019). The protective effect of intermittent fasting in an EAE mouse model is also, at least partly, mediated by the gut flora (Cignarella et al., 2018). Other studies have shown that fasting and calorie restriction may also lead to redistribution of monocytes and lymphocytes from the blood and peripheral organs to the bone marrow, providing beginning mechanistic insights (Collins et al., 2019; Jordan et al., 2019; Nagai et al., 2019). Notably, these studies reported differential effects on immune cell organization depending on the type and form of nutritional intervention, underscoring the tremendous adaptability of metabolism and immunity but also calling for strict methodology and design in future studies.

The mechanisms underlying the association between obesity and autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and psoriatic arthritis remain poorly understood. The family of adipokines, cytokines expressed by fat tissue, are increasingly recognized as central immune mediators that may play a role. Because obesity can be transferred through microbiome transplantation (Ridaura et al., 2013), the microbiome might link food intake, obesity, and autoimmune disease.

Overall, there is a paucity of human studies probing the efficacy of dietary interventions in autoimmune disease, and most evidence remains anecdotal. However, according to a survey of inflammatory bowel disease patients (Holt et al., 2017), 71% of inflammatory bowel disease patients "assumed that diet affects their disease," and 61% "considered their therapist disregarded the importance of diet in the management of their disease." Increasing awareness of dietary aspects among patients and specialists, combined with rapidly growing insight into the mechanism of host-microbiota-nutrient interactions informing future clinical trials, will likely lead to diet-based adjunctive treatments.

Finally, thousands of recently discovered small-protein families from human microbiomes are predicted to play a key role in the crosstalk among bacteria and human hosts. They are easily engineered because of their small size and may have potential as novel biological building blocks in drug development (Sberro et al., 2019).

Protection of Organs

As well as targeting the immune system in autoimmune diseases, it is clearly also important to develop adjunctive therapies that prevent and protect inflamed tissue from damage and restore function. In atopic dermatitis and psoriasis, moisturizers are traditionally used to protect and restore epidermal barrier function. New types of moisturizers combine improved or novel combinations of ingredients with more specific delivery systems; for instance, microscopic polymer particles that can absorb, trap, or bind to specific ingredients. An example is a new non-corticosteroid topical cream with a drug targeting JAK1/2 that was recently tested in a phase III clinical trial for atopic dermatitis (Kim et al., 2020).

Intestinal permeability is associated with numerous inflammatory diseases. For instance, disruption of the tight junction in celiac disease facilitates passage of gliadin peptides into the submucosal layer, where they may induce an inflammatory

cascade, eventually leading to destruction of the villous architecture. Thus, therapeutic agents protecting the tight junctions and, thereby, protecting or restoring function of the epithelial barrier may have the potential to prevent or halt intestinal inflammation. The peptide arazotid acetate preserves normal tight junctions and inhibits gliadin-induced macrophage accumulation in the intestine of a mouse model of celiac disease (Gopalakrishnan et al., 2012). Indeed, as the first drug for celiac disease reaching phase III, a clinical trial was commenced in August 2019 with fast track designation by the US Food and Drug Administration (FDA).

Intestinal barrier function is also compromised in inflammatory bowel disease. A small molecule targeting the myosin light chain kinase (MLCK) improves colitis-associated intestinal barrier function (Graham et al., 2019) but cannot be used as a therapeutic agent because of toxic side effects. However, upon inflammatory stimuli, a splice variant of MLCK is recruited to the perijunctional actomyosin ring, where it regulates intestinal tight junctions. The structural feature of the isoform was exploited in a large screening of small drug-like molecules that led to the identification of divertin. Rather than inhibiting the enzymatic activity of MLCK, divertin prevents recruitment of MLCK1 to the subcellular sites of action. Thus, MLCK-mediated dysregulation of the tight junction can be therapeutically blocked by divertin while sparing MLCK function in other tissues, such as smooth muscles.

Strategies to protect axons against degeneration are valuable in multiple sclerosis. SARM1, a central mediator of axonal damage, is activated during injury and disease and initiates a cascade of events leading to axonal degeneration. *SARM1*$^{-/-}$ gene knockout mice as well as gene therapy targeting SARM1 blocks or reduces axon degeneration in mice after nerve transection (Geisler et al., 2019).

Protecting oligodendrocytes from apoptosis could limit tissue damage in multiple sclerosis. Oligodendrocytes are sensitive to oxidative stress, and the radical scavenger edavarone, currently used for stroke and amyotrophic lateral sclerosis, protects several types of brain cells, including oligodendrocytes and oligodendrocyte precursor cells (OPCs), that proliferate and differentiate upon oligodendrocyte damage. Most myelination occurs during infancy, but OPCs persist in the brain during adulthood, where they comprise approximately 5% of CNS glial cells. A recent study has demonstrated that OPCs from aging mice show decreased metabolic function, increased DNA damage, and unresponsiveness to pro-differentiation signals (Neumann et al., 2019). Remarkedly, these age-related changes could be reverted by alternate-day fasting or by treatment with metformin, leading to improved remyelination capacity. A fasting-mimicking diet has been shown previously to ameliorate demyelination and reduce clinical severity in a murine model of multiple sclerosis (Choi et al., 2016).

Other new and old drugs probed for remyelination potential include, but are not limited to, opicinumab targeting Lingo-1 (Tran et al., 2014); the anti-fungal miconazol and the steroid clobetasol (Najm et al., 2015); TFA-12, a member of the vitamin E family (Blanchard et al., 2013); and lithium chloride (Meffre et al., 2015). Intriguingly, Tregs can promote myelin regeneration independent of immunomodulation (Dombrowski et al., 2017). The process is impaired in Treg-deficient mice but rescued upon adoptive transfer of Tregs. Moreover, in brain slice cultures, Tregs accelerate developmental myelination and remyelination in the absence of clear inflammation. In summary, there is an unmet need for therapeutic strategies focusing on protecting tissues under attack from the immune system. Optimally, such strategies should be initiated from the onset of disease to prevent or minimize damage and optimally to also restore lost function.

Genomics

Genome-wide association studies (GWASs) and whole-exome and genome sequencing studies have provided a better understanding of the pathogenesis of autoimmune diseases by identifying genes and pathways that confer inherited risk to disease. Translation into a clinical setting has been more challenging but could transform disease risk prediction, diagnosis, prognosis, stratification, choice of treatment, response to treatment, and drug discovery, and notable examples of such clinical utility have been reported. The strongest and first discovered genetic risk factors across autoimmune diseases are the *HLA* genes that have now been shown to predict disease severity and responsiveness to biological treatment (Zeggini et al., 2019). The challenge that remains, however, is how to use this knowledge for therapeutic development, an issue compounded by the fact that, in many cases, the nature of the autoreactive self-epitopes that trigger and/or drive autoimmunity remains obscure. Moreover, therapeutic approaches that target the HLA molecule, including biologic drugs and small-molecule therapeutics, have met with limited success to date, in part likely because of the highly polymorphic nature of HLA. Indeed, antigen-specific therapies to treat autoimmune diseases have often been considered and applied (Serra and Santamaria, 2019) and have shown promise in animal models of disease. Nevertheless, such approaches have invariably met with difficulty and or/failure in humans. This indicates that, although mouse models are useful in helping us understand aspects of disease mechanisms, they cannot recapitulate the inherent complexity of the human immune system and its interaction with environmental factors.

GWAS-identified non-HLA genes are beginning to show clinical utility. For instance, GWASs have identified a variant in the TNF receptor that confers risk of multiple sclerosis. Follow-up functional studies have shown that this genetic variant results in exon skipping and generation of a novel, soluble form of the factor TNF receptor, which binds to active TNF, inhibiting its action. This finding has contributed to understanding the biological basis of a completely unexpected side effect associated with TNF inhibitors, where some treated patients experienced exacerbation of existing multiple sclerosis or induction of multiple sclerosis or multiple sclerosis-like demyelinating disease. Retrospectively, this pharmacogenetic knowledge could have spared multiple sclerosis patients from being exposed to TNF inhibitors (Gregory et al., 2012).

GWAS have focused on cohorts of patients with uniform clinical manifestations and, therefore, do not fully capture disease heterogeneity or that the associated genetic risk factors often are pleiotropic, thus affecting other autoimmune and non-autoimmune diseases. Cross-disease components of genetic risk

have been identified in a heterogeneous population of patients and controls in the UK Biobank and helped defined overall disease relationships that reflect underlying pathogenic mechanisms, which will be helpful for future drug development. Delineation of genetic pleiotropy will, in particular, be helpful in the near future to predict which drugs may be repositioned from one indication to another or should only be used for certain diseases and not others because of opposite directions of pleiotropic effects (Cortes et al., 2020).

Genome editing technologies are likely to play an increased role in treatment of monogenic autoimmune diseases in particular; newer technologies offer higher precision and less off-target effects. CRISPR-Cas9 was used to correct a pathogenic cytokine receptor mutation important for T cell signaling function (Roth et al., 2018). The newest genome editing approaches, base editors and prime editors, for example, are better suited for correcting single base pair mutations and, furthermore, do not cause double-stranded DNA breaks, which can lead to random insertion or deletion of base pairs or deletion or rearrangement of large chromosomal segments (Anzalone et al., 2019). Although the new technologies are being further refined and are moving toward potential clinical applicability, it will be equally important to optimize how the editors are delivered to the cells.

Environmental Factors

Environmental factors play a major role in conferring risk for autoimmune diseases and are estimated to account for to 40% of the risk in rheumatoid arthritis and 75% in multiple sclerosis. Although environmental factors are complex and differ between diseases and patients, some broad commonalities exist and include tobacco smoking, infection, obesity, and diet, and a molecular understanding of their pathogenic roles is beginning to emerge. To showcase this progress, we selected examples in which environmental factors exert their pathogenic role in the context of immunogenetic risk factors to arrive at a nascent understanding of the combined influence of genetic and environmental risk. However, it is probable that environmental risk factors can differentially affect all components of the immune system and also cause direct tissue damage, which will further fuel autoimmune responses by releasing autoantigens into the periphery, breaking tolerance and slowing down any healing and compensatory mechanisms in the inflamed organs and immune system.

Smoking is associated with development of autoantibodies in systemic lupus erythematosus and rheumatoid arthritis. This break of tolerance has been explained by smoking-induced post-translational modification of autoantigens through citrullination or carbamylation and is assumed to occur in the periphery rather than in the thymus. Citrullinated peptides that are presented to CD4+ T helper cells via disease-associated HLA-DR4 on B cells (Scally et al., 2013) facilitate their class switching and production of autoreactive antibodies, propagating the disease process.

Large numbers of infectious pathogens have been associated with risk of developing autoimmune diseases; however, none of these pathogens have been demonstrated convincingly to have a causal effect. This might simply reflect that different pathogens differentially trigger the immune system in individuals with different genetic backgrounds but lead to an apparently final common pathogenic path that, in clinical terms, is classified as a single disease. More elaborate explanations include molecular mimicry, where an autoimmune response is triggered by foreign antigens that mimic a self-peptide. For instance, one study demonstrated how a microbial peptide found in major classes of bacteria can cause multiple sclerosis-like disease in a humanized mouse model. These mice expressed the dominant multiple sclerosis-associated risk factor HLA-DR2 (DRB1*1501) as well as a cross-reactive TCR, which was isolated and cloned from a multiple sclerosis (MS) patient. This TCR recognized the microbial peptide as well as an autoantigen, myelin basic protein, when presented by HLA-DR2. Subsequent immunization of these mice with the bacterial peptide induced a multiple sclerose-like disease. Importantly, this autoreactive TCR predominantly binds only a small area of the peptide, a phenomenon called hotspot molecular mimicry. This may also help to explain how peptides from different pathogens can trigger an autoimmune response in this manner (Harkiolaki et al., 2009). Hotspot molecular mimicry is also of potential relevance in development of type 1 diabetes. We have already discussed the interplay between obesity and diet and the risk of developing autoimmune disease. However, celiac disease deserves further mention because there is a strong and clear HLA association, and the triggering environmental risk factor is known. Intriguingly, post-translational modification of this antigen and molecular mimicry have also been shown to play roles in the pathogenesis of the disease. Celiac disease, described as an autoimmune-like disease or an immune-mediated enteropathy, is predominantly triggered by ingestion of gluten in HLA-DQ2-positive (HLA-DQA1*0501 and HLA-DQB1*0201) and HLA-DQ8-positive (HLA-DQA1*03 and HLA-DQB1*0302) individuals. A major component of gluten is gliadin, and posttranslational modification in the form of deamidation by transglutaminase 2 of the immunogenic T cell epitope in gliadin is required for an HLA-DQ-restricted T cell response to be initiated (Sollid and Jabri, 2013). Furthermore, molecular mimicry may also play a role in the disease process; crystal structures of TCRs bound to HLA-DQ2 presenting two different bacterial peptides show how molecular mimicry causes cross-reactivity toward the gliadin epitopes (Petersen et al., 2020). This study suggests that a combination of different environmental factors, microbes and food, may play a role in autoimmune diseases.

Knowledge about disease-triggering factors are increasingly being incorporated into clinical practice. Thus, even after onset of disease, multiple sclerosis patients are advised to stop smoking, and those who do will have reduced progression of their disease (Olsson et al., 2017). In the context of celiac disease, patients are advised to adhere to a strict and life-long adherence to a gluten-free diet, which ameliorates symptoms, prevents further damage, and heals intestinal lesions in the majority of patients (Sollid and Jabri, 2013).

Preventive Medicine

Disease risk prediction and prevention or delay of onset by early intervention are ultimate goals of medicine, and a recent proof-of-principle study has demonstrated that an Fc receptor-nonbinding anti-CD3 monoclonal antibody, without deleting

CD3-positive T cells, delays progression to clinical type 1 diabetes in high-risk individuals and possibly also has a disease-modifying effect in new-onset type 1 diabetes. The beneficial effect of this antibody has been explained by modification of the cytotoxic effect of CD8+ T lymphocytes on insulin-producing β cells (Herold et al., 2019).

Genomic studies have allowed construction of disease-specific polygenic risk scores, which sum the effects overall of associated variants for a given disease. It is important to bear in mind that polygenic risk scores give better estimates of the probability of developing diseases that affect more than 5% of the population than in autoimmune diseases that individually have a much lower prevalence (Zeggini et al., 2019). Accordingly, in autoimmune diseases, polygenic risk scores should not be viewed in isolation but considered along with lifestyle and environmental factors, increasingly with longitudinal monitoring of the immune status of high-risk patients by using the various omics technologies, such as proteomics and transcriptomics, and imaging of the suspected target organ to identify preclinical parameters in multivariate evaluation of disease risk. Further, the ability to interrogate the immune cell phenotype and repertoire at a large scale and monitor perturbations in it may lend itself toward immunodiagnostics for disease progression and offer opportunities for specific targeting of autoreactive immune cells to ameliorate disease.

Overall, to more effectively treat autoimmune diseases and ultimately prevent or cure them, there is an urgent need to chronologically map the pathways leading from increased risk of disease to disease manifestation. Current approaches aim to perform high-throughput analysis of integrated datasets, combining genetic, biochemical, epigenetic, RNA, as well proteomics data to expose vulnerable patterns of susceptibility, partition risk into groups, and expand treatment options. Acquiring such information at the population level affords statistical power, eliminates medical anomalies, and ensures alignment of multiple resources into one line of thought. Nevertheless, such powerful insight does not provide patient-specific resolution of disease and does not consider the medical anomaly that may occur in that patient, nor does the treatment option available have any means to reflect this. Moving this field forward requires high-level data machinery and must also harness the information that can be collected on a per-patient basis, using invaluable clinical insight and allowing each patient and each disease to be considered independently.

Moreover, having one autoimmune disease makes developing another more likely. A systematic and multi-disciplinary approach to identify and describe such comorbidities at different stages of the life course of patients and define shared determinants and mechanistic pathways will allow early detection, prediction, and prevention by early interception (Matusiewicz et al., 2019).

Conclusions

The complexity of autoimmune diseases has become increasingly clear, but current treatments are based on a simplistic and reductionist pathogenic understanding. In clinical practice, patients are treated in a reactive step-up, trial-and-error manner starting with different conventional disease-modifying drugs, such as methotrexate for rheumatoid arthritis, interferon-β for multiple sclerosis, and corticosteroids for inflammatory bowel disease and psoriasis. If they fail to adequately respond, they will be escalated to newer drugs, such as JAK inhibitors or biologic drugs. All classes of drugs have in common that they are broadly acting, not disease specific, and associated with considerable side effects and, thus, impersonalized, in contrast to the more personalized treatment that has already entered the oncology field. To achieve more specific and personalized treatment of patients with autoimmune diseases will require a more detailed understanding of the complexity of individual autoimmune diseases and how they unfold in individual patients. To begin to map this complexity, we need to profile bodily fluids and biopsies from affected tissues in a longitudinal manner by applying multi-omics techniques and integrate this information with detailed clinical phenotyping. Such heterogeneous datasets should be leveraged through development of novel statistical methods to support development of new drugs that are more specific and have fewer side effects but could also be used to develop biomarkers. In combination, these approaches should improve treatment decisions so that the right treatment is given to the right patient at the right time.

Here we have outlined exciting new lines of research that are shedding light on the pathogenesis of autoimmune diseases and also contribute to an ever-expanding idea catalog for development of new therapies (Figure 2). Such new therapies need to consider the inter- and intra-complexity of autoimmune diseases but also allow being combined, which is not possible with current disease-modifying drugs because that will lead to an even higher risk of side effects. Optimally, combinatorial therapy should be based on drugs that modify more than one disease-associated pathway in a subtle way, where the immune system is modified enough to curb autoimmunity but, at the same time, allowed to deal effectively with infection and malignant transformation. Defining such sweet spots should allow more specific and efficacious therapies and this could be done, for instance, by identifying disease-protective variants from human genetic studies. With the hindsight offered by the UK Biobank, we could find out whether such variants are associated with side effects such as infection and, if not, then we could understand the molecular mechanisms behind the protective effects and try to mimic them in a drug (Dendrou et al., 2016).

As we move toward patient-centric precision medicine, it will be equally important to move toward patient-centric clinical trial designs to test new therapeutic interventions. The classical way of testing new drugs is by random controlled trials, which are often rigid, costly, slow, and not always easy to interpret. Furthermore, the participating patients and controls are mostly white, which is problematic because there is evidence that the efficacy and safety of drugs differ across populations. One new trial design is the adaptive platform trial, which is much more flexible and faster than the random controlled trial and which, on a rolling basis, compares and identifies drugs and dosages that have the best efficacy and fewest side effects and identifies the subgroup of patients that benefits the most (Angus et al., 2019). It will also be important to include patient-reported outcome measures and ethnically diverse patients and controls

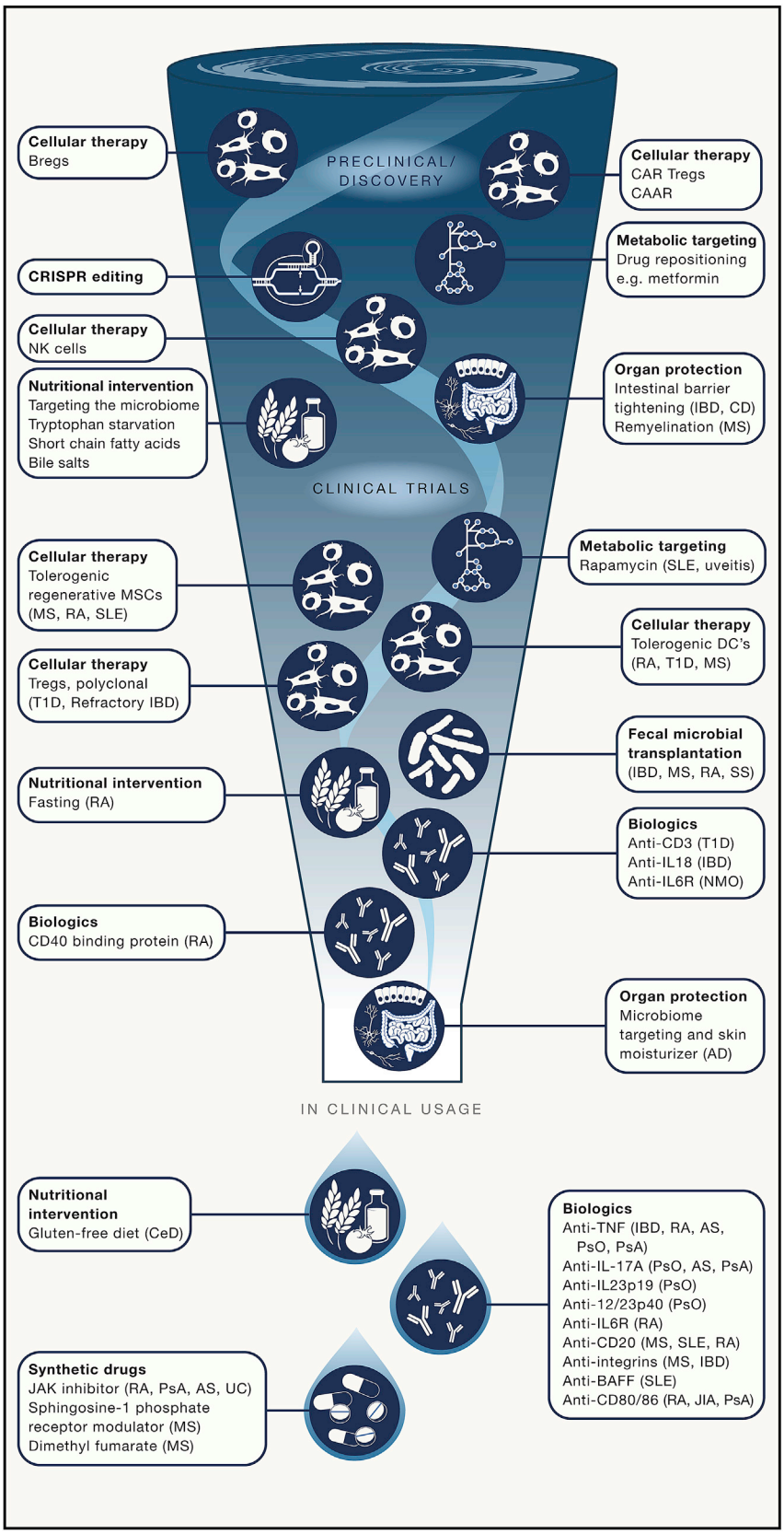

Figure 2. Graphical Summary of Current Therapies, Pipeline of Interventions Being Tested in Clinical Trials, and Potential New Treatment Strategies for Autoimmune Diseases Described in the Text

AD, atopic dermatitis; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; CD, Crohn's disease; CeD, celiac disease; JIA, juvenile idiopathic arthritis; MS, multiple sclerosis; NMO, neuromyelitis optica; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; T1D, type 1 diabetes, UC, ulcerative colitis; DC, dendritic cell; MSC, mesenchymal stromal cell.

in new clinical trials to ensure that new drugs are not only benefitting white patients (Knepper and McLeod, 2018). Last, it is increasingly being recognized that targeting a patient's specific symptom (for example, a swollen joint) is not sufficient for many patients because they also often suffer from more unspecific symptoms, such as fatigue, which is not being treated. Future clinical trials should include reported outcome measures to strive to treat the patient and not only the target (Taylor and Pope, 2019).

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