TARGETED INNOVATIONS IN PRECISION MEDICINE: ADVANCING PERSONALIZED THERAPIES FOR IMMUNE-MEDIATED INFLAMMATORY DISEASES

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Abstract: Immune-Mediated Inflammatory Diseases (IMIDs) pose a significant therapeutic challenge due to their diverse manifestations and the absence of universal treatments. Computational molecular science has enabled the identification of immunological targets for tailored therapies. The review focuses on IMIDs and rheumatoid disorders, showcasing progress in targeted treatments.

Key efforts target T helper 17 (Th17) cells, particularly interleukin 17, with therapies like secukinumab and ixekizumab demonstrating efficacy in conditions such as rheumatoid arthritis and psoriasis. Interleukin 12 and 23-targeting therapies like ustekinumab show promise in diseases like psoriasis and inflammatory bowel disease.

In the realm of Type I Interferons (IFNs), drugs such as sifalimumab and anifrolumab highlight encouraging progress in systemic lupus erythematosus treatment. Integrin and sphingosine-1-phosphate receptor modulation have also shown potential in treating IMIDs. Moving forward, advances in stromal cell targeting, epigenetic regulation, and immune pathway interventions offer promising directions for precision therapies in IMIDs.

In conclusion, the evolving landscape of IMID therapeutics holds promise for improving patient outcomes by addressing the complexities of these conditions with innovative approaches and cutting-edge technologies.

Keywords: autoimmunity; rheumatoid arthritis; psoriasis; connective tissue diseases; inflammation.

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Introduction

IMID is a common immune disorder which can demonstrate various clinical manifestations. Presently there is no universal treatment found for immune-mediated inflammatory diseases. The latest methods of computational molecular science can be used to find immunological targets and develop treatment. These disorders display similar pathologic characteristics (public pathways) as well as individualized characteristics (private pathways) which determine the way they are distributed by phenotype, gender and age, as well as localization and the response to treatment [1]. Among immune-mediated inflammatory diseases there are such disorders as rheumatoid arthritis, spondyloarthropathy, bronchial asthma, CTDs, skin inflammation, e.g. eczema and psoriasis, IBD, multiple sclerosis (MS) and other neurological disorders. Hereby, this series of disorders is in fact challenging. Furthermore, such disorders frequently coincide with multiple pathologies, e.g. CVD, bone diseases, metabolic diseases, cognitive impairment, which aggravate the adverse effects even more. In this review, we mainly concentrate on IMIDs and rheumatoid disorders, since they represent a good example of progress made in targeted disorder treatment [2].

In the last twenty years, immune-mediated inflammatory diseases therapeutic arsenal was modified. Therapy using specific agents has taken the place of widespread use of broad-spectrum immunomodulators. Such agents were developed using medicinal chemistry as well as monoclonal and molecular technology. We list the main factors that have contributed to the development of new targeted therapies, and also suggest next steps that can be taken along this promising path [3].

Table 1. Therapeutic Strategies for Targeting Immune-Mediated Inflammatory Diseases

Target Disease	Therapeutic Strategy	Target Molecule/Pathway	Drug
Rheumatoid Arthritis	Blocking IL-17	Interleukin 17 A	Secukinumab, Ixekizumab
Psoriasis	Blocking IL-17	Interleukin 17 A	Secukinumab, Ixekizumab, Bimekizumab
Psoriatic Arthritis	Blocking IL-23	Interleukin 23 p19	Guselkumab, Risankizumab
Inflammatory Bowel Disease	Blocking IL-12/23	Interleukin 12 and Interleukin 23	Ustekinumab, Risankizumab
Systemic Lupus Erythematosus	Blocking IFN-α	Interferon Alpha	Sifalimumab, Anifrolumab
Multiple Sclerosis	Integrin inhibition	α4 and other integrin interactions	Natalizumab, Efalizumab
Dry Eye Syndrome	Integrin inhibition	Integrin αL	Lifitegrast
Ulcerative Colitis	Sphingosine-1-phosphate receptor modulation	S1P receptors	Fingolimod, Ozanimod
Systemic Sclerosis	Upstream inhibition of IFN-1	Plasmacytoid dendritic cell signaling	Talacotuzumab
Tolerance Induction	Enhancing Treg populations	Regulatory T cells	IL-2, tolerogenic dendritic cells

The Th17 axis

T helper lymphocytes are at the junction of the innate and acquired immune systems. They are believed to be responsible for response of the acquired immunity. Previous research on T helper lymphocytes revealed 2 mutually exclusive phenogroups: type 1 and type 2 helper T lymphocytes. Type 1 helper T lymphocytes stimulate cell immune response against intracellular foreign microorganisms by producing IFNγ, while Type 2 helper T lymphocytes stimulate humoral immune response and reaction to helminthiasis by releasing IL4, IL5 and IL13. At first, type 1 helper T lymphocytes have been considered to promote numerous immune-mediated inflammatory diseases, such as RA [4,5]. However, results of animal and human studies have shown that in some cases type 1 helper T lymphocytes are not necessary, thus stimulating the search for other explanations. In a number of disorders T helper 17 cells were found to be involved. Interleukin 17, a cytokine generated by this subgroup, is a powerful proinflammatory cytokine, that, along with tumor necrosis factor alpha and interleukin-1 beta takes part in recruiting neutrophils, stimulating production of osteoclasts and suppressing chondrocyte metabolic function [6]. Since the finding of T helper 17 cells, they have been detected in numerous immune-mediated inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, prosiasis, IBD, and spondyloarthritis. Suppressing T-helper 17 cells, whether through suppressing interleukin 17 or T-helper 17 cells differentiation, is presently a field of increasing therapeutic interest [7].

Strategies to block IL-17

Interleukin 17 is a family of 6 cytokines: A, B, C, D, E, and F. Interleukin 17 A is the prevalent, powerful and the most described one. Interleukin 17 self-dimers and heterodimers transmit signals through interleukin 17 receptors: IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE. The exact interleukin 17 receptors cell distribution, binding affinity and the following activity are still not completely studied.

However, it is clear that suppression of interleukin 17 or interleukin 17 receptors may produce various responses in terms of quantity and quality [8,9].

Secukinumab is one of fully human MABs against interleukin 17 A. It is reported to be effective against spondyloarthritis, psoriatic arthritis, and psoriasis vulgaris. However, it did not show positive results against rheumatoid arthritis [10,11]. Ixekizumab is a humanized anti-interleukin 17 A MAB. It was proved to be efficient against psoriatic arthritis and psoriasis. The studies on psoriatic arthritis showed that joint effectiveness of interleukin 17 suppression is identical to tumor necrosis factor suppression and higher than in rheumatoid arthritis, while cutaneous effectiveness is higher than that of tumor necrosis factor suppression [12,13]. Bimekizumab is a humanized monoclonal antibody which is targeted against interleukin 17 A and interleukin 17 F epitope. It demonstrated positive results against psoriatic arthritis and psoriasis [14,15]. More biological products which exert a neutralizing effect on interleukin 17 A and interleukin 17 F, such as BsMABs, are presently being developed. Interleukin 17 suppression is related to Candida infection progression, that is mostly not grave, but it emphasizes the major role of interleukin 17 in protection against fungi [16,17].

Besides neutralizing of cytokines, interleukin 17 suppression may be reached by inhibition of interleukin 17 receptor. Brodalumab is a human monoclonal antibody that is directed against interleukin 17 receptor A, that is necessary for interleukin 17 A, interleukin 17 F, interleukin 17 A/F, interleukin 17 C, and interleukin 17 E (interleukin 25) signaling [18]. Brodalumab shows a much wider suppression effect on interleukin 17 signaling than specific cytokines targeting. However, interleukin 17 E blockade, that stimulates a type 2 helper T lymphocytes response whereas possibly suppressing differentiation of T-helper 17 cells in mouse model, and in human rheumatoid arthritis and inflammatory bowel disease, might be in some cases not productive [19]. Patel and Kuchroo reported that it could account for the brodalumab inefficiency in rheumatoid arthritis, even though ixekizumab and secukinumab show moderate effectiveness [20]. Brodalumab is licensed for psoriasis therapy in the US and Japan, and will soon be authorized for marketing in Europe.

The same way as in rheumatoid arthritis, interleukin 17 suppression seems to be less effective against noninfectious uveitis. These data emphasize that cytokines may not be essential in the pathogenic process even if detected in affected tissue [21]. Moreover, brodalumab and secukinumab were proved to exacerbate Crohn's disease, a type of IBD. Hereby, contrary to its proinflammatory activity in other disorders, interleukin 17 A can act as a downregulator of immune system in the intestinal mucosal barrier, possibly through interplay with elements of fungi of the gut flora [22,23]. These findings are essential in context of overlap of seronegative immune-mediated inflammatory diseases, e.g., studies on interleukin 17 suppression in psoriasis showed hemorrhagic diarrhea as a side effect. Also, concerns regarding a probable connection of brodalumab and suicidal thoughts hindered moving forward with studies on this drug. However, those concerns could be exaggerated [24].

Th17 differentiation and the IL-12 superfamily

Members of the interleukin 12 family, such as interleukin 12, interleukin 23, interleukin 27, and interleukin 35, play a critical role in the polarization of naive T helper lymphocytes to different effector phenotypes. Those interleukins and their receptors can be found in the form of dimers which are significantly homologous in sequence among subunits. However, their roles in the immune system are frequently opposite [25]. Growing understanding of this family, especially interleukin 12 and interleukin 23, has opened the door to therapeutic approaches targeted at suppression of T helper 17 lymphocytes differentiation [26].

Ustekinumab is a human monoclonal antibody against interleukin-12/interleukin-23 p40, which received a license to be used in Crohn's disease, psoriatic arthritis and psoriasis therapy. This drug also demonstrated efficacy in spondyloarthritis in an open trial and a post-hoc study [27]. It is noteworthy that contrary to interleukin 17 A suppression, ustekinumab shows efficacy against Crohn's disease with signs of long-term positive effect after one infusion. Interestingly, secukinumab was superior to ustekinumab in grave psoriasis with similar safety characteristics. These findings show that T helper 17 lymphocytes differentiation suppression by suppressing interleukin 23 is different from the direct interleukin 17 A suppression, and also that relative effects vary by disorder [28,29].

There is an option of selective blockade of interleukin 23 via targeting interleukin 23p19. A number of monoclonal antibodies are presently being developed for inflammatory bowel disease and psoriasis therapy. Intended benefits of selective suppression of interleukin 23 over interleukin 12 and 23 suppression involve the possibility of a reduction in infections gravity and risk of malignity. In fact, post-marketing info on psoriasis indicate an elevated risk of nonmelanoma cutaneous cancer with ustekinumab. This could be a result of suppression of cell immunity mediated by interleukin 12. It is yet to explore if these possible positive effects lead to actual benefits [30].

Head-to-head trials in psoriasis

H2H clinical trials in psoriasis were especially revealing regarding the relative prevalence of pathological pathways in this disorder. E.g., guselkumab suppression of interleukin 23 and ixekizumab suppression of interleukin 17 A showed better results than tumor necrosis factor alpha suppression with adalimumab and etanercept, respectively [31,32]. Other studies showed that secukinumab suppression of interleukin 17 A, brodalumab suppression of interleukin 17 receptor, and risankizumab suppression of interleukin 23 p19 subunit led to better results than ustekinumab suppression of interleukin 12 and 23 subunit p40. Inhibition of interleukin 17 A, interleukin 17 A/F, interleukin 17 receptor, and interleukin 23 subunit p19 showed similar efficacy in different studies. However, as in Crohn's disease, inhibition of interleukin 23 subunit p19 seems to exert especially prolonged effect [33,34].

The difference between the interleukin 17 and interleukin 12/23 subunit p40 inhibition is yet to be explained. Although, T helper 17 lymphocytes release not only interleukin 17 A, but other cytokines as well, and interleukin 17 A is also generated by other cell types besides T helper 17 lymphocytes. Those are affected by interleukin 23 family signaling to a lesser extent [35]. There are environments, such as the

intestine, where interleukin 17 can act as a regulator. Moreover, inhibition of interleukin 12/23 subunit p40 results in suppression of interleukin 12 signaling, which is a pro-Type 1 helper T cells cytokine that is crucial in development of Crohn's disease. Thus, it is clear that inhibition of several cytokines or inhibition of one immune axis at distinct levels may lead to numerous results that vary by the tissue and disorder [36].

Interleukin 17 is essential in various immune-mediated inflammatory disease. Although, the fact that it is detected does not mean its prevalent role in development of the disease. In a particular case, e.g. in psoriatic arthritis, its impact can be different in different tissues. Moreover, inhibition of the same axis at different levels may lead to various outcomes [37].

The type I IFN axis

Interferons are a family of powerful immunostimulators that can belong to one of 3 groups: type 1 (interferon alpha, beta, epsilon, kappa and omega), type 2 (interferon gamma) and type 3 (interferon lambda). Interferon alpha is the most described and prevalent of all type 1 interferons. It can be found in thirteen different but homologous states. Interferon-1 genesis is highly controlled so its concentrations normally are almost not detectable. Although, in inflammation interferon 1 is massively and quickly generated [38]. Plasmacytoid dendritic cells are particularly prone to production of interferon 1. They release large amounts of intracellular PRRs, e.g. TLR7 and TLR9. Upon ligation of interferon-1 receptor, interferon 1 enhances the expression of interferon-stimulated genes (ISG) [39,40]. Interferon exerts a major proinflammatory effect, which involves driving pDCs to mature and activate, as wells as triggers polarization of type 1 helper T cells and T helper 17 cells, downregulates T-regs activity, and stimulates activation of B lymphocytes and the following genesis of antibodies [41].

Interferons involvement in immunity is emphasized by evidence of lupus-like autoimmune disorders reoccurring in individuals getting interferon alpha therapy for cancer and CVH. Moreover, interferon-stimulated genes are enhanced in various stages of disorder, such as SLE. Expression of interferon-stimulated genes is in correlation with more serious disorders [42,43]. They are enhanced in pSjS, scleroderma and rheumatoid arthritis as well. In fact, major genesis of interferon 1 by plasmacytoid dendritic cells, which was detected after ligation of toll-like receptor 7/9 by endogenous nucleoacids, could possibly account for the origin of cytokines in systemic lupus erythematosus development, while therapeutic approaches to inhibit interferon 1 pathway are presently being developed [44].

Blocking IFN-α signaling

Sifalimumab is a human monoclonal antibody against various interferon alpha types, particularly interferon alpha 6, interferon 2 b and interferon 2 a. This drug demonstrated a positive effect in a phase IIb study in systemic lupus erythematosus. In this trial, 431 subjects were randomly divided into two groups, one of which would get monthly administration of this drug and the other would get placebo [45,46]. Whereas the study did not meet its main endpoint in dose groups, the highest dose turned out to show better effects than placebo. As was prognosed, subjects with a high interferon signature demonstrated better results. In line with the interferon alpha involvement in antiviral immunity, VZV infections have been elevated in sifalimumab subgroup depending on dosage [47]. Some studies on sifalimumab were conducted in other immune-mediated inflammatory disease. A study on polymyositis and dermatomyositis showed that sifalimumab induced a 53-66 precent inhibition of 13-gene interferon signature, which is in direct correlation with amelioration of muscle strength. Although, sifalimumab administration did not lead to an inhibition of interferon gene signature in phase 1 trial on psoriasis [48,49].

Rontalizumab is a human monoclonal antibody against 12 interferon-alpha types. This drug was studied in systemic lupus erythematosus and did not show desired results. Notably, subjects who demonstrated some efficiency of the drug had lower levels of interferons [50]. This drug did not show a connection to elevated viral infections. These findings can indicate ineffective on-target interactions. However, different trial design, especially regarding accompanying immune suppression, hinder comparing with sifalimumab treatment. Distinctions between interferon-alpha inhibition by sifalimumab and rontalizumab can have impact on the relative effectiveness as well [51,52].

Enhancement of active immunization against interferon alpha in a form of vaccine is presently being developed. Interferon alpha kinoid is conjugated protein of inactive interferon alpha coupled to KHL. A randomized study on systemic lupus erythematosus was conducted and involved twenty-eight subjects [53]. From three to four doses of interferon alpha kinoid were administered which led to an enhancement of anti-interferon alpha antibodies. Notably, anti-interferon alpha antibodies titers turned out to be greater in subjects who showed positive baseline interferon gene signature and at 112^{th} day were in inverse correlation with interferon gene expression. Safety of this treatment is yet to be investigated [54,55].

In addition to interferon alpha neutralization, there is an option of suppressing interferon alpha receptor. Anifrolumab is a human monoclonal antibody against IFNAR1. A phase IIb study of 305 subjects with systemic lupus erythematosus demonstrated that anifrolumab exerts positive effect against single-organ and global impacts of the disorder [56]. This drug was proved to have higher efficacy in subjects with higher interferon levels and showed a similar risk of VZV as sifalimumab. In Japan, 2 cohort studies on systemic lupus erythematosus showed that anifrolumab is more powerful and consistent in inhibition of interferon gene in comparison to sifalimumab. Anifrolumab is presently being developed (phase 1) to be applied in scleroderma therapy [57,58].

Upstream inhibition of the IFN-I axis

A number of therapeutical approaches of upstream suppression of interferon 1 generation are presently being developed. Litifilimab (BIIB059) is a humanized monoclonal antibody against BDAC2. BDAC2 is a plasmacytoid dendritic cells-specific surface receptor which controls downregulation of generation of interferon 1. A phase Ib study of twelve subjects with systemic lupus erythematosus showed amelioration of cutaneous lesions as well as a decrease in interferon gene

release [59,60]. Talacotuzumab is a humanized cytotoxic monoclonal antibody against interleukin-3 receptor which is massively released on plasmacytoid dendritic cells. In vitro, this drug decreased the levels of plasmacytoid dendritic cells in blood of subjects with systemic lupus erythematosus, resulting in suppression of interferon 1 gene release. Aside from AB treatments, various molecular suppressors of toll-like receptor 7/8/9 signaling are presently being developed for psoriasis and systemic lupus erythematosus therapy. However, discoveries made in early stages of the studies are still not officially published [61].

Inhibition of type II IFNs

Whereas interferons 1 are a major trigger for interferon gene signature, interferons 2 and 3 also contribute to these genes signature. Unlike interferon 1, interferon gamma signaling is carried out through interferon gamma receptor, albeit some overlap is present. AMG 811 is a monoclonal antibody against interferon gamma. It is currently being developed and is has demonstrated a decrease in blood concentrations of interferon-gamma-dependent CXCL-10 and interferon-gamma mediated gene release in whole blood of subjects with systemic lupus erythematosus [62,63]. Moreover, in a phase I trial, AMG 811 therapy decreased these two markers in subjects with active LN, however, temporarily and without significant clinical effect. There is presently little evidence for the role of interferon gamma in autoimmune disorders, however new signs of its involvement in systemic lupus erythematosus pathogenesis are constantly being found [64].

Systemic lupus erythematosus is a difficult disorder to find a treatment for. There have been numerous unsuccessful attempts and only one successful (belimumab). Information on interferon axis targeting is still incomplete and conflicting. Nevertheless, the biology seems convincing and a number of substances are being developed. Moreover, with Janus kinase suppressors being approved, there is a promising path of targeting interferon signaling pathways directly with substances whose characteristics are fully understood. Thanks to this wide arsenal and thoughful design of studies, we can expect to obtain a definitive answer to the theory connecting interferon function and systemic lupus erythematosus [65,66].

Targeting cell adhesion

Integrin blockade

Cell adhesion molecules (CAMs) are of great importance in intercellular interplay and are critical to recruit ICs from vascular system to local tissues. Integrin family is particularly crucial in this context, since it binds to ECM contents and specific receptors and thus modulates strong adhesion of mucosal ECs and endothelial ECs with leukocytes. There are 6 integrins that are released only on leukocytes: lymphocyte function-associated antigen 1 (LFA1), macrophage-1 antigen (Mac1), integrin alpha X (αX), integrin αDβ2, integrin α4β7, integrin αEβ7 [67,68]. Particularly interesting are LFA1, α4β7 and αEβ7. Lymphocyte function-associated antigen 1 is essential for immune synapse (IS) formation. A4β7 binds to mucosal vascular addressin cell adhesion molecule 1 on intestinal ECs surface and thus modulates intestine-specific homing of lymphocytes. AEβ7 binds epithelial cadherin on intestinal ECs surface and could be essential for retention of lymphocytes in the mucous membrane. Hereby, suppression of recruitment of lymphocytes to organs may be reached by blockade of this interplay, which specificity is defined by cell tropism of CAMs of the targeted cells [69,70].

Natalizumab is a monoclonal antibody against integrin alpha 4. This drug was one of the first to be applied in therapy on autoimmune disorders. Natalizumab suppresses recruitment of lymphocytes at BBB and intestine (α4β1 and α4β7 respectively). It has shown effectiveness against MS and Crohn's disease [71]. Although, follow-up observation of subjects administered this drug revealed occurrence of PML, a grave and mostly fatal CNS disease induced by John Cunningham virus. Hereby, whereas this drug is still applied for multiple sclerosis, it has adverse effects which restrict its application in Crohn's disease [72]. Albeit licensed in the United States, natalizumab could not get European approval for Crohn's disease treatment. Efalizumab is a monoclonal antibody against integrin alpha L which showed efficacy against psoriasis. Likewise, in 2009 it was removed from the market after it was revealed that this drug leads to progression of progressive multifocal leukoencephalopathy. Nonetheless, there is a molecule suppressor of LFA1 – lifitegrast, which topical application in the eyes has got a license for dry eye syndrome therapy. Moreover, AJM300 and firategrast, molecule suppressors of integrin alpha 4, are presently being developed for UC and multiple sclerosis therapy [73,74].

A number of specific integrins were discovered for reduction of OIs risk. Specifically, there were discovered various monoclonal antibodies against intestine-specific integrin α4β7 or mucosal vascular addressin cell adhesion molecule 1. Etrolizumab is a monoclonal antibody that is targeted exclusively against integrin beta 7 [75,76]. This drug suppresses αEβ7 binding to epithelial cadherin. It is yet to investigate if this leads to significant clinical effectiveness. Although, a phase II trial in ulcerative colitis showed that etrolizumab administration effectiveness is in direct correlation with αE release in gut mucosal barrier, thus suggesting a promising stratification biomarker for its application. Presently, there seems to be no connection between intestine-specific integrin suppressors and elevated progressive multifocal leukoencephalopathy risk [77].

Except for the short period of efalizumab application in psoriasis, suppression of integrins for now has little clinical use aside from the central nervous system and intestinal autoimmune disorders context. A post-hoc study of an RCT of vedolizumab in Crohn's disease showed a tendency toward EIMs resolvement, that has been represented by early results of a cohort study of subjects with ulcerative colitis and Crohn's disease [78,79]. Although, recently several cases of sacroiliitis and arthritis were found in subjects administered vedolizumab. Along with the bell-shaped dose response curve in etrolizumab study in ulcerative colitis, these findings could mean that integrin suppression affects proinflammatory and antiinflammatory lymphocytes [80,81].

Sphingosine-1-phosphate receptor blockade

S1P receptor family involves 5 members which affect cellular lifespan, migration and proliferation, as well as cell-

to-cell communications, functioning of endothelial barrier, and blood vessel tone. Specifically, S1P-1 receptor is essential for lymphocyte transfer from lymph nodes, the spleen, the tonsils and other secondary lymphoid organs. Receptor agonists help avoid B-lymphocytes and T-lymphocytes escape into bloodstream by internalizing and degrading receptors [82,83]. Fingolimod is a small molecule sphingosine-1-phosphate receptor agonist that has been licensed for RRMS treatment, although it was related to serious VZV infections and a negative impact on heart and liver. Ozanimod is a selective small molecule sphingosine-1-phosphate receptor 1 and 5 agonist. In a recent phase II study of ulcerative colitis this drug showed effectiveness against the ulcerative colitis with a dose-dependent decrease in lymphocyte levels in blood and an acceptable adverse-event profile [84,85].

Future perspectives in IMID therapeutics

In context of immune-mediated inflammatory diseases there are still a lot of unresolved issues. Especially, remission is still not reached in desirable numbers, as well as a prolonged DFR. It is still impossible to repair immune dysfunction. In addition, whereas there are findings that indicate that some autoimmune disorder manifestations can be relieved, e.g. sleep disorder or chronic fatigue, in presence of appropriate treatment, pain pathways seem to differ from inflammatory pathways, hence pain can continue even though inflammatory process is properly regulated [86]. Presently in clinical studies there is in fact a wide range of targets. Additional studies of the kinome, involving targeting tyrosine kinase 2 and interleukin-1 receptor-associated kinase 4, can potentially provide positive results. Cell therapy should also be closely investigated, including studies on application of stem cell, altered Tregs, CAR-T cells, and tolerized DCs. There are phase II studies in progress that investigate creative approaches to treat rheumatoid arthritis that include interplay of the immunity and nervous system with application of biostimulating [87,88].

New targets

More and more intricate use of avant-garde tissue testing used on image-guided biopsy of diseased tissue shows new therapeutical targets for immune-mediated inflammatory disease. Specifically, available biopsies in eczema, inflammatory bowel disease, synovitis and psoriasis not just let researchers conduct trials, but let identify molecular disease phenotypes called pathotypes. This could open the door to new therapeutic approaches, which, taken together with potent biological and computational methods, is able to elucidate new targets such as cells or molecules [89,90]. Single-cell RNA-seq technologies also offer opportunity to find essential cell sets. $PD1^{hi}CXCR5$-peripheral T_h cells are able to assist B lymphocytes in nonlymphoid tissues in rheumatoid arthritis, which represents a new promising therapeutic approach [91,92].

Biopsy samples single-cell analysis has attracted attention to nonprofessional ICs, particularly to those in tissue stroma. Endothelial, angiogenesis and CAMs targeting is already closely investigated, while newer trials show a potential of fibroblast cells targeting in immune-mediated inflammatory disease. Various trials have identified stromal cell sets and divided them into groups based on membrane biomarkers, including CD90 membrane glycoprotein, FAP-alpha and PDPN, that are essential in tissue inflammatory processes [93,94]. Targeting them showed promising results in vivo in animal model studies. Might the neglect of the stromal role in previous trials account for the unsuccessful results of many immune-mediated diseases treatment? That would be in accordance with integrated model of immunity response, hereby, in case of chronic conditions, healthy simultaneous control and emergence of activator and regulator pathways in immunity are gone. Those stroma pathways, which are possibly reacting to epigenetic mediators, involving hypoxia, constant injury or repeated exposure to cytokines, hereby facilitate the disorder development. A recent study in subjects with rheumatoid arthritis demonstrated presence of CD45−CD31−podoplanin preinflammatory MSCs. The detected MSCs indicate a possible subsequent clinical manifestation of the disorder [95].

New strategies

A molecular revolution is about to occur in the study and treatment of immune-mediated inflammatory diseases. New approaches will rely on the studies of epigenome, metabolome, proteome and transcriptome. These novel techniques are presently investigated for their capacity to predict progression of the disorder, appropriate treatment methods and possible undesirable effects for subjects with immune-mediated inflammatory diseases [96,97]. Preliminary results of blood and tissue tests of subjects with rheumatoid arthritis, inflammatory bowel disease and psoriasis are encouraging. To date, there is little critical confirmation of this molecular theory, although its success is quite possible [98].

Future strategic strides will address the strategies that lead to strong remission and subsequent sustenance, which can appear from identifying stroma or immunity pathways related to remission in immune-mediated inflammatory diseases. These methods are believed to be the optimal treatment in oncology [99]. However, it was not as widely applied in immune-mediated inflammatory diseases. Possibly, the growing number of accessible methods and a connection between some methods with determinable states and immune statuses could be acquiescent in this context. Is there a way to discover an immunity targeting drugs that would help achieve desirable results in terms of remission? A major challenge is still the finding of a way to evaluate immunity condition. The ultimate result of this high-precision resolvement of disorder progression would be to support new combined immunotargeted treatment methods in immune-mediated inflammatory diseases [100].

As we advance towards digital clinical records and major biobanks, future promising approaches could be found using comparisons which are presently available in immune-mediated inflammatory diseases. There are major well-described biobanks for immune-mediated inflammatory diseases which are ready for comparisons to identify immunity pathways, which are mostly involved or insufficient in immune-mediated inflammatory diseases and which can provide more disorder-specific knowledge [101]. E.g., IMID-Bio-UK metaconsortium, that involves evidence from rheumatoid arthritis, psoriatic arthritis, autoimmune hepatitis, psoriasis, SLE, SjS, and PBC, provides such opportunities.

Surveying such evidence provides opportunity for development or confirmation of detected pathways prior to clinical studies. It is promising that clinical studies are quickly developing to comprise close computational investigation of novel agents prior to clinical administration. Moreover, availability of such banks related to phase 2/3 clinical studies should provide opportunity to conduct large-scale surveying of the cohorts to reveal information on understanding and clinical effectiveness [102].

Table 2. Emerging Therapeutic Strategies for Immune-Mediated Inflammatory Diseases

Strategy	Description	Potential Benefits
Biologics Targeting Cytokines	Use of monoclonal antibodies to inhibit specific pro-inflammatory cytokines	Reduced inflammation and faster symptom relief
Small Molecule Inhibitors	Introduction of targeted therapies for intracellular signaling pathways	Greater specificity and fewer side effects
Immune Checkpoint Modulators	Reinforcement of immune regulation through checkpoint inhibitors	Restoration of immune balance and tolerance
Stem Cell Therapy	Application of stem cells to regenerate damaged tissue and modulate the immune response	Long-lasting effects on inflammation and repair
Microbiome Modulation	Use of prebiotics, probiotics, and fecal transplants to influence immune function	Improved gut health and immune regulation
Nanotechnology	Delivery of therapeutics via nanoparticles for targeted treatment	Enhanced delivery efficiency and reduced toxicity
Gene Editing	Application of CRISPR to correct genetic mutations leading to autoimmune responses	Potential for permanent resolution of disease
Combination Therapies	Strategic use of multiple therapeutic modalities for synergistic effects	Increased efficacy and reduced likelihood of resistance

Tolerance induction and other novel approaches

The main goal in immune-mediated inflammatory disease area is still the ability to repair homeostasis of ICs. It is yet to investigate if this is doable on the basis of the present knowledge of the immune-mediated inflammatory diseases which includes the tolerance impairment. Multiple promising methods are concentrated on extending Treg sets (e.g. interleukin 2), application of tolerogenic DCs, etc. Another new direction is the application of CAR T cells targeted against B lymphocytes in auto-antibody genesis disorders, e.g. SLE. Furthermore, myeloablative autologous HSCT was successfully applied for severe disorders, e.g. scleroderma, and could turn out to be useful in more immune-mediated inflammatory diseases. [103] Another interesting possibility is to describe of molecular pathways which underlie progression of irAEs subsequent to the application of ICIs in oncology. This allows to conduct a natural experiment, where regulation checkpoints are circumvented and the following tissue injury may be assessed in a real time manner, whereas the exact manifestation point is known. Moreover, whereas upstream pathways which trigger immune-mediated inflammatory diseases are more and more identified, e.g. microbiota and tobacco use impact in lung lesions in rheumatoid arthritis, more methods of prevention of immune-mediated diseases will emerge [104,105].

Conclusion

The exploration of immunological targets and tailored therapies for Immune-Mediated Inflammatory Diseases (IMIDs) represents a significant advancement in addressing the complexities of these conditions. Targeting specific pathways, such as T helper 17 (Th17) cells and Type I Interferons (IFNs), has shown promise in conditions like rheumatoid arthritis, psoriasis, systemic lupus erythematosus, and inflammatory bowel disease.

Therapies like secukinumab, ixekizumab, ustekinumab, sifalimumab, and anifrolumab highlight the progress made in developing targeted treatments that aim to modulate key immunological factors involved in IMID pathogenesis. Additionally, approaches focusing on integrin and sphingosine-1-phosphate receptor modulation offer further avenues for therapeutic intervention.

Looking ahead, advancements in stromal cell targeting, epigenetic regulation, and immune pathway interventions indicate a promising future for precision therapies in IMIDs. The intersection of computational molecular science with clinical insights has set the stage for personalized treatment strategies tailored to individual patient profiles and disease characteristics.

In conclusion, the ongoing evolution of IMID therapeutics underscores a transformative era in precision medicine, where the intricate interplay of immune responses and molecular pathways is leveraged to enhance patient outcomes and quality of life for individuals affected by these challenging diseases.

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