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Triggers, Timescales, and Treatments for Cytokine-Mediated Tissue Damage

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Abstract

Inflammation is an essential cytokine-mediated process for generating a neutralizing immune response against pathogens and is generally protective. However, aberrant or excessive production of pro-inflammatory cytokines is associated with uncontrolled local and systemic inflammation, resulting in cell death and often irreversible tissue damage. Uncontrolled inflammation can manifest over timescales spanning hours to years and is primarily dependent on the triggering event. Rapid and potentially lethal increase in cytokine production, or a 'cytokine storm,' develops in hours to days and is associated with cancer cell-based immunotherapies, such as CAR-T cell therapy. On the other hand, some bacterial and viral infections with high microbial replication or highly potent antigens elicit immune responses that result in supraphysiological systemic cytokine concentrations which manifest over days to weeks. Immune dysregulation in autoimmune diseases can lead to chronic cytokine-mediated tissue damage spanning months to years, which often occurs episodically. While the initiating events and cellular participants may differ in these disease processes, many of the cytokines that drive disease progression are shared. For example, upregulation of IL-1, IL-6, IFN-γ, TNF, and GM-CSF frequently coincides with cytokine storm, sepsis, and autoimmune disease. Targeted inhibition of these pro-inflammatory molecules via antagonist monoclonal antibodies has improved clinical outcomes, but the complexity of the underlying immune dysregulation results in high variability. Rather than a "one size fits all" treatment approach, an identification of disease endotypes may permit the development of effective therapeutic strategies that address the contributors of disease progression. Here, we present a literature review of the cytokine-associated etiology of acute and chronic cytokine-mediated tissue damage, describe successes and challenges in developing clinical treatments, and highlight advancements in preclinical therapeutic strategies for mitigating pathological cytokine production.

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Introduction

Cytokines are essential regulators of the immune response that mediate protective inflammation, but uncontrolled production by hyperactivated immune cells induces toxicity and adverse conditions. Pathologies that arise from excessive inflammation driven by a ‘cytokine storm’ are observed in cytokine release syndrome (CRS), systemic inflammatory response syndrome (SIRS), and sepsis.[1,2] The severity can vary substantially, ranging from mild symptoms to potentially life-threatening conditions. Mild symptoms are temporary and include fatigue, muscle and joint pain, headache, fever, and rash. In more severe cases, immune hyperactivation may lead to acute respiratory distress syndrome (ARDS), hemophagocytic lymphohistocytosis (HLH), disseminated intravascular coagulation (DIC), and multi-organ failure.[3] These symptoms are driven by local and systemic hyper-physiological concentrations of one or more cytotoxic effector cytokines which includes interleukin (IL)-6, IL-1, granulocyte macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFN-γ) and tumor necrosis factor (TNF).[4] Innate immune cells, primarily monocytes and macrophages, as well as T cells of the adaptive immune system are key participants and often work in concert to amplify cytokine production which results in the characteristic symptoms (Table 1).[5,6]

Aberrant cytokine production by hyperactivated immune cells may be triggered by infections, immunotherapies and autoimmune conditions. The manifestation of excessive cytokine production may be immediate, delayed, and/or persist as a longer-term organ- or tissue-specific chronic inflammatory condition.[7] Rapid development of CRS over a few hours to days has been documented in monoclonal antibody (mAb) therapies designed to promote graft acceptance or cancer clearance, as well as post-infusion of engineered T cell therapies (Figure 1a).[8-11] On the other hand, infection by microbes that elicit a particularly intense immune response or that have a high replicative potential may result in SIRS-associated sepsis that manifests over several days to weeks (Figure 1b).[12] Exemplary SIRS-like pathology is observed in some patients with acute manifestations of COVID-19, in which elevated serum IL-6 correlates with respiratory and organ failure, with adverse clinical outcomes.[13] The use of immunosuppressive drugs has had limited success in managing SIRS-like pathologies. For example, the use of corticosteroids to treat inflammation arising from SARS and MERS did not improve mortality but delayed viral clearance.[14,15] On the other hand, dexamethasone treatment lowered mortality among COVID-19 patients receiving respiratory support but not among those who did not receive respiratory support, suggesting that the benefit of glucocorticoid modulated inflammation to mitigate lung injury maybe nuanced and depend on disease severity.[16] Other long-term and episodic inflammation is associated with autoimmune conditions and spans weeks to years, such as that observed in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or chronic graft-versus-host disease GvHD (cGvHD) (Figure 1c). For such conditions, broad immunosuppressive drugs increase susceptibility to opportunistic infections.

Common features associated with the hyper-production of cytokines permit the development of therapies that might be applicable across different forms of CRS that have similar etiology. A widely used strategy is to block the activity of the cytokines or their cognate receptors, an approach with origins in the management of rheumatic disease. As a participant in RA, TNF was the first cytokine to be fully validated as a therapeutic target.[17] Clinical trials using a combination of mAbs targeting TNF (adalimumab) and methotrexate (MTX) have an established record of safety and clinical efficacy for effectively reducing cytokine-mediated tissue damage in RA.[18] However, in RA refractory to TNF inhibition, alternative therapeutic targets are necessary to induce remission. IL-6 is a participant in both RA and more acute forms of CRS, and the administration of mAbs against the IL-6 receptor (tocilizumab) is frequently used to treat RA that is refractory to MTX or TNF inhibition.[19] Tocilizumab is also is clinically approved by the U.S. Food and Drug Administration (FDA) for the treatment of chimeric antigen receptor (CAR) T cell–induced CRS, with proven efficacy, minimal side effects and without negatively affecting response to therapy.[20] More recent developments in RA focus on inhibiting GM-CSF using mavrilimumab, an inhibitor of GM-CSF receptor-α. In clinical phase II RA trials, GM-CSF antagonism has efficacy similar to that of TNF blockade in mitigating tissue destruction.[21] Early clinical data from GM-CSF inhibition in patients with COVID-19 pneumonia suggests potential efficacy in improving clinical outcomes, and a follow-up randomized controlled trial is underway (COMBAT-19, NCT04397497).[22] Siltuximab, an FDA approved IL-6 agonist for use in multicentric Castleman disease, is undergoing phase III clinical trials for the treatment COVID-19 associated immune hyperactivation (NCT04330638 and NCT04329650). However, the complete cytokine profile of CRS is diverse, involving the monocyte and macrophage-associated cytokines IL-8, IL-10, IL-12, TNF, IFN-α, monocyte chemotactic protein (MCP)-1 and macrophage inflammatory protein (MIP)-1α, in addition to the aforementioned cytokines.[23] Therefore, while targeted cytokine inhibitors mitigate aberrant cytokine-mediated tissue destruction, the effectiveness of cytokine targeted therapeutics are difficult to predict due to the complex network of cytokines and disease heterogeneity.

In this review, we discuss recent work that has advanced the understanding of cytokine mediated tissue damage with distinct onset profiles arising from cancer immunotherapy, infection, and autoimmune disease. We describe the contributions of cytokines in disease pathogenesis, and how existing mAb therapies are repurposed to treat cytokine-mediated tissue damage. Lastly, we describe recent pre-clinical work in developing new therapeutic options to mitigate damage from hyperactivated immune cells.

Cytokine-Mediated Tissue Damage on Short Timescales: Immunotherapies

Acute cytokine release is associated with cell-based cancer therapies such as engineered T cells, and T cell activating immunotherapies. It is well-recognized that abrogating cytokine-mediated off-target toxicity is a critical step in their widespread application. These therapies derive their efficacy, in part, from non-physiologic T cell activation that permits rapid and sustained production of effector cytokines. While such behavior is programmed to promote anti-tumor efficacy, it also leads to the unintentional consequence of notable toxicity in some cases, which typically develops within a few days after infusion and, if left untreated, may lead to death. Serum IL-6, IL-10, and IFN-γ are among the core cytokines that are consistently found to be elevated in serum CRS, which is initiated by the release of IFN-γ by activated T cells or the tumor cells.[4] Generally, a higher tumor burden at the time of infusion and a greater peak in the expansion of chimeric antigen receptor (CAR) T cells increases the risk of severe CRS. Conversely, an improved clinical outcome is not predicated on the development of severe CRS, and an effective antitumor response may be induced in the absence of this toxicity.[24]

While initiated by T cell-produced cytokines, CRS in CAR T cell therapy is also dependent on the engagement of the innate immune system.[6] CAR T cell produced IFN-γ and GM-CSF activate macrophages and monocytes, resulting in upregulation of interleukin IL-1 and IL-6 signaling. In a murine leukemia model treated with CAR T cell infused intraperitoneally, it was observed that macrophages in the peritoneal cavity, and not the spleen had upregulated activation, suggesting that localized macrophage signaling plays a key role in the pathogenesis of CRS.[6] Due to the involvement of macrophages, the inducible nitric oxide synthase (iNOS), an enzyme indicative of macrophage activation, has been identified as a potential biomarker of CRS, in addition to IL-1 and IL-6. Current therapeutic options for CAR T-cell associated CRS involve the blocking of inflammatory cytokine-mediated signaling. IL-6R blockade has generally been accepted as the front-line treatment for CAR T-mediated CRS. The IL-6R blocker tocilizumab has been shown to reverse CRS in some patients, however some patients manifest tocilizumab-refractory CRS.[25] Furthermore, early clinical results suggest that successful ablation of CRS symptoms with tocilizumab may not be sufficient to prevent delayed neurotoxicity.[26,27] The pathology of CAR T cell induced CRS was studied in a humanized mouse model, and the upregulation of IL-1 preceded IL-6 upregulation. Treatment with an IL-1 receptor antagonist (anakinra) successfully inhibited both short-term CRS-mediated tissue damage and long-term neurotoxicity, while tocilizumab only mitigated short-term CRS, indicating that IL-1 signaling may be the initiator of CRS.[28] This was further corroborated by successful treatment of CRS-like pathology in mice by inhibiting IL-1 signaling via an IL-1R antagonist.[6]

While high IL-6 and IFN-γ are associated with CRS in CAR-T cell-based therapy, CRS may also manifest at lower levels of IL-6 and IFN-γ, and instead, present as a higher concentration of IL-2 and GM-CSF.[29] Because IL-2 is necessary for CAR-T cell activity, approaches that inhibit GM-CSF may be preferable to mitigate this form of CRS.[30] Ibrutinib, a drug which inhibits the IL-2-induced tyrosine kinase activity has been shown to reduce serum cytokine levels in mice.[31] GM-CSF neutralization with lenzilumab prevents CRS and neuroinflammation in mouse models of ALL. Additionally, mice treated with lenzilumab and CD19-targeted CAR T (CART19) cells had enhanced antitumor efficacy compared to those treated with CAR-T cell therapy alone. When engineered with a GM-CSF knockout gene, CAR-T cells had enhanced survival rates and tumor control. These results suggest that among the inflammatory milieu, GM-CSF may be one of the crucial mediators of CRS-associated complications and could be an effective therapeutic target for controlling CRS.[32]

Cytokine Mediated Tissue Damage on Intermediate Timescales: Viral and Bacterial Infections

Excessive cytokine production is associated with complex interactions between bacterial or viral pathogens and the host, which induces hyperactivation of immune cells.[33] The immune response is typically characterized by an initial intense inflammatory response that rapidly peaks to increase local coagulation and thereby restrict tissue damage.[34] However, an overwhelming production of these pro-inflammatory cytokines can result in infection-induced SIRS, termed sepsis, and disrupt regulation of the immune response and induce pathological inflammatory disorders, such as capillary leakage, tissue injury and lethal organ failure. Generally, a high infection burden, superantigens, virulence factors, resistance to opsonization and phagocytosis, and antibiotic resistance leads to sepsis progression when the host cannot inhibit the infection. In addition, serum concentrations of the anti-inflammatory cytokine IL-10 has been shown to parallel the sepsis score and a high IL-10:TNF-α ratio is a predictor of severity and a fatal outcome in sepsis.[35]

In contrast to CRS in T cell engaging therapies, sepsis due to persistent bacterial and viral infection develop primarily via the innate immune system.[36] Innate immune cells are activated upon recognition of exogenous pathogen associated molecular patterns (PAMPs) as well as endogenous damage associated molecular patterns (DAMPs). High microbial replication may induce hyperactivation of innate immune cells, and additional off-target tissue destruction may result in a positive feedback loop of tissue destruction and immune activation. For example, in H5N1 human influenza A high viral load and excess cytokine production were associated with fatal outcomes, even with low T cell counts.[37] In addition, genetic polymorphisms contribute to excess cytokine production and impaired resolution of inflammation and contribute to the variability in sepsis pathogenesis. A single nucleotide polymorphism (SNP) on the IL-1 receptor antagonist gene is associated with lower plasma levels of IL-1β and improved sepsis survival, while specific alleles of the TLR4 and TLR1 genes have negative impacts on sepsis outcomes due to enhanced signaling and cytokine production.[38,39] While these and several other polymorphisms relating cytokine signaling to sepsis and severe infection outcomes have been identified, clinical trials targeting individual cytokine pathways related to identified polymorphisms have demonstrated limited efficacy.[36]

Colonization of barrier tissues by bacterial biofilms elicits an immune response that may lead to localized and potentially systemic cytokine-mediated tissue damage, of which periodontitis (PD) is exemplary. Although periodontopathic bacteria are the etiological agents in PD, the primary determinant of disease progression and clinical outcome is the host immune response, which involves the generation of cytokines, and recruitment of inflammatory cells.[40] While the ideal outcome of inflammation is resolution, uncontrolled inflammation, mediated by IL-17, TNF, IL-6, and IL-1 in PD, upregulates matrix metalloproteinases (MMPs) and receptor activator of NF-κB ligand (RANKL), the primary activation factor for osteoclasts, leading to tissue injury and scarring, fibrosis, alveolar bone destruction and tooth loss.[41-44] Surgical intervention may be necessary in severe forms of PD. However, in the face of uncontrolled inflammation, reconstruction of periodontal tissues is significantly hampered.[45-47] Furthermore, chronic PD may lead to increased systemic inflammation either via locally produced cytokines entering systemic circulation, or via translocation of pathogenic bacteria to lung or heart tissues from the initial gingival ulcers.[48]

Severe and often lethal clinical outcomes of COVID-19 infection are associated with CRS-like symptoms that affected multiple organs, including the lungs. In a murine model of SARS-CoV-2, a delayed hyperproduction of IFN-β was linked to high levels of inflammatory monocyte-macrophage (IMMs) infiltration to the lungs, resulting in mortality.[49] Early administration of intranasal IFN-β or depletion of IMMs improved survival and T cell response. Early clinical results testing IFN-β for treating severe COVID-19 suggest a lower 28-day mortality, consistent with results from the murine model of SARS-CoV.[50] Delayed hyperproduction of IFN-β also induced T cell lymphopenia in mice which may further contribute to increased viral load and IMM hyperactivation, as virus-specific T cells are required for viral clearance.[51,52] Similar to cancer immunotherapy associated CRS, high levels of IL-1 and IL-6 were correlated with disease severity. However, while early results suggested that using tocilizumab alone to target IL-6R might be an effective therapeutic target to suppress hyperactive inflammation in CRS, a recently concluded phase 3 clinical trial (COVACTA, NCT04320615) did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality, underscoring the complexity of the cytokine network underlying the disease.[53] Results from ongoing clinical trials testing single-target cytokine inhibition for the treatment of severe COVID-19 are awaited, with additional testing planned for antibody cocktails consisting targeting one or more of IL-6, IL-1, TNF and GM-CSF.[54]

Cytokine Mediated Tissue Damage on Extended Timescales: Autoimmune Diseases and Autoimmune-like Conditions

In autoimmune diseases and autoimmune-like conditions, immune dysregulation contributes to episodic elevation in cytokine production and chronic inflammation that may last over a lifetime. In contrast to acute CRS that is associated with multi-organ failure, damage from autoimmune diseases are primarily tissue-specific, but chronic conditions contribute to long-term collateral damage of organs such as the skin, eyes, lungs and heart. Pro-inflammatory cytokines drive pathogenesis in rheumatoid arthritis (RA) as well as systemic lupus erythematosus, and flares of disease activity are associated with increase cytokine production.[55] Comprehensive efforts have developed a high resolution map of the hierarchical position of distinct cytokines which mediate the overlapping innate and adaptive immune responses associated with disease onset and persistence in RA pathogenesis.[56] Pre-clinical and clinical studies, along with the success of cytokine-targeting drugs, such as anti-TNF and anti-IL-6R, have validated the pivotal contribution of cytokines in the pathogenesis of RA. In RA, cytokines regulate cellular phenotype, localization, activation status and longevity in the synovial and lymphoid microenvironments, supporting a role for cytokines in the licensing of cell function in RA rather than simply as strict differentiation factors. However, in contrast to a specific antigen- or pathogen, the immune response in RA is not thought to be synchronized by a specific initiating event and therefore the usual innate and adaptive cellular responses are unlikely to operate in the rheumatoid joint. The net effect of this cellular profile is the generation of tissue-destructive enzymes, reactive oxygen and nitrogen intermediates, prostaglandins and leukotrienes, and a broad range of effector cytokines, outside their normal homeostatic 'on–off' regulatory cycle, often following an unpredictable schedule. The result is that the therapy needs for each patient maybe distinct and an ad-hoc combination is often employed to induce disease remission.

In chronic graft-versus-host disease (cGvHD), cytokine production by autoreactive donor T cells drives immunological dysregulation and tissue damage. IL-17-producing T helper (Th17) cells are thought to drive the pathogenesis of cGvHD and targeting the Th17 axis has been shown to ameliorate cGvHD in preclinical models.[57,58] A monoclonal antibody targeting the p40 subunit found on both IL-12 and IL-23 reduced the production of both IFN-γ and IL-17 and reduced tissue damage in the skin and salivary glands in a preclinical model of cGvHD.[57] In a retrospective analysis, Tocilizumab has shown potential in treating cGvHD, as IL-6 signaling is necessary for Th17 differentiation. However, more comprehensive clinical studies may be necessary to establish clinical efficacy.[59] Furthermore, the contributions of cytokines in cGvHD is complex and may be source dependent. Host and donor cytokines may play opposing roles, and cytokines may be protective in some tissues but damaging in others, which may drive the selection of the which cytokines to suppress. For example, recipient IL-22 has been demonstrated to be protective for intestinal stem cells in cGvHD, whereas donor derived IL-22 plays a critical role in driving cutaneous cGvHD.[60] Therefore, while broadly targeting IL-22 may alleviate cGVHD symptoms, it may not represent the optimal cytokine for inducing disease remission.

To date, there is no single successful strategy to manage cGvHD in the clinic. The clinical gold standard of using combination cyclosporin and methotrexate, which has remained unchanged for decades, is only partially effective.[61] In addition to lengthening the period of immune deficiency, on the order of several years or even the lifetime of the individual, some patients may develop steroid resistant GvHD. A strategy that has demonstrated promise in controlling cGvHD is the selective expansion of T_{regs}, mediated by systemic IL-2 infusions.[62,63] However, in clinical trials daily injections were needed for therapy and patients experienced symptoms of cGvHD immediately following cessation of treatment. mAbs such as the anti-CD20 antibody rituximab have been shown to be useful in several clinical trials for the treatment of cGVHD. However, these therapies are administered over the lifetime of the patients, significantly impacting the immune competence of an individual and thereby limiting its applicability.

Innovative Treatments in the Clinical and Preclinical Pipeline:

While current frontline mAb treatments for specific cytokines are effective at mitigating CRS in some patients, targeting multiple pathways may improve efficacy and applicability (Figure 2a). One method employed is broad-spectrum cytokine absorption with biomimetic nanoparticles to reduce undesired cytokine signaling (Figure 2b). Nanoparticles coated with neutrophil membrane have been shown to reduce pro-arthritogenic factors such as IL-1β, TNF-α and MMP-3 and ameliorate experimental arthritis in both a collagen induced arthritis model as well as in a TNF-transgenic mouse.[64] Dendrimers, which are highly branched macromolecules with polyvalent adsorption capabilities, have been demonstrated to mitigate adverse cytokine-mediated tissue damage. In a rhesus macaque model of *Shigella dysenteriae* infection, orally administered dendrimer glucosamine significantly reduced colonic levels of IFN-γ, IL-1β, IL-6 and IL-8 and conferred protection against neutrophil-mediated vasculitis and gut wall necrosis.[65] A hydroxy dendrimer, termed OP-101, has been shown to inhibit multiple macrophage cytokine pathways and is currently undergoing phase II clinical trials for the treatment of patients with severe COVID-19 (PRANA, NCT04458298). Such nanoparticle medicines have the advantage of being able to simultaneously target multiple pathways while still providing rapid clearance and off-the-shelf convenience.

Alternatively, directly targeting cells affected by CRS may prove useful to reduce tissue damage (Figure 2c). Recent multi-omics profiling of endothelial, epithelial and stromal cells demonstrated that these structural cells play critical roles in immune regulation in a tissue dependent manner.[66] In a murine model of influenza infection, agonism of sphingosine-phosphate-1 reduced chemokine production by pulmonary endothelial cells and mortality due to cytokine storm.[67] Additionally, the Slit2-Robo4 signaling in endothelial cells may be a therapeutic target, as Slit2 inhibits ICAM-1 expression on endothelial cells that promotes monocyte adhesion, as well as reducing LPS-induced production of pro-inflammatory cytokines by endothelial cells.[68]

In addition to treatments for acute manifestation of cytokine mediated tissue damage, several treatments for chronic conditions are currently being explored (Figure 2d). Preclinical models of tolerogenic vaccination to enhance regulatory immune cell subsets and promote antigen-specific tolerance show promise and have been reviewed extensively elsewhere.[69,70] Cell-based therapies to restore immune homeostasis in autoimmune disease have shown great promise.[71-75] Clinical trials evaluating the efficacy of transfusion of autologous tolerogenic dendritic cells and regulatory T cells are underway for type-1 diabetes as well as RA.[73,76] While clinical outcomes and efficacy are awaited, the prospect of cell-based therapy combined with front-line therapies targeting cytokines for debilitating chronic inflammatory disease may be a promising strategy for patient specific long-term disease remission.

Conclusion

Cytokine-mediated inflammation is an essential component of the natural course of an immune response. However, immunological dysregulation that arise from immunotherapies, persistent or highly immunogenic microbial infection, and underlying genetic predisposition, can result in the supraphysiological production of cytokines that results in harmful toxicity. Common features associated with the hyper-production of cytokines have resulted in therapies that are transferable and effectively manage symptoms independent of disease etiology. Current treatments for these pathologies using monoclonal antibodies to inhibit key inflammatory cytokines have shown promise, but patient to patient response can be highly variable, in part due to the complex underlying cytokine network. Therefore, therapies targeting multiple pathways may improve outcomes and management of CRS. Identifying the key cellular and molecular determinants of immune tolerance and their role in immune dysregulation will characterize differences between distinct manifestations of CRS, as well as classify patient subsets and better predict therapeutic targets.

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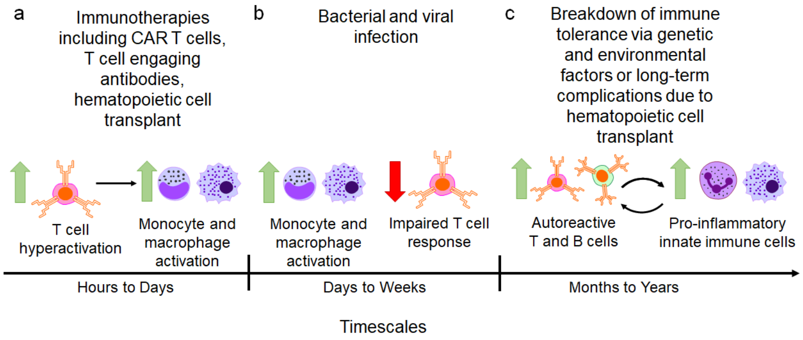

Figure 1. Triggers and timescales in the development of cytokine-mediated tissue damage.
Cytokine-mediated tissue damage may manifest in different forms across a range of timescales depending on the triggering events. (a) Immunotherapies, including CAR T cells, T cell engaging antibodies, and hematopoietic cell transplant can all drive rapid T cell hyperactivation and subsequent activation of innate immune cells that may result in cytokine release syndrome (CRS) within hours. (b) Microbial infections with high replicative potential or particularly virulent antigens may result in hyperactivation of innate immune cells over days to weeks. Delayed viral clearance leading to sepsis may also be associated with impaired T cell responses. (c) Genetic factors and environmental triggers can combine to result in the breakdown of immune tolerance mechanisms, leading to chronic autoimmune disease in which autoreactive adaptive immune cells mediate cyclic cytokine driven inflammation and tissue damage.

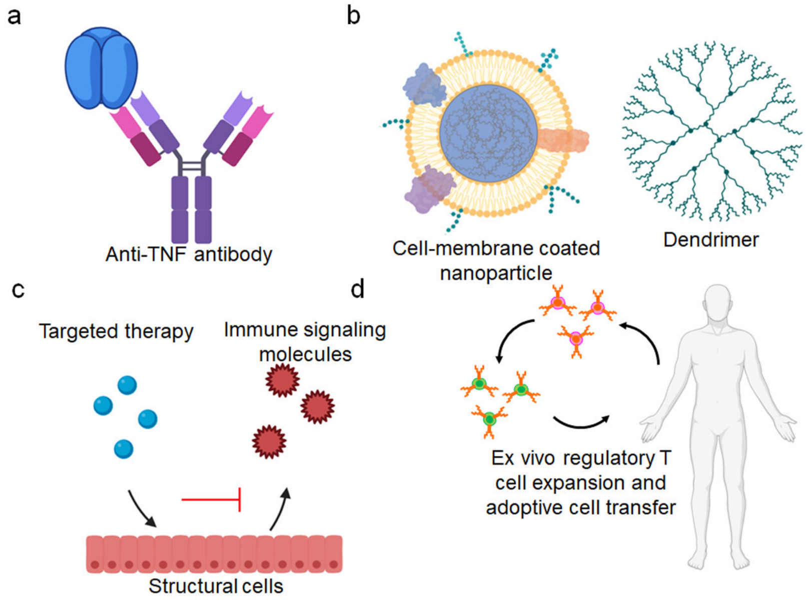

Figure 2. Treatments for cytokine-mediated tissue damage.

(a) Monoclonal antibodies and broad-spectrum immunosuppressive molecules such as steroidal anti-inflammatory medications are current frontline therapeutics for the mitigation of cytokine mediated tissue damage. (b) Nanomedicines offer the advantage of targeting multiple pathways via a single platform and may be engineered with enhanced targeting capabilities to minimize off-target immune suppression. (c) Advanced –omic profiling has shed light on the involvement of structural cells such as endothelial, epithelial and stromal cells in orchestrating immune responses, and preclinical therapies targeting these cell types have shown promise in mitigating cytokine-mediated tissue damage. (d) Immunomodulatory tolerogenic vaccines and cell therapies to enhance the number and function of regulatory immune cells may hold the key to restoring immune homeostasis in chronic diseases with complex underlying cytokine networks such as chronic graft-versus-host disease and autoimmune diseases.

Table 1.

Key cytokines, their sources, physiological effects and treatments

Cytokine	Source Cells	Physiological Effect
IL-1	Macrophages, DCs, Endothelial cells	Fever, hematopoeisis. Activates innate immune cells
IL-6	Macrophages, Monocytes	Fever, capillary leakage, coagulation, hypotension, and complement pathway activation. Promotes granulo- and hematopoiesis
IL-2	T cells	Promotes T cell proliferation and cytokine production
IL-12	Macrophages, DCs, B cells	Drives T cell differentiation and T cell and NK cell activation
IFN-γ	T cells, Innate Lymphoid Cells (ILC)	Flu-like symptoms and macrophage activation.
TNF	Macrophages, DCs, Endothelium, lymphocytes, myocytes	Flu-like symptoms and cell death in some cell types which plays a role in capillary leakage, cardiomyopathy and lung damage.
GM-CSF	T cells, Macrophages, Endothelium, Fibroblasts, NK cells	Enhances innate and immune cell activity and is linked to neurotoxicity in severe CRS.
IL-10	Lymphocytes, Macrophages, DCs	While IL-10 upregulation is consistent in CRS, it is classically thought to have anti-inflammatory properties and its role in CRS remains unclear.
IL-17	T cells	Promotes innate immune cell recruitment and activation.