Immunomodulators in Autoimmunity and Viral Infections

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Abstract

Immunologically-based therapies are steadily moving from the laboratory to clinical practice. In that regard, the elevated levels of “immunocytokine” gene expression, including, tumor necrosis factor-α, various interleukins, cytotoxic T-cell antigen-4, B-cell activating factor, and others, are characteristic of autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel diseases, psoriatic arthritis and lupus erythematosus and, some cancers as well. Treatment of these autoimmune diseases with first-line Immunologically-based therapies can ameliorate the pathology associated with autoimmunity and cancer and, can also inhibit transplant rejection. Importantly, drugs containing immunomodulatory activity are now also known to have significant and effective anti-viral activity which may result from their role in reducing the impact of “immunocytokines” on viral infectivity and disease progression. Although vaccine development continues to alter the landscape of virally-associated diseases, immunomodulation has become a useful paradigm for reducing the pathology associated with viral infection(s) going forward.

Keywords: Immunocytokine; Inflammatory bowel disease; Autoimmune disease; Host response

Introduction

Many drugs are immunomodulatory because they have significant clinical efficacy in the therapy of autoimmune diseases, cancer, infection and transplantation [1-3]. For example, methotrexate (MTX), cyclosporine and tacrolimus are three immunomodulatory drugs which are commonly employed in the first-line therapy of rheumatoid arthritis (RA) [4-6] and various forms of irritable bowel disease (IBD) [7] because of their potent effects on suppressing immune mechanisms that contribute to the progression of these diseases. In that regard, MTX has also recently been classified as an inhibitor of Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling [8], the activation of which contributes to the significant up-regulation of pro-inflammatory cytokine gene expression [9-11] as well as aberrant cell survival [12,13] which are both associated with RA and IBD.

Immunomodulation has also been a focus for altering host responses in the therapy of viral and other forms of infection. Thus, interferon-α (INF-α) and IFN-β, commonly referred to as the type I interferons are the major effector cytokines orchestrating the host’s response to viral [14,15] and bacterial infections [16,17]. In several of these cases, the immunomodulatory function(s) of effective agents can be traced back to their capacity to block various inhibitory signals that impair immune cell function, including, cytotoxic T-lymphocyte-associated protein, (CTLA-4), also known as CD152, programmed cell death-1 (PD-1) protein and B-and T-lymphocyte attenuator (BTLA) protein, [1], as well as additional various targets on tissue-resident memory T-lymphocytes [18], the latter cell type having been shown to be an important immune cell target for inducing immunomodulation. More recently, the immunomodulatory activity of mesenchymal stem cells (MSCs) have also become increasingly appreciated [19,20].

Of particular interest in the context of future cancer therapies [21], and perhaps even autoimmune diseases, is the role played by PD-1 as a regulator of T-cell immune function. PD-1 is a member of the CD28 superfamily of proteins that convey negative signaling after PD-1 interacts with 2 of its ligands, namely, PD-L1 or PD-L2. In that regard, the PD-1 signaling pathway is known to modify the induction and maintenance of peripheral tolerance which if “broken” can result in autoimmune disease [21], various types of cancer [22-24] and infections [23]. Thus, monoclonal antibodies which block PD-1-mediated signaling have been shown to produce a measurable and sustainable clinical response in a subset of patients diagnosed with breast or ovarian cancers [24], especially in those patients with PD-L1-positive cells. Importantly, immunomodulation of PD-L1-positive cancer cells could result in the long sought-after specific therapy of these cancers.

“Immunocytokines”: Role in Autoimmunity and Infection

The conceptual framework underpinning immunomodulation [25] has moved forward by employing a strategy for the development of clinical therapies for various adult and pediatric immune-mediated diseases, cancer, as well as viral and bacterial infections [26-39]. Noteworthy also is the recent attention paid to the D3 metabolite of vitamin D [35,40], antibiotics [41], probiotics [42], and long chain omega-3 fatty acids [43] therefore adding to the list of potential immunomodulating agents.

As expected to be the case that is based on the underlying pathogenesis of autoimmune diseases, cancer and viral infections, “immunocytokines” have become one of the most critical targets for inducing immunomodulation in autoimmune diseases and viral infections [44]. Among these targeted “immunocytokines” are the more classical anti-cytokine targets such as TNF-α [45] IL-6 [46], IL-1β [47], cytotoxic T-lymphocyte antigen-4 (CTLA-4) [48], B-cell...
activating factor (BAFF) [49], nuclear factor κ-B ligand (RANKL) [50], and INF-γ [51,52]. However, more recently, complement receptors [53,54], IL-9 [55,56], IL-12 [57], IL-23 [58], IL-17 [59], IL-23 [60], IL-33/ST2 [61] and IL-35 [62] have been added to the list of potential targets for immunomodulation (Table 1). In that regard, drug development is underway to explore how intervening in the activity of these factors might alter host immune responses. Even immune checkpoint inhibitors, in addition to CTLA-4/1g [49], are in development although their long-term clinical efficacy and potential adverse effects have yet to be established [63]. What does appear to be the case is that all of these molecules have been established as potential targets through basic and pre-clinical research which ascribed important roles to them in these various autoimmune, cancer and viral conditions. The results of these studies indicated that autoimmune diseases, cancer and viral infections were modifiable through immunomodulation which should result in improved clinical responses.

| Cytokine   | Function(s)                  | References |
|------------|------------------------------|------------|
| TNF-α      | ↑Apoptosis; Gene Expression-- | 45, 46     |
| IL-6       | ↑Apoptosis; Gene Expression-- | 46         |
| IL-1β      | ↑Apoptosis; Gene Expression-- | 47         |
| CTLA-4     | T-cell activation; Checkpoint | 48         |
| BAFF       | B-cell activation            | 49         |
| RANKL      | Osteoclast Development       | 50         |
| INF-γ      | Anti-proliferation; Intracellular Signaling | 51, 52 |
| C3aR, C5aR, CD21 | T-cell activation; C3d binding | 53, 54 |
| IL-9       | Co-stimulatory with TGF-β, IL-4 | 55, 56 |
| IL-12      | Anti-microbial; Anti-cancer  | 57         |
| IL-23      | Regulation of TH1 and TH17   | 58         |
| IL-17      | Expressing RORγt+/CD4+ T cell | 59         |
| IL-23      | Regulation of memory T-cells | 60         |
| IL-33/ST2  | Enhancement of natural killer, TH1 and CD4 and CD8 T-cell functions | 61         |
| IL-35      | Immunosuppression of Treg and B-cells | 62         |

Table 1: Immunocytokines: Influence on Immunomodulatory Functions.

Is there a connection between “Immunocytokine” activity and viral infections?

Compelling evidence now links the elevated production of “immunocytokines” characteristic of autoimmune diseases with the pathogenesis and progression of viral infections [61]. This link includes an association between “immunocytokines” and influenza [64,65], hepatitis C [66,67], enterovirus [68] and HIV-1 [69], to name only a few. At the cellular level Jenabian et al. [70] showed that T-regulatory (Treg) cells whose function is compromised in RA, can also affect the development of anti-HIV responses as evidenced by the finding that Treg cells could suppress anti-HIV-specific immune responses and may even alter the rate of HIV-1 progression to full-blown acquired immune deficiency syndrome. This is likely to occur as a result of enhanced cytokine production as a component of Treg cell function, although the continued attention paid to the possibility that Treg cells may also cause adverse events in persons infected with HIV-1 as a result of hyperimmune activation must also be considered.

In addition to the apparent link between the elevated production of “immunocytokines” and viral infection, increased vigilance must be paid to the possibility that immunomodulation of the progression of RA with drugs such as MTX or leflunomide may also have distinct deleterious effects if patients with active RA also become virally-infected, although no evidence supported a connection between the therapy of RA with MTX and varicella herpes zoster [71]. On the other hand, the anti-viral activity associated with leflunomide [72] did not protect patients from various secondary skin infections. Finally, the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies, in certain individuals which have been recently touted as a powerful biomarker and positive predictor for the later development of RA [73] are also associated with the development of some viral infections, such as tuberculosis, but anti-CCP antibodies were rarely seen in patients with hepatitis infection [74].

The current status of employing immunomodulation to treat viral infections

Direct therapy of viral infections is a daunting medical problem that is compounded by the fact that one must know the extent to which modification or targeting non-specific or specific innate or adaptive immune responses will result in a clinical response to the virus. Because vaccine development is a slow and laborious proposition, immunotherapy has become a potential suitable alternative for treating viral infections [75-78]. For example, some of the appropriate targets for immunomodulation of severe influenza proposed by Darwish et al. [77] were TNF blockade, statins, glucocorticoids, cyclooxygenase-2 (COX-2), macrolides, peroxisome proliferator-activated receptor agonists, AMP-activated protein kinase agonists and high mobility group (HMG) box 1 antagonists. Interestingly, some of these targets, in particular, TNF-α, COX-2, HMG, are also critical factors for sustaining chronic inflammation associated with autoimmune diseases [79]. In fact, the TNF receptor has been considered a potential adjuvant for viral vaccines based on the role played by CD8+ lymphocytes during viral infection [80]. Another target that appears to have clinical utility for treating viral infections such as hepatitis C is INF-α combined ribovarin with or without ribovarin [81,82]. In that context, changes in the level of interferon-stimulated CXCL10 was considered a useful biomarker and positive predictor for the later development of RA [73]. Of note, according to Pulliam [83] the INF-α strategy might also have utility for identifying HIV-1-infected individuals with associated immune activation and resultant cognitive abnormalities. A few more recent approaches for immunomodulation of viral infections include, strategies for ramping up the activity of natural killer cells [84], developing what has been termed a, “killer peptide” to seek out and kill viral and other microbial-based infectious organisms [85], employing “decoy” receptors that do have host counterparts [86], and poxviral proteins, such as is found in variola (smallpox) virus which are formed...
from genetic sequences that alter the function of immunomodulatory proteins that bind cytokines [87].

Conclusions and Future Perspectives

At the present time, there is every indication that “immunocytokines” drive the pathogenesis and progression of autoimmune diseases. However, “immunocytokines” are also significantly involved in the host’s response to viral infections. Therefore, experimentally-based strategies designed to harness the power of immunomodulation which has been foremost in the development of biologic drugs for treating RA, IBD, including Crohn’s disease; psoriatic arthritis, ankylosing spondylitis and lupus also appear to have a strong rationale for current and future development of anti-viral drugs. Vaccine development for autoimmune diseases, such as RA, [88] is a lengthy and costly venture. This makes the exploitation of recent discoveries in the field of immunomodulation an alternative strategy worth considering for treating viral illnesses.

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