Botanical immunodrugs: scope and opportunities

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Modulation of the immune system can be addressed through a variety of specific and non-specific approaches. Many agents of synthetic and natural origin have stimulatory, suppressive or regulatory activity. There is growing evidence that drugs or biological agents capable of modulating single pathways or targets are of limited value as immune-related therapies. Systems biology approaches are now gaining more interest compared with monovalent approaches, which can be of limited benefits with complications. This has stimulated interest in the use of 'cocktails' of immunodrugs to restore immunostasis. Botanicals are chemically complex and diverse and could therefore provide appropriate combinations of synergistic moieties useful in drug discovery. Here, the importance of traditional medicine in natural product drug discovery related to immunodrugs is reviewed.

The immune response requires the timely interplay of multiple cell types within specific microenvironments to maintain immune homeostasis. The selectivity and flexibility that is necessary to regulate cell traffic under homeostatic and diseased conditions is provided by the differential distribution and regulated expression of cytokines and their receptors. As a consequence, cytokines are responsible for the development of phenotypes and are, therefore, logical targets for therapeutic immune modulation [1]. Immunodrugs include synthetic organics, biologicals, such as cytokines and antibodies, and microbial and botanical natural products, which influence immunoregulatory cascades to bring about their specific stimulatory, suppressive or regulatory effect. Immune suppression has been widely studied for clinical applications [2]. Historically, botanicals have been a mainstay of drug treatments and are currently receiving attention as sources of synergistic combinations. Here, recent developments in botanical immunodrug discovery are reviewed.

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Immunodrugs in cancer

Although the treatment of cancer using active immunotherapy has had limited success, passive immunotherapy with antibody and cytokine therapies brings new hope. The most widely studied approaches consist of whole-cell vaccines, dendritic cell-based immunotherapy and peptide vaccines. Many clinical studies have demonstrated safety but not necessarily the efficacy of such strategies [3]. Moreover, there is emerging consensus that the most efficacious therapy should activate several components of the immune system [4]. Cytokine therapy in cancer is another attractive approach; however, balancing optimal doses to avoid toxic reactions remains challenging [5]. Several cytotoxic drugs have immunomodulatory effects at relatively low doses and can exert immunity-dependent curative effects in animal models of cancer. Combination therapies involving low-dose anticancer agents and cytokines have demonstrated some benefits. For example, combinations of appropriate regimens of doxorubicin plus interleukin (IL)-2

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or tumour necrosis factor (TNF) could be curative and produced a life-long immunological memory in an EL4 lymphoma C57BL/6 mouse model. Many researchers have demonstrated that the induction of T-helper (Th) 1-promoting cytokines, using specific adjuvants, can enhance antitumour immunity and can prevent or reduce tumour growth. These trends substantiate the possibility of establishing combination regimens based on low-dose anticancer drugs, specific cytokines and immunological adjuvants [6].

Immunodrugs in infection

Immunomodulators could also have beneficial roles in the prevention and treatment of infectious disease. A diverse array of synthetic, natural and recombinant compounds are available. Of the synthetic immunomodulators, Levamisol, Isoprinosine, Pentoxifilline and Thalidomide are some of the more significant [7]. Microbial immunomodulators, such as bacille Canette-Guérin, have been in use for years for non-specific activation of the immune system in some forms of cancer (bladder) and infectious disease [8].

Targeting cytokines is now considered to be one of the logical approaches for the prevention and treatment of infectious disease. Some of these substances, such as granulocyte colony-stimulating factor (G-CSF), interferons, IL-12, various chemokines, synthetic cytosine phosphate-guanosine (CpG) oligodeoxynucleotides and glucans are being investigated in preclinical and clinical studies [9]. Interferons are widely used for the treatment of chronic infections, particularly hepatitis B, D and C viruses [10]. Pegylated interferon is a recently developed pharmaceutical preparation that has proven beneficial in non-responsive patients, particularly in those with cirrhosis or hepatitis C virus genotype 1 [11]. Other cytokines, such as IL-1, IL-2 and IL-17, have shown potential in augmenting immune responses in various infectious conditions and malignancies. The therapeutic effect of cytokine blockers is also reported in septic shock [12]. A recent study on hepatitis C has shown that interferon-γ (IFN-γ), in combination with ribavirin, induces a higher percentage of lymphocyte activation [13] than for IFN-γ alone. Such approaches are currently being examined for their potential to boost host immune response to fight infection.

Immunomodulation and inflammation

Many immune targets have been identified as having potential for the central control of inflammation. Targeting activated T-cell subsets was considered to be one of the most rational approaches and biologicals, such as monoclonal antibodies (mAbs) against CD4, CD5, CD7, CD25 and CD52, were evaluated in patients with autoimmune disorders. Limited clinical benefit and complications, such as the prevalence of opportunistic infection and/or malignancies, were observed and the hope of reprogramming the host immune response remained unfulfilled [14,15].

Studies on targets related to leukocyte infiltration, such as leukocyte-function associated antigen-1 (LFA-1), CD11α/CD18 (adhesion-receptor–counter-receptor pair) and intercellular adhesion molecule-1 (ICAM-1) CD54, are in progress; however, the development of humanized antibodies and their long-term safety evaluation have yet to be established [16]. Cytokine therapy, such as anti-TNF-α or IL-1, has been an attractive treatment option; however, an optimal treatment regimen with respect to dosage, interval and particularly long-term safety needs to be explored [17–19]. The use of the effector functions of Th cells is now considered to be one of the more promising innovative therapeutic strategies. Thus, the idea of switching Th1-dominated responses into Th2-mediated responses appears intriguing. This approach has been studied in various animal models of autoimmune diseases but clinical validation has not been achieved [20–22]. Newer targets central to innate and adaptive immunity, such as Toll-like receptors (TLR) and the complement system and nuclear factor-κB (NF-κB) activation, are being studied [23–25]. Combination approaches to the treatment of inflammatory diseases appear promising; in particular, combining methotrexate with TNF-α inhibitors has provided some encouraging results [26].

Immunodrugs and vaccine adjuvants

The combined use of vaccines and immunomodulators are innovative strategies in vaccine design and development. Many synthetic, biological and natural immunomodulators are under evaluation as vaccine adjuvants. Administration of cytokine genes along with DNA vaccines has been shown to achieve selective modulation of T-cell responses [27]. Moreover, innate immunity targets, such as TLR, and their modulation are currently being researched for their ability to provide effective adjuvant action. QS-21 and glucans are experimental adjuvants currently under clinical evaluation with different vaccines [28–30].

Immunostasis: targets and regulation

Th lymphocytes are divided into distinct phenotype subsets of Th1 (e.g. IFN-g, IL-2 and TNF-a) and Th2 (e.g. IL-3, IL-4, IL-5, and so on) effector cells. This classification is based on their functional capabilities and cytokine profiles. Th1 cells drive the cellular immunity to fight intracellular organisms, eliminate cancerous cells and stimulate delayed-type hypersensitivity reactions. By contrast, Th2 cells drive humoural immunity and upregulate antibody productions to fight extracellular organisms. T-cell homeostasis or immunostasis requires a fine balance between Th1–Th2 response and such agents could exhibit stimulatory, suppressive or regulatory activity [31]. Currently, much of the literature supports the view that Th1–Th2 is essential to immunostasis and many of the T-cell-directed therapies have provided modest clinical benefits [32]. Although this view of signal conversion looks relatively simplistic, mediators of signal transduction do not interact in a linear

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