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Review

Co-signaling molecules in psoriasis pathogenesis: Implications for targeted therapy

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ABSTRACT

Psoriasis is a T cell-dependent immune-mediated disease of the skin and joints. It is clear that co-stimulatory and co-inhibitory molecules (currently named co-signaling molecules collectively) synergize with TCR signaling to promote or inhibit T cell activation and function. In recent years, enthusiasm in the field of co-signaling research has been fueled by the success of co-stimulatory and co-inhibitory immunotherapy for the treatment of human diseases. This review outlines the involvement of several sets of co-signaling molecules in the immunopathogenesis of psoriasis. We then describe the relevant preclinical studies and summarize recent clinical findings on targeting these molecules for the treatment of psoriasis.

Contents

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1. Introduction

Psoriasis is one of the most common immune-mediated chronic, inflammatory skin diseases characterized by hyperproliferative keratinocytes and infiltration of T cells, dendritic cells, macrophages and neutrophils. Although the pathogenesis of psoriasis is not fully understood, there is ample evidence suggesting that the dysregulation of immune cells in the skin, particularly T cells, plays a critical role in psoriasis development [1]. The evolution of the psoriatic lesions is based on a complex interplay between environmental and genetic factors. A cascade of events leads to activation of dendritic cells (DCs) and, in turn, the generation of effector T cells that emigrate to and reside in skin tissue. Cross-talk between epithelial cells and immune cells shapes and maintains the inflammatory milieu [2]. T helper (Th) 1 and Th17 lymphocytes contribute to the disease pathogenesis through the release of inflammatory cytokines that promote further recruitment of immune cells, keratinocyte proliferation, and sustained chronic inflammation [3].

In recent years, through increased understanding of the immunopathogenesis of psoriasis, major advances have been made in the realm of treatments for psoriasis. Comparing to traditional systemic agents, targeted biologic therapies have dramatically improved clinical outcomes in psoriatic patients. However, there are subpopulations of patients that are either nonresponders to currently available biological agents and/or have experienced diminishing therapeutic benefit over time. Moreover, current biologic agents still have the potential to cause significant side effects in a subset of patients, with their longer-term safety yet to be fully evaluated. Therefore, researchers continue to elucidate the immunopathogenesis of psoriasis in an attempt to develop new therapeutic agents [4].

It is considered that T cells play a dominant pathogenic role in the initiation and maintenance of psoriasis and T cell co-stimulatory or co-inhibitory signals are essential for T cell activation and function. Therefore, medicines designed specifically to prevent T-cell activation and differentiation by targeting T-cell co-signaling molecules are expected to provide novel pharmacological tools for treating psoriasis.

2. T cell co-signaling molecules

T-cell activation is determined by the presence of three distinct signals: (1) T-cell receptor (TCR)–MHC class I and II interaction, (2) co-stimulatory molecule interaction, and (3) cytokine signalings [5]. The discovery of CD28 as a prototype co-stimulatory receptor on T cell provided evidence for the two-signal model of T cell activation, according to which both TCR and co-stimulatory signaling are required for full T cell activation [6]. Recently, the complexity of the model increased following the discovery of co-inhibitory molecules triggering inhibitory signals. The functional outcome of co-stimulatory and co-inhibitory molecule signaling is either an enhancement or inhibition of TCR-mediated immune responses [5]. Co-stimulatory signals are mandatory for the initiation of effective immunity and the absence of co-stimulatory signals results in abortive T cell response and T cell anergy. Co-inhibitory signals afford an additional layer of control that play important regulatory functions thereby contributing to the maintenance of peripheral tolerance as well as to the termination of immune responses after clearance of infections [7]. Currently, co-stimulatory and co-inhibitory molecules are collectively named co-signaling molecules for simplicity [6].

Co-signaling is a complex event that is coordinated through a network of ligand–receptor interactions on the cell surface [8]. Various co-signaling receptors have their matched ligands which are expressed on the surface of cells that interact with T cells. Co-signaling ligands have now been identified on nearly all cell types, although their expression has been most well characterized on professional antigen-presenting cells (APCs). It is now clear that co-signaling molecules have a crucial role in regulating T cell activation, subset differentiation, effector function and survival [6].

In recent years, enthusiasm in the field of co-signaling research has been fueled by the success of co-stimulatory and co-inhibitory immunotherapy for the treatment of human diseases [6]. Co-signaling molecules belong to three major families, namely the immunoglobulin (Ig) superfamily, the tumor necrosis factor (TNF)–TNF receptor (TNFR) superfamily and the emerging T cell Ig and mucin (TIM) domain family [9] The Ig superfamily includes the co-stimulatory receptors CD28 and inducible co-stimulator (ICOS), and the inhibitory receptors cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), B- and T-lymphocyte attenuator (BTLA), and CD160. The TNF-TNFR superfamily includes the co-stimulatory receptors CD40, OX40, herpes virus mediator (HVEM) [10] and CD27 [5]. The TIM family includes the co-stimulatory receptor TIM-1 and the inhibitory molecule TIM-3 [11]. Emerging evidences have indicated that some of the co-signaling molecules are involved in the immunopathogenesis of psoriasis, and may be potential targets for treatment.

3. CD28/CTLA4:B7-1/B7-2 pathway

3.1. CD28/CTLA4:B7-1/B7-2 pathway

CD28 is a receptor constitutively expressed on T cells. It binds two ligands on the surface of APCs, namely B7-1 (CD80) and B7-2 (CD86), and induces T cell proliferation by up-regulating the transcription of IL-2 and the anti-apoptotic Bcl-X_L. Another member of the Ig superfamily receptors, CTLA-4, is expressed on both activated CD4 and CD8 T cells upon stimulation. It negatively regulates T cell activation by competing with CD28 for access to B7-1 and B7-2. In fact, the affinity of CTLA-4 for these ligands is much higher compared to that of CD28. B7-1 and B7-2 are expressed on APCs, but also on activated T cells [12].

3.2. CD28/CTLA4:B7-1/B7-2 pathway and psoriasis

As the critical role of T cell activation in psoriasis pathogenesis has been established, the CD28 pathway in psoriasis becomes an object of study. Nickoloff et al. [13,14] reported that in the psoriatic lesion, particularly in the epidermal zone at the tips of the dermal papillae where epidermal T cells trafficking occurs, there are T cells stained positive for CD28. Staining of serial sections showed that greater than 95% of the T cells in the psoriatic plaque were CD28 positive. At the same time, a double-stained cryostat section examined by fluorescence microscopy confirmed co-expression of B7-1 on the CD28+ T cells. Psoriatic T cells have enhanced expression of CD28 antigen, and its receptor, B7-1, is up-regulated in psoriatic lesional skin, suggesting that T cell co-stimulation through CD28/B7-1 signaling may contribute to perpetuate T cell proliferation [15]. B7-2 is another ligand of CD28. Mitra et al. [16] reported that B7-2-expressing dermal DCs are more prevalent in psoriatic plaques compared with normal skin. In an immunohistochemical study, Ohki et al. [17] detected B7-1 and B7-2 on DCs in both the epidermis and dermis in the lesions of psoriasis ($n = 11$). B7-1 was expressed in 4 cases (35%) while B7-2 in 11 cases (100%). These molecules were not detected in normal control subjects ($n = 8$). Up-regulation of B7-1 and B7-2 by DCs in psoriatic lesions suggests a critical role for the CD28/B7 co-stimulatory system in the pathogenesis of psoriasis [18].