Acupuncture and Herbal Medicine

New perspective on the treatment of rheumatic arthritis based on "strengthening body resistance (Fú Zhèng)" in the theory of co-inhibitory receptor-regulated T-cell immunity

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Abstract

Co-inhibitory receptors serve as crucial regulators of T-cell function, playing a pivotal role in modulating the delicate balance between immune tolerance and autoimmunity. Initially identified in autoimmune disease models, co-inhibitory receptors, including CTLA-4, PD-1, TIM-3, and TIGIT, were found to be integral to immune regulation. Their blockade or absence in these models resulted in the induction or exacerbation of autoimmune diseases. Additionally, scholars have observed that co-inhibitory receptors on lymphocytes hold the potential to influence the prognosis in the context of chronic inflammation. Consequently, the blocking of co-suppressor receptors has emerged as a novel therapeutic approach for inhibiting refractory inflammatory diseases, particularly rheumatoid arthritis. From the standpoint of traditional Chinese medicine (TCM), the treatment of rheumatoid arthritis based on the "strengthening body resistance (Fú Zhèng)" theory can be construed as the regulation of co-suppressor receptors to modulate the body's immune function in combating chronic inflammation. This article provides a succinct overview of the role of co-suppressor receptors in anti-inflammatory processes and explores the research prospects of co-suppressor receptor intervention in the treatment of rheumatoid arthritis. The exploration integrates the "strengthening body resistance (Fú Zhèng)" theory with relevant Chinese medicine formulations.

Keywords: Combination of Chinese and Western Medicine, Co-inhibitory receptors, Rheumatic arthritis, T-cell exhaustion

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Introduction

T-lymphocytes are pivotal in immune regulation by overseeing T-cell responses to prevent inappropriate reactions, including autoimmunity. During T cell development, the thymus orchestrates central tolerance mechanisms to eliminate self-reactive T cell clones[1,2]. Factors such as the nuclear factor autoimmune regulator (AIRE), expressed by medullary thymic epithelial cells, facilitate the ectopic expression of tissue-restricted antigens within the thymus, contributing to the negative regulation of autoreactive T cells. Despite these regulatory efforts, some autoreactive T cells escape negative regulation and enter peripheral immune compartments due to the absence of self-tissue antigen expression within the thymus[3]. Consequently, the orchestration of peripheral T-cell responses is crucial for preventing excessive autoimmunity.

In the context of rheumatoid arthritis (RA), cell responses closely correlate with disease development and prognosis[4]. Traditional Chinese medicine (TCM) emphasizes internal balance and deficiency in the presence of external factors. Recognizing the role of balanced *qi* in disease processes, including onset, evolution, and outcome, TCM employs interventions such as nourishing *qi* and reinforcing yang to treat refractory RA[5]. These interventions utilize traditional herbal medicine, acupuncture, and exercise to modulate immune responses, demonstrating their efficacy in the prevention and treatment of RA[6]. The activation of co-inhibitory factors that influence T cell immune composition is considered a potential intervention strategy. Future research will integrate the principles of "nourishing the righteous" with TCM prescriptions to explore the nuanced role played by T cell co-inhibitory molecules,

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particularly those associated with exhaustion, in the context of autoimmunity and the therapeutic management of RA.

Regulatory impact co-stimulatory and co-inhibitory receptors on T-cell response

The activation of naive T cells requires stimulation of the T-cell receptor (TCR) through major histocompatibility complex-peptide complexes (Signal 1). Additionally, co-stimulatory receptors (Signal 2) on antigen-presenting cells (APCs) must be engaged by their corresponding ligands[7,8]. Co-stimulatory receptors on T cells, including both co-stimulatory and co-inhibitory receptors, are cell surface receptors that modulate signals driven by TCR, thereby regulating T cell activation. These receptors are essential to the T cell immune process, directing the activation, proliferation, and differentiation of T cells, and influencing their functional fate. The expression of these receptors and their ligands is meticulously regulated within T cells and the tissue microenvironment. An illustrative example of a costimulatory pathway is the CD28:B7 axis. The costimulatory receptor CD28 on T cells interacts with its ligands B7-1 or B7-2 on activated APCs, amplifying the TCR signal and resulting in T cell proliferation and interleukin (IL)-2 production[9,10]. Various costimulatory receptors have been identified, including ICOS, CD226, OX-40, 4-1BB, and GITR. Several co-inhibitory receptors, such as CTLA-4, PD-1, TIM-3, TIGIT, and LAG-3, have also been identified. Co-inhibitory receptors play pivotal roles in distinct T cell subsets, delineating them as activated T cells, regulatory T cells (Tregs), and exhausted T cells. Within activated T cells, co-inhibitory receptors regulate the contraction and expansion of T cell populations. Co-inhibitory receptors such as CTLA-4 and PD-1 enhance the suppressive function of Tregs[11,12]. Recent investigations have highlighted the crucial involvement of T-cell exhaustion in the chronic inflammation observed in RA. However, the use of targeted co-inhibitory receptors in the treatment of RA is constrained by the occurrence of adverse events, such as immune-related adverse events (irAEs), which resemble autoimmune reactions[13].

T-cell exhaustion in autoimmune pathogenesis

T cell exhaustion was first identified over two decades ago when virus-specific $CD8^+$ T cells in mice infected with lymphocytic choriomeningitis virus (LCMV) exhibited reduced functionality, characterized by diminished effector cytokine production and cytolytic activity[14]. During chronic inflammation, the decline in T cell function follows a hierarchical pattern. Early stages are marked by the overproduction of IL-6 and reduced T-cell proliferation[15]. In later stages, exhausted $CD8^+$ T cells lose the ability to produce interferon-γ (IFNγ) and TNFα cytokines and show decreased degranulation capacity[16]. Another hallmark of exhausted $CD8^+$ T cells is the impaired maintenance of T-cell memory, regulated by Foxo1 expression[17]. Although T cell exhaustion primarily affects $CD8^+$ T cells, $CD4^+$ T cells can also become exhausted and may contribute significantly to the exhaustion of $CD8^+$ T cells[18,19].

Genomic methodologies such as RNA sequencing and assays for transposase-accessible chromatin using high-throughput (ATAC) sequencing have been utilized to investigate the molecular pathways involved in T cell exhaustion. Unlike studies focusing on T-cell activation or memory, these approaches help delineate the distinct molecular phenotypes of exhausted T cells, defining them as a unique state of T-cell differentiation. The molecular changes in exhausted $CD8^+$ T cells include alterations in metabolism, chemokine and chemokine receptor expression, and cytokine signaling pathways. For example, signaling initiated by the binding of the inhibitory receptor PD-1 to its ligand PD-L1 induces T-cell exhaustion. During chronic phases, inhibiting this pathway combined with IL-2 therapy can promote proliferation, regulate cytokine secretion, and reduce inflammation, thereby delaying $CD8^+$ T cell exhaustion[20,21]. Notably, T cell exhaustion is associated with the clinical outcomes of various human autoimmune diseases, including systemic lupus erythematosus (SLE), autoimmune hepatitis (AIH), and RA, where it is linked to the regulation of PD-1 protein transport in persistent inflammatory conditions[22–24].

Novel insight into "strengthening body resistance (Fú Zhèng) theory": traditional Chinese herbal interventions targeting co-inhibitory receptors on T cells in RA—emphasis on CTLA-4, PD-1, TIM-3, and TIGIT

The identification of receptors such as CTLA-4, PD-1, TIM-3, TIGIT, and LAG-3 has advanced research targeting common inhibitory receptors and the development of innovative immune therapeutic models for inflammation control. CTLA-4, recognized for its role in attenuating T cell responses, is expressed by activated $CD4^+$ and $CD8^+$ T cells, Tregs, and inflammatory cells during chronic inflammation[25]. Abnormal CTLA-4 expression has been observed on $CD4^+$ T cells, $CD25^+$ T cells, and Tregs in patients with RA[26]. This observation has spurred research into TCM for refractory chronic inflammatory diseases, focusing on targeting CTLA-4 in TCM prescriptions. Previous studies have explored Sinomenine Hydrochloride for mediating CTLA-4 treatment in RA[27]. Animal studies have shown that oxymatrine mediates the CTLA-4 axis, activates T cell immune mechanisms, and delays T cell exhaustion[28]. In the context of an aging society and the post-COVID era, characterized by refractory chronic inflammatory diseases, these findings offer new avenues for personalized and moderate treatment approaches.

PD-1 was initially identified as a T cell receptor linked to programmed cell death[29]. Subsequent studies have revealed its involvement in anti-inflammatory immune responses. PD-1 ligands, PD-L1, and PD-L2, are expressed on various inflammatory cells and modulate immune responses against chronic inflammation. In prolonged chronic inflammatory states, abnormal PD-L1 expression stimulates $CD8^+$ T cells, promotes T cell exhaustion, and results in immune dysregulation. Increased expression of PD-1/PD-L1 in RA is often

associated with poor prognosis[30–32] and T cell exhaustion, corresponding to the concept of "Insufficient righteous Qi, unable to resist pathogenic factors." This has prompted the application of TCM interventions targeting the PD-L1/PD-1 axis. Astragalus, a representative Chinese medicine used to reinforce righteous aspects, has been studied for its targeted regulation of PD-1/PD-L1[33]. In a mouse study on RA, oxymatrine mediated the PD-1/PD-L1 axis, activated T cell immune mechanisms, and delayed T cell exhaustion[28,34]. The positive effects of TCM interventions on delaying T cell exhaustion and controlling chronic inflammation highlight the distinctive features of TCM's theory of "strengthening body resistance (Fú Zhèng)" in RA treatment. Research on TCM-mediated PD-L1/PD-1 pathway treatment for chronic inflammation reintroduces the "strengthening body resistance (Fú Zhèng)" anti-cancer theory into RA treatment, demonstrating the robust internal optimization and evolution of modern TCM theory.

Clinical evidence has substantiated the involvement of two common inhibitory receptors, TIM-3 and TIGIT, in chronic inflammation. TIM-3, due to its distinct role in regulating type I immune responses, has been extensively studied for its expression and functional attributes[35]. TIM-3 exhibits increased expression in $CD8^+$ PD-1 T cells, regulating T cell exhaustion[36]. Clinical observations indicate that TIM-3 significantly influences RA progression[37]. Coordinated modulation of TIM-3 and PD-1 through appropriate Chinese medicine formulations has shown promising clinical outcomes. Studies on TCM interventions for RA progression revealed the efficacy of the Baihu Jiaguizhi decoction in regulating PD-1 and TIM-3 proteins in the peripheral blood of patients[38]. The precision targeting of T cells by TIM-3, regulated by TCM against chronic inflammation, represents a pioneering avenue, offering a contemporary medical perspective on the theory of "supporting the righteous, dispelling obstruction" (Fú Zhèng Juān Bì).

TIGIT is highly expressed in natural killer (NK) cells, $CD8^+$ T cells, and Tregs within the inflammatory milieu[39]. Studies have confirmed TIGIT signaling's role in inhibiting T cell activation[40]. Intriguingly, most inflammation-infiltrating Tregs express TIGIT rather than $CD8^+$ T cells, contributing to the attenuation of chronic inflammatory development and propagation[41]. Recent investigations suggest that Buzhong Yiqi pills can modulate memory T cell differentiation for treating ulcerative colitis. Potential mechanisms involve blocking anti-TIGIT antibodies, slowing T-cell overdifferentiation and exhaustion, and regulating inflammation[42]. Concurrently, studies indicate that combining Jin Gu Lian capsules with anti-rheumatic drugs may regulate cytokine expression, such as IL-17, thereby retarding disease progression in RA[43]. Faced with refractory RA, the "strengthening body resistance (Fú Zhèng)" theory centered on delaying T cell exhaustion offers a fresh perspective. Research integrating "strengthening body resistance" formulations with T cell exhaustion, a central phenomenon in chronic inflammation, not only enhances the theoretical foundation for controlling RA in TCM but also augments clinical methodologies.

Conclusion and perspectives: pioneering a new era in RA treatment through supportive therapies

Immunotherapy, particularly immune checkpoint blockade, has proven effective in treating various chronic inflammatory conditions, marking a significant shift in therapeutic strategies. However, the considerable autoimmune-like adverse effects associated with immune checkpoint blockade limit its widespread application. The increasing use of immune checkpoint blockade in RA has highlighted the need for new perspectives and mechanistic pathways in TCM research for RA interventions. By understanding the pivotal role of co-inhibitory receptors in autoimmunity and aligning this with TCM's "strengthening body resistance (Fú Zhèng)" theories, we can integrate network pharmacology of supportive formulations, foundational knowledge of tissue-specific autoimmune responses, and the molecular dynamics within specific effector T cells to enhance the investigation into immune checkpoint blockade mechanisms.

Future studies should consider incorporating the concept of TCM pharmacogenomics and using unbiased genomic methodologies to identify immune-inflammatory-specific targets for immunotherapy. This approach heralds a new era in TCM diagnostic and therapeutic strategies, combining symptomatology with precision therapy. Notably, there has been a growing focus on TCM strategies for supporting and regulating immunity in treating RA since the advent of anti-cancer supportive therapy theory. Leveraging the synergies between inflammation and cancer research, a reassessment of immune-related co-inhibitory molecules combined with supportive therapy theory unveils novel pathways for TCM in managing rheumatic diseases. This represents a compelling and pioneering exploration paradigm with immense potential.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Xu Yifei participated in the writing of the paper; Hao Xu, Linda Zhong and Qianqian Liang co-guided Xu Yifei to revise this article.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

All the authors agreed to publish.

References

[1] Anderson MS, Venanzi ES, Klein L, et al. Projection of an immunological self-shadow within the thymus by the aire protein. *Science* 2002;298(5597):1395–1401.
[2] Derbinski J, Schulte A, Kyewski B, et al. Promiscuous gene expression in medullary thymic epithelial cells mirrors the peripheral self. *Nat Immunol* 2001;2(11):1032–1039.
[3] Richards DM, Kyewski B, Feuerer M. Re-examining the nature and function of self-reactive T cells. *Trends Immunol* 2016;37(2):114–125.
[4] Pan S, Xiao X, Li T, et al. Definition of follicular helper T cell and cytokines expression in synovial fluid of rheumatoid arthritis. *Clin Rheumatol* 2023;43:129–135.
[5] Piao X. Clinical observation on the treatment of acute rheumatoid arthritis by acupuncture and moxibustion. *Hubei Univ Tradit Chin Med* 2023;1:12–14.
[6] Meng F, Tao X, Li L, et al. Network pharmacology and molecular docking explore the mechanism of Mubiezi-Yinyanghuo herb pair in the treatment of rheumatoid arthritis. *Evid Based Complement Alternat Med* 2023;2023:4502994.
[7] Mueller DL, Jenkins MK, Schwartz RH. Clonal expansion versus functional clonal inactivation: a costimulatory signalling pathway determines the outcome of T cell antigen receptor occupancy. *Annu Rev Immunol* 1989;7:445–480.
[8] Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat Rev Immunol* 2013;13(4):227–242.
[9] June CH, Ledbetter JA, Gillespie MM, et al. T-cell proliferation involving the CD28 pathway is associated with cyclosporine-resistant interleukin 2 gene expression. *Mol Cell Biol* 1987;7(12):4472–4481.
[10] Moorman CD, Sohn SJ, Phee H. Emerging therapeutics for immune tolerance: tolerogenic vaccines, T cell therapy, and IL-2 therapy. *Front Immunol* 2021;12:657768.
[11] Francisco LM, Salinas VH, Brown KE, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *J Exp Med* 2009;206(13):3015–3029.
[12] Wing K, Onishi Y, Prieto-Martin P, et al. CTLA-4 control over Foxp3+ regulatory T cell function. *Science* 2008;322(5899):271–275.
[13] Frenz T, Grabski E, Buschjäger D, et al. CD4(+) T cells in patients with chronic inflammatory rheumatic disorders show distinct levels of exhaustion. *J Allergy Clin Immunol* 2016;138(2):586–589.e10.
[14] Zajac AJ, Blattman JN, Murali-Krishna K, et al. Viral immune evasion due to persistence of activated T cells without effector function. *J Exp Med* 1998;188(12):2205–2213.
[15] Fang L, Liu K, Liu C, et al. Tumor accomplice: T cell exhaustion induced by chronic inflammation. *Front Immunol* 2022;13:979116.
[16] Wherry EJ. T cell exhaustion. *Nat Immunol* 2011;12(6):492–499.
[17] Delpoux A, Michelini RH, Verma S, et al. Continuous activity of Foxo1 is required to prevent anergy and maintain the memory state of CD8+ T cells. *J Exp Med* 2018;215(2):575–594.
[18] Lang KS, Recher M, Navarini AA, et al. Inverse correlation between IL-7 receptor expression and CD8 T cell exhaustion during persistent antigen stimulation. *Eur J Immunol* 2005;35(3):738–745.
[19] Wherry EJ, Barber DL, Kaech SM, et al. Antigen-independent memory CD8 T cells do not develop during chronic viral infection. *Proc Natl Acad Sci U S A* 2004;101(45):16004–16009.
[20] Hashimoto M, Araki K, Cardenas MA, et al. PD-1 combination therapy with IL-2 modifies CD8+ T cell exhaustion program. *Nature* 2022;610(7930):173–181.
[21] Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000;192(7):1027–1034.
[22] Greisen SR, Yan Y, Hansen AS, et al. Extracellular vesicles transfer the receptor programmed death-1 in rheumatoid arthritis. *Front Immunol* 2017;8:851.
[23] Guo C, Liu Q, Zong D, et al. Single-cell transcriptome profiling and chromatin accessibility reveal an exhausted regulatory CD4+ T cell subset in systemic lupus erythematosus. *Cell Rep* 2022;41(6):111606.
[24] Czaja AJ. Introducing molecular chaperones into the causality and prospective management of autoimmune hepatitis. *Dig Dis Sci* 2023;68:4098–4116.
[25] Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 1996;271(5256):1734–1736.
[26] Jaen O, Rullé S, Bessis N, et al. Dendritic cells modulated by innate immunity improve collagen-induced arthritis and induce regulatory T cells *in vivo*. *Immunology* 2009;126(1):35–44. doi:10.1111/j.1365-2567.2008.02875.x
[27] Li J, Cao J, Chen Q, et al. Investigating the therapeutic potential of sinomenine in rheumatoid arthritis: anti-inflammatory, antioxidant, and immunomodulatory mechanisms. *Naunyn Schmiedebergs Arch Pharmacol* 2023;397:3945–3958.
[28] Cao G, Mao Z, Niu T, et al. Oxymatrine ameliorates rheumatoid arthritis by regulation of Tfr/Tfh cell balance via the TLR9-MyD88-STAT3 signaling pathway. *J Sci Food Agric* 2023;103(12):6017–6024.
[29] Ishida Y, Agata Y, Shibahara K, et al. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J* 1992;11(11):3887–3895.
[30] Xiong J, Yang J, Sun Y, et al. Dysregulated PD-L2 is correlated with disease activity and inflammation in rheumatoid arthritis. *Immunogenetics* 2023;75(5):425–431.
[31] Lowe K, Small A, Song Q, et al. Transcriptomic profiling of programmed cell death 1 (PD-1) expressing T cells in early rheumatoid arthritis identifies a decreased CD4 + PD-1 + signature post-treatment. *Sci Rep* 2023;13(1):2847.
[32] Pedersen K, Nielsen MA, Juul-Madsen K, et al. Galectin-3 interacts with PD-1 and counteracts the PD-1 pathway-driven regulation of T cell and osteoclast activity in rheumatoid arthritis. *Scand J Immunol* 2023;97(2):e13245.
[33] Sun Y, Jing Y, Huang M, et al. The PD-1/PD-Ls pathway is up-regulated during the suppression of experimental autoimmune encephalomyelitis treated by Astragalus polysaccharides. *J Neuroimmunol* 2019;332:78–90.
[34] Small A, Lowe K, Wechalekar MD. Immune checkpoints in rheumatoid arthritis: progress and promise. *Front Immunol* 2023;14:1285554.
[35] Monney L, Sabatos CA, Gaglia JL, et al. Th1-specific cell surface protein Tim-3 regulates macrophage activation and severity of an autoimmune disease. *Nature* 2002;415(6871):536–541.
[36] Anderson AC, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: co-inhibitory receptors with specialized functions in immune regulation. *Immunity* 2016;44(5):989–1004.
[37] Wu J, Yu X, Chen Z, et al. Expression of TIM-3 in rheumatoid arthritis peripheral blood regulatory T cells and clinical study of IL-17. *Minerva Med* 2023;114(3):420–422.
[38] Meng Q, Li D, Liu L. Therapeutic efficacy of Bai Hu plus Gui Zhi Tang plus reduction in treating patients with rheumatoid depression-heat type acute gouty arthritis. *Chin Mod Drug Appl* 2022;16(19):174–176.
[39] Boles KS, Vermi W, Facchetti F, et al. A novel molecular interaction for the adhesion of follicular CD4 T cells to follicular DC. *Eur J Immunol* 2009;39(3):695–703.

[40] Joller N, Hafler JP, Brynedal B, et al. Cutting edge: TIGIT has T cell-intrinsic inhibitory functions. *J Immunol* 2011;186(3):1338–1342.
[41] Wells AC, Pobezinskaya EL, Pobezinsky LA. Non-coding RNAs in CD8 T cell biology. *Mol Immunol* 2020;120:67–73.
[42] Fang W. Mechanism of action of tonifying spleen and intestines pill interfering with IL-21/IL-21R regulation of memory T cell differentiation in the treatment of ulcerative colitis. *Jiangxi Univ Tradit Chin Med* 2023;2:45–48.
[43] Chen T, Li S, Lian D, et al. Integrated network pharmacology and experimental approach to investigate the protective effect of Jin Gu Lian capsule on rheumatoid arthritis by inhibiting inflammation via IL-17/NF-κB pathway. *Drug Des Devel Ther* 2023;17:3723–3748.