Review

Dendritic Cells as a Pharmacological Target of Traditional Chinese Medicine

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Dendritic cells (DCs) represent a heterogeneous population of professional antigen-presenting cells (APCs) that play a central role in the initiation and regulation of immune responses. There is considerable evidence that DCs can be used as therapeutic targets for pharmacological modulation of immune responses. Traditional Chinese medicine (TCM) has a long-standing history of using herbal medicine in the treatment of variety of human diseases. Many of the clinical effects of TCM have reportedly been attributed to the up- or down-regulation of immune responses. Accumulating evidence indicates that TCM and its components can interfere with immune responses at the earliest stage by targeting key functions of DCs. Here, we review those published studies of TCM with respect to their effects on immunobiological functions of DCs. Investigations based on both chemical entities derived from TCM as well as TCM herbal mixtures are presented. These studies suggest that various TCM herbal medicines have the capacity to inhibit or promote major functions of DCs, such as differentiation, maturation, cytokine production, survival, antigen uptake and presentation as well as trafficking. These studies have revealed novel biological effects of TCM and documented the utility of this approach to discover novel biological modifier of DC functions derived from natural sources. *Cellular & Molecular Immunology*. 2006;3(6):401-410.

Key Words: dendritic cell, traditional Chinese medicine

Introduction

Dendritic cells (DCs) are a subpopulation of bone-marrow-derived myelocytic leukocytes that specialize in the uptake, processing, transport and presentation of antigens to effector cells participating in both innate and adaptive immune systems. Immature DCs are distributed in peripheral tissues and act as sentinels, by constantly sampling the environmental antigens. After encounter with microbial products or damaged tissue, DCs are induced to mature and as a result switch their expression pattern of surface chemokine receptors and acquire the capacity to migrate to draining LNs by expressing chemokine receptor 7 (CCR7). The microbial products are processed and presented on the surface of DCs as antigenic peptides by major histocompatibility complex (MHC) molecules. In the course of maturation, the surface expression of co-stimulatory molecules is also up-regulated, which enables DCs to become effective activator of effector lymphocytes. DCs thus initiate immunity by activating effector T and B cells in the adaptive immune system and by producing cytokines which activate cells of innate immune system, such as natural killer (NK) cells (1-3). In addition to initiating innate and adaptive immunity, DCs regulate immunity through their ability to induce antigen-specific unresponsiveness of lymphocytes in primary and secondary lymphoid tissues by mechanisms that include deletion of effector cells and induction of regulatory T cells (4, 5).

Given the central role of DCs in immunity and tolerance, they are ideal therapeutic targets for pharmacological modulation of immune responses (6, 7). Indeed, a large spectrum of structurally diverse immunosuppressive drugs has been shown to exert potent inhibitory effects on DC

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Abbreviations: AGI, astragulus injection; APC, antigen-presenting cell; ASP, astragulus polysaccharide; BMDC, bone-marrow derived dendritic cell; BZYQT, Bu Zhong Yi Qi Tang; DC, dendritic cell; GL*, ganoderma lucidum*; GL-M, *ganoderma lucidum* mycelium extract; GL-S, *ganoderma lucidum* spore extracts; LBP*, Lycium barbarum* polysaccharide-protein complex; LPS, lipopolysaccharide; MHC, major histocompatibility complex; MoDC, monocyte-derived DC; PS-G*, ganoderma lucidum* polysaccharide; TCM, traditional Chinese medicine; TPT, triptolide.

maturation and function, such as rapamycin (8), Cyclosporin A (9), dexamethasone (10), aspirin (11), α,25-dihydroxyvitamin D3 (12), LF15-0195 (13) and mycophenolate mofetil (MMF) (14), etc. DCs with an immature DC phenotype, as assessed by low expression of MHC class II, CD40, CD80, CD86 and absence of IL-12 production are reportedly tolerogenic (15). Tolerogenic DCs have been generated by immunosuppressive drugs such as LF15-0195 (in combination of anti-CD45RB) (16), vitamin D3 in combination of mycophenolate mofetil (16) or in combination with dexamethasone (17). Some of these drugs also have the potential to generate of $CD4^+CD25^+$ T regulatory cells (16). For example, we reported that *in vivo* administration of dexamethasone (or in combination with IL-2) increased the proportion of $FoxP3^+CD4^+CD25^+$ T regulatory cells in mice (18, 19) and this observation was confirmed in a human-based study (20). Recently, several lines of evidence indicate that dexamethasone can induce tolerogenic DCs, which are characterized by expressing low level of co-stimulatory molecules and producing high level of IL-10 (21-23). Since Tregs are well known to arrest DCs in an immature state, presumably, corticosteroids establishes an immunosuppressive feedback loop between tolerogenic DCs and regulatory T cells.

Traditional Chinese medicine (TCM) has been used in China and other Asian nations for thousands of years for the treatment of a wide variety of diseases and disorders. Most of the clinical effects of TCM has been reportedly attributable to its immunoregulatory activity (24, 25). Studies aimed at understanding the action of TCM on DCs have been gaining increasing attention. Accumulating data indicate that some immunosuppressive TCM have the capacity to suppress the development and function of DCs, while some of the TCM that enhance host resistance to infection and tumor are able to promote the activation of DCs.

The inhibitory effect of TCM on development and biological function of DC

Chinese herbal medicines with immunosuppressive activity are successfully used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), as well as for improving the outcome of solid organ transplantation (26). Indeed, we have reported that some multi-component herbal mixtures were potent inhibitors of leukocyte chemotactic responses and cytokine/chemokine production (27, 28) and we have successfully identified some of the active components contained in these herbal medicines (29-35). Recently, we and others have reported that some of anti-inflammatory TCMs and their active components actually inhibit various functions of DCs, as reviewed below.

Triptolide

Triptolide (TPT) is a chemically defined, potent immunosuppressive compound isolated from *Tripterygium wilfordii Hook F* (Lei Gong Teng, which translates into the "thunder god" vine, a vinelike member of the Celastraceae plant family),

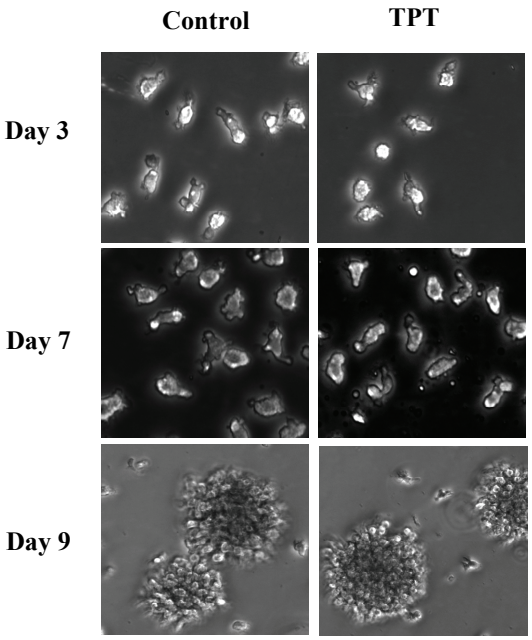

Figure 1. **Morphological appearance of TPT-treated DCs.** Human monocyte-derived immature DCs were generated by incubating purified monocytes at 1×10^6 cells/ml in G4 medium (RPMI 1640 containing 10% FBS, 2 mM glutamine, 25 mM HEPES [*N*-2-hydroxyethylpiperazine-*N*'-2-ethanesulfonic acid], 100 U/ml penicillin, 100 μg/ml streptomycin, 50 ng/ml rhGM-CSF, and 50 ng/ml rhIL-4) at 37°C in a CO_2 (5%) incubator for 7 days. The cultures were supplemented with the same cytokine-containing medium every 2 to 3 days. To induce DC maturation, iDCs were cultured in the same cytokine cocktails with the addition of LPS (10 ng/ml) for 2 days. TPT (2.5 nM) treatment began at day 2 to day 7 (D2-7). After thorough washing, cells were suspended in G4 medium supplemented with 10 ng/ml of LPS and cultured for an additional 48 hours. The photographs were taken at day 3, day 7 and day 9 of culture under a light microscope (200×). Data shown are representative of three separate experiments with similar results.

an anti-inflammatory Chinese herbal medicine (36). TPT has been reported to inhibit autoimmunity, allograft rejection, and graft-versus-host disease (GVHD), and its efficacy was previously attributed to the suppression of T cells (37, 38). Since DCs play a major role in the initiation of T-cell-mediated immunity, we studied the effects of TPT on the phenotype, function, and migration of human monocyte-derived DCs (MoDCs). TPT treatment, over a pharmacologic concentration range (IC50: 2.5 nM or 0.9 ng/ml), inhibited the lipopolysaccharide (LPS)-induced phenotypic changes characteristic of mature DCs and the production of interleukin-12p70 (IL-12p70). Notably, TPT at this concentration was not cytotoxic, did not alter the morphology of cultured MoDCs and did not inhibit cellular aggregation of LPS-stimulated MoDCs (Figure 1). The allostimulatory functions of DCs were impaired by TPT treatment. Furthermore, the chemotactic responses of LPS-stimulated MoDCs to secondary lymphoid tissue chemokine (SLC)/CC chemokine ligand 21 (CCL21), the ligand for CCR7, were

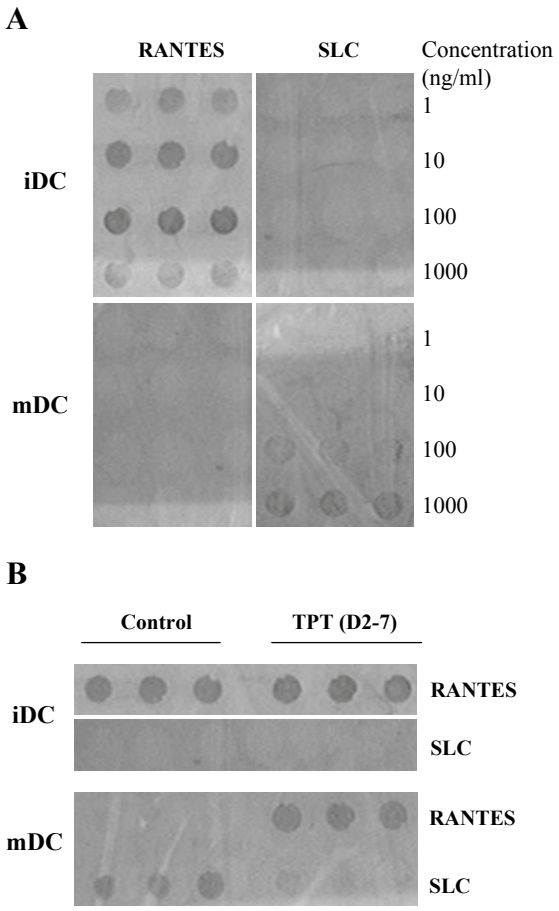

Figure 2. Effect of TPT on the chemotactic response of DCs and LPS-stimulated DCs. (A) Normal chemotactic response of cultured immature DCs (iDCs) and LPS-stimulated DCs (matured DCs, mDCs) to RANTES (CCL5) and SLC (CCL21). Chemokine (RANTES and SLC) was placed in the lower well of chemotaxis chamber. Suspension of DCs was placed in the upper well of the chemotaxis chamber. Polycarbonate filters separated the upper and lower wells. After incubation, the cells migrated across the filters were stained and photographed. Chemokine concentrations in the lower well are shown in the figure. (B) Effects of TPT (D2-7) treatment on chemotactic response of DCs to RANTES and SLC. Human monocyte derived DCs were cultured and treated with TPT as Figure 1 and chemotaxis assay was performed as in Figure 2A. Data shown are representative of at least three separate experiments with similar results.

significantly lower in TPT-treated than untreated DCs. The intrinsic chemotactic response of TPT-treated DCs was not inhibited, since they still exhibited normal response to RANTES-mediated cell migration and this capacity was preserved after LPS-stimulation (Figure 2). TPT-treated MoDCs consistently expressed lower CCR7 and higher CCR5 expression after LPS stimulation. Egress of Langerhans cells (LCs) from explanted mouse skin in response to macrophage inflammatory protein-3β (MIP-3β)/CCL19 was arrested by TPT. *In vivo* administration of TPT markedly inhibited hapten (fluorescein isothiocyanate [FITC])-stimulated migration of mouse skin LCs to the draining lymph nodes. These data provide new insight into the mechanism of action of TPT and indicate that the inhibition of maturation and trafficking of DCs by TPT contributes to its immunosuppressive effects (39).

Consistent with our observation, Zhu et al. found that TPT inhibited differentiation of immature MoDCs by inhibiting CD1a, CD40, CD80, CD86 and HLA-DR expression, but instead up-regulating CD14 expression, as well as by reducing the capacity of MoDCs to stimulate lymphocyte proliferation in the allogeneic mixed lymphocyte reaction. TPT completely blocked the induction of CD83 expression and inhibited up-regulation of CD40, CD80, CD86 and HLA-DR by LPS-activated MoDCs. In addition, a higher concentration of TPT (20 ng/ml) was found to induce apoptosis of MoDCs (40). Furthermore, TPT also was reported to inhibit TNF- and LPS-mediated expression of co-stimulatory molecule (CD80, CD86) and production of IL-12 from human mononuclear THP-1 cell lines (41).

Liu et al. reported that TPT reduced cell recovery by inducing apoptosis of DCs at concentration of 10 ng/ml, as demonstrated by phosphatidylserine exposure, decreased in the potential of mitochondria, and nuclear DNA condensation. TPT induced activation of p38 MAPK in DCs, which precedes the activation of caspase 3. SB203580, a specific kinase inhibitor for p38, was able to block the activation of caspase 3 and inhibited TPT-induced apoptosis of DCs (42).

Chemoattraction of neutrophils and T cells by DCs may favor their interactions with these cells and initiation of immune responses. Liu et al. reported that that TPT significantly impaired DC-mediated chemoattraction of neutrophils and T cells both *in vitro* and *in vivo* by suppressing DC production of CC and CXC chemokines including MIP-1α, MIP-1β, MCP-1, RANTES, TARC, and IP-10 in response to LPS. Furthermore, TPT-mediated inhibition of NF-κB activation, Stat3 phosphorylation and increases in SOCS1 expression in DCs might be involved in the inhibitory effect of this compound (43).

Thus, multiple mechanisms may contribute to the inhibitory effect of TPT on DCs. Based on these published data, it appears that lower concentrations of TPT interfere with the maturation of DCs and therefore inhibit DC's capacity to produce cytokines/chemokines, while higher concentrations of TPT induce apoptotic cell death of DCs. Further *in vivo* study is needed to distinguish between those alternatives mechanism.

Luteolin

The flavonoid luteolin found in various Chinese herbal extracts reportedly possesses antitumorigenic (44), anti-angiogenetic (45), antioxidant (46) and anti-inflammatory properties (28, 47). By using bone-marrow derived dendritic cells (BMDCs) isolated from recently engineered transgenic mice expressing the enhanced green fluorescent protein (EGFP) under the transcriptional control of NF-κB cis-elements (cis-NF-κB(EGFP)), Kim et al. found that luteolin blocked LPS-induced IκB phosphorylation and IKK activity, and decreased EGFP, IL-12 and TNF-α gene expression.

Moreover, intraperitoneal administration of luteolin significantly inhibited LPS-induced EGFP expression in both peripheral blood mononuclear cells and splenocytes (48). These results suggest that luteolin-containing TCMs may also have the capacity to block NF-κB signalling and proinflammatory gene expression by DCs.

Chinese herbal mixture: Zemaphyte

Langerhans cells and inflammatory dendritic epidermal cells contribute to the pathogenesis of atopic dermatitis (49) by increasing expression of CD23, the high-affinity receptor for immunoglobulin E (50). Zemaphyte is a standardized extract from 10 Chinese herbs that has been well established as a treatment for atopic eczema in clinical trials in Europe (51, 52). Novak et al. investigated the effect of Zemaphyte on the generation of MoDCs from atopic donors. They found that Zemaphyte treatment results in a significant change of DC morphology and decreases the expression of CD1a as well as the low-affinity IgE receptor CD23 on MoDCs. Furthermore, DCs exposed to Zemaphyte exhibited a diminished stimulatory activity toward autologous antigen-specific and allogeneic T cells, while secreting high amounts of IL-10 (53). Thus, TCM herbal mixtures are able to inhibit DC activation *in vitro* which may contribute, at least in part, to the therapeutic effect of this treatment in atopic dermatitis *in vivo*. Xu et al. reported that after two months treatment with Zemaphyte, CD23 levels are significantly reduced on dendritic cells and macrophages in the lesional skin (54). Furthermore, Banerjee et al. reported treatment with this Chinese medicine tends to selectively reduce CD23 expression on mature antigen presenting cells in lesional skin, but not on peripheral blood monocytes (55), suggesting this TCM may selectively impact the inflammatory environment of the lesion. Latchman and colleagues observed that Zemaphyte inhibited IL-4-induced CD23 expression by PBMC *in vitro* (52, 56). Thus, the clinical effect of this Chinese medicine on atopic dermatitis may be associated with inhibition of functions of DCs.

The promoting effect of TCM on development and biological function of DCs

Polysaccharides and polysaccharide-protein complexes isolated from mushrooms, fungi, yeasts, algae, lichens and plants, have been shown to have immunomodulatory and antitumor effects (57). These naturally occurring polysaccharides are a class of macromolecules that can profoundly affect the immune system and therefore have the potential to act as immunomodulators (58). It was reported that polysaccharides purified from mushrooms have the capacity to activate macrophages and have anti-tumor activities (57, 59). β-Glucans (glucose polymers) isolated from the cell walls of plants, fungi, and bacteria were reported to exhibit anti-tumor and anti-infection activities (60, 61). Polysaccharides from various traditional medicinal herbs have been shown to boost immune responses both *in vitro* as well as *in vivo* (62-72), including activation of DCs. We have presented data concerning effect of TCM-derived polysaccharides as well as other components from TCM on the development and function of DCs in this part of review.

Ganoderma lucidum

Ganoderma lucidum (GL) (known in China as Ling Zhi and in Japan as Reishi) is a medicinal mushroom used in Asia, for its activity in boosting immune response and consequently anti-tumor and antiviral effects (73). The major biology active component in GL has been proposed to be polysaccharides which reportedly have the capacity to activate antigen presenting cells, mononuclear phagocytes as well as T and B lymphocytes (74).

Chan et al. compared the effects of GL mycelium extract (GL-M) and spore extracts (GL-S) on human PBMCs and MoDCs. They found that GL-M induced the proliferation of PBMCs, whereas GL-S showed a mild suppressive effect. Both extracts stimulated Th1 and Th2 cytokine mRNA expression, but GL-M was a relatively more potent Th1 stimulator. Unlike GL-S, GL-M enhanced maturation of DCs including up-regulation of CD40, CD80, and CD86, and reduction in endocytosis of fluorescein isothiocyanate-dextran. However, GL-M-treated DCs only modestly enhanced lymphocyte proliferation in allogeneic mixed lymphocyte culture with a low degree of enhancement in Th development (75). Thus, it remains to be established whether GL-M may prove sufficiently potent as a natural adjuvant for cancer immunotherapy by activating DCs.

Lin et al. reported that development of human MoDCs with polysaccharide from GL (PS-G) enhancement their surface expression of CD80, CD86, CD83, CD40, CD54, HLA-DR and production of IL-12p70, p40, and IL-10. PS-G treatment inhibited endocytosis by DCs and increased the capacity of DCs to activate T cells. Antibody against TLR4 inhibited the PS-G-induced activation of DCs, suggesting a vital role for TLR4 in the effect of PS-G. Furthermore, PS-G treatment resulted in activation of IκB kinase, NF-κB and in an increase in MAP kinase phosphorylation. Inhibition of NF-κB by helenalin and p38 MAPK by SB98059 prevented PS-G-induced activation of DCs (76). Thus, PS-G is able to activate DCs by a NF-κB and MAPK pathway, presumably mediated by TLR4 signaling. The evidence that toll like receptors are utilized by PS-G is supported by studies showing that TLR4 was used by PS-G to activate macrophages (77-79), and TLR4/TLR2 was used by PS-G to activate B cells (79, 80). Furthermore, these effects of PS-G were reportedly not mediated by any contaminating LPS (77).

Lin's group further examined the effects of PS-G on human MoDCs with microarray analysis. In comparing mean signal values between PS-G-treated DCs with untreated DCs, 3477 (17%) probe sets were up-regulated, and 4418 (19%) probe sets were down-regulated after PS-G treatment. These results demonstrate that genes associated with phagocytosis (CD36, CD206, and CD209) are decreased and genes associated with proinflammatory chemokines (CCL20, CCL5, and CCL19), cytokines (IL-27, IL-23A, IL-12), and costimulatory molecules (CD40, CD54, CD80, and CD86)

are increased. To confirm the microarray data, they further investigated the effect of PS-G on antigen-specific antibody and cytokine production in BALB/c mice. Immunization with ovalbumin (OVA)/PS-G showed that the anti-OVA IgG2a levels were increased compared with OVA alone in BALB/c mice (81). These data demonstrate that PS-G could effectively promote the activation and maturation of immature DCs which have the capacity to preferentially stimulate Th1 responses.

Besides polysaccharide, other components in GL may also contribute to the activation of DCs. For example, Wang et al. reported that ganoderma triterpene (40-200 μg/ml) stimulated the proliferation of DCs derived from mouse spleen. Furthermore, ganoderma triterpene enhanced the GM-CSF/IL-4-mediated development of DCs (82). Thus, ganoderma triterpene may have differentiating effects on DCs.

Astragalus membranaceus

The root of *Astragalus membranaceus* (known in China as Huang Qi) is used in TCM to enhance host defense and for cancer therapy. Its effects were attributed to boosting anti-tumor immunity (83). Dong et al. reported that Astragulus injection (AGI) enhanced DC-based vaccine-mediated inhibition of metastasis in a mouse tumor model. In their study, myeloid DCs from C57BL/6 mice were pre-sensitized by Mut1 (a MHC class I-restricted polypeptide tumor antigen expressed by Lewis lung cancer). These DCs were then used to treat mice with metastatic lung cancer in combination with AGI or IL-2. After being treated with tumor antigen polypeptide sensitized DCs plus AGI or IL-2, the size of lung cancer modules decreased, the proportion of subsets $CD4^+$ and $CD8^+$ T cells in mouse spleen increased, and the IL-2/IL-4 ratio in serum also increased significantly. During the observation period, the growth rate of tumor in mice treated with DCs combined with either IL-2 or AGI, was lower than that in mice treated with DCs alone (84).

The pharmacological activity of Astragulus is likely due to polysaccharide fractions (71, 85). Shao et al. reported that Astragulus polysaccharide (ASP, 10-250 μg/ml) increase the surface expression of CD11c, MHC II and production of IL-12, while decreasing the phagocytic capacity, by murine BMDCs (86). Polysaccharides from Astragalus also are reported to bind directly to TLR4 on macrophages (87). Thus activation of DCs by this polysaccharide may also be mediated by TLR4.

Lycium barbarum

Used for over 2,000 years in China, *Lycium barbarum* fruits (known in China as Guo Ji Zhi) have a large variety of biological activities and pharmacological functions and have been used in TCM to prevent and treat various chronic diseases (88). *L. barbarum* polysaccharide-protein complex (LBP) is a major active component. LBP3p, the third fraction of LBP, was reported to suppress the growth of sarcoma S180 solid tumor *in vivo* and to restore the immune status of S180-bearing animals (89). This compound was also reported to stimulate the production of IL-2 and TNF from cultured human PBMCs (90). Gan et al. studied the effects of LBP on T-lymphocyte subsets and dendritic cells in the tumor microenvironment of solid H22 hepatoma-bearing mice. Oral delivery of LBP increased the numbers of $CD4^+$ and $CD8^+$ T cells in tumor infiltrating lymphocytes (TIL) as compared with those in control group ($p < 0.05$). Furthermore, LBP treatment increased the number of tumor infiltrating DCs and B7.1 expression by DCs (91). Thus, activation of DCs may contribute to the anti-tumor activity of LBP.

Ginsenoside

Ginseng (in China known as Ren Shen) is a widely used medicinal herb, and many of its pharmacological actions are attributed to the ginsenosides (83). Takei et al. investigated effects of M1 and M4, the end products of metabolized steroidal ginseng saponins in digestive tracts, on the maturation of DCs *in vitro*. Human monocytes were cultured with GM-CSF and IL-4 for 6 days, followed by another 2 days in the presence of M1, M4 or TNF-α as a maturation stimulus. Stimulation with 20 μM of M1 or M4 increased the expression level of CD80, CD83 and CD86 and decreased endocytic activity. M4-primed mature DCs also displayed enhanced T cell stimulatory capacity in a MLR, as measured by T cell proliferation. M1- and M4-mediated maturation of DCs endows them with the capacity to polarize naïve T cells towards Th1 cytokine production (92). These results suggest that M4 may be useful in DC-based vaccines for cancer immunotherapy.

Chinese herbal mixture (Bu Zhong Yi Qi Tang, BZYQT)

BZYQT, also known as Hochu-ekki-to (HOT) in Japan, is extracted from 10 herbal plants by boiling in water. BZYQT is one of the most popular traditional herbal medicines used in Southeast Asian nations and is prescribed mainly for chronic fatigue, immune deficiency and malnourished patients (93). BZYQT has various biological effects, including enhancing immune response. Preliminary clinical data suggest that BZYQT may be beneficial for tumor patients, presumably by boosting anti-tumor immunity (94). BZYQT was reported to promote anti-tumor immune response in mice by inducing tumor-specific type 1 cytokine production (95, 96) and to stimulate GM-CSF and TNF production by PBMCs from both healthy subjects and hepatocellular carcinoma patients (97). This TCM was also reported to increase IL-18-induced ICAM-1 and B7.2/CD86 expression as well as TNF and IFN-γ production by human PBMCs (98).

Nabeshima et al. observed the effect of this herbal remedy on the maturation of DCs. In their study, immature human MoDCs were stimulated with BZYQT, TNF-α, or LPS (BZYQT-DC, TNF-DC, and LPS-DC, respectively) for 2 days. Flow cytometric analysis showed that BZYQT dose-dependently stimulated DCs to express the surface maturation markers CD80, CD83, and CD86 which was comparable to the effects of TNF-α and LPS. Similar to LPS-DC, BZYQT-DC reduced their albumin uptake capacity and exhibited potent allogeneic stimulatory activity. However, IL-12 (p70) production by BZYQT-DC and TNF-DC was

Table 1. Effects of components of Chinese medicine on dendritic cells

Compound	Parent Botanic name	Effect on DCs	Therapeutic potential of compound
Triptolide	*Tripterygium wilfordii Hook F (Lei Gong Teng)*	1. Inhibits LPS-stimulated maturation of human MoDC (down-regulation of MHC and co-stimulatory molecules, IL-12, allostimulatory activity) (39-41) 2. Inhibits LPS-mediated expression of CCR7 and chemotactic response to CCL21 (39) 3. Inhibits hapten-stimulated migration of mouse skin LC to the draining LNs (39) 4. Induces mouse BMDC apoptosis through caspase 3 pathway (40, 42) 5. Inhibit chemokine production and NF-κB activation and Stat3 phosphorylation, enhances SOCS1 exspression by LPS-stimulated DC (43)	Inhibits collagen induced arthritis (101-103), experimental autoimmune uveoretinitis (104), prolongs allograft survival (103), prevents GVHD (105)
Luteolin	Various	1. Blocks LPS-induced IκB phosphorylation and IKK, NF-κB activity, IL-12 and TNF gene expression by mouse BMDC (48) 2. Intraperitoneal administration of luteolin significantly inhibited LPS-induced NF-κB activation (48)	May be used as an agent for tumor chemo-prevention (44, 46), antiangiogensis (45) and anti-inflammation (28, 47)
Polysaccharide	*Ganoderma lucidum (Ling Zhi)*	1. Up-regulates MHC and co-stimulatory molecules (76, 81) 2. Stimulates production of inflammatory cytokines and chemokines (76, 81) 3. Decreases endocytosis (76, 81) 4. Stimulates proliferation of DCs (82) 5. Promotes Th1 responses *in vivo* (81) 6. Activates NF-κB and MAPK signaling pathway (76) 7. Activates TLR4/TLR2 (76-80)	May be used as an adjuvant for immuno-therapy against tumor and viral infection
	Astragalus membranaceus (Huang Qi)	1. Increases surface expression of CD11c, MHC II and production of IL-12 (86) 2. Binds directly to TLR4 (87)	
	Lycium barbarum (Guo Ji Zhi)	Increases the number of tumor infiltrated DC and B7.1 expression by DC (91)	
GL mycelium extract	*Ganoderma lucidum (Linag Zhi)*	Enhances maturation of DCs (up-regulation of CD40, CD80, and CD86) (75)	
Ganoderma Triterpene		Stimulates proliferation of mouse splenic DC (82)	
Ginsenoside	*Ginseng (Ren Shen)*	Promotes maturation of DC (up-regulation of co-stimulatory molecule, increase T cell stimulatory capacity and differentiation of Th1) (92)	

lower than that by LPS-DC (93). Thus BZYQT has the capacity to stimulate maturation of DC and therefore may be beneficial for the establishment of anti-tumor immunity.

The modulatory effect of non-TCM herbal medicine on the function of DCs

Some herbal medicines derived from medical traditions other than TCM were also reported to modulate DC function. For example, extracts of *Jatoba* (a South American herb) suppresses the development of the experimental autoimmune encephalomyelitis (EAE). The active compounds were polymerized polyphenol polymers (procyanidins) which decreased the proportion of DCs in the spleen (99). Another example is *Echinacea purpurea*, a naïve North American herbal medicine which is popularly used as a food supplement in the US for enhancing immune response (83). Wang et al. found that the plant extracts from root [R] and stem plus leaf [S+L] tissues of *Echinacea purpurea* exhibited opposite (enhancing *vs* inhibitory) effects on the expression of the CD83 marker of human DCs. DNA microarray analysis revealed that [S+L]-treated DCs exhibited decreased mRNA expression of specific chemokines (e.g., CCL3 and CCL8) and their receptors (e.g., CCR1 and CCR9). Other chemokines and regulatory molecules (e.g., CCL4 and CCL2) involved in the c-Jun pathway were up-regulated in [R]-treated DCs (100). These results suggest that *Echinacea purpurea* extracts can promote DC differentiation and expression of specific immune-related genes in DCs. Thus, besides TCM, the herbal medicines derived from other traditional medical system also have the capacity to affect

Table 2. Effects of multiple component Chinese herbal medicine on DCs

Chinese herbal medicine	Ingredients	Clinical indications	Effect on DCs
Zemaphyte	*Ledebouriella seseloides, Potentilla chinensis, Anebia clematidis, Rehmannia glutinosa, Paeonia lactifora Lophatherum gracile, Dictamnus dasycarpus, Tribulus terrestris, Glucyrrhiza uralensis, Schizonepeta tenuifolia*	Atopic eczema	1. Reduces number of dendritic cells and macrophages in the lesional skin (54) 2. Inhibits CD1a and CD23 expression by MoDC (52-56) 3. Decreases allogeneic and autogenic stimulatory activity (53) 4. Induces production of IL-10 (53)
Bu Zhong Yi Qi Tang	*Ginzeng Radix, Atractylodis Rhizoma, Astragali Radix, Angelicae Radix, Aurantii Nobilis Pericarpium, Zizyphi Fructus, Bupleuri Radix, Glycyrrhizae Radix, Zingiberis Rhizoma, and Cimicifugae Rhizoma*	Chronic fatigue, immune deficiency and malnutrition	1. Induces expression of co-stimulatory molecules (93) 2. Enhances allogeneic stimulatory activity (93) 3. Reduces the capacity of endocytosis (93) 4. Induces modest production of IL-12 (93)
Astragulus Injection	Extract of *Astragalus membranaceus*	Viral myocarditis, hepatitis	Enhances DC-based vaccine-mediated inhibition of metastasis in a mouse tumor model (84)

biological function of DCs.

Concluding remarks

Accumulating evidence presented in this review indicates that numerous TCM and their components have the capacity to down- or up-regulate the development and function of antigen-presenting DCs. The impact of TCM-derived compounds and TCM herbal mixtures on DC functions are summarized in Table 1 and Table 2, respectively. These studies reveal TCMs to modulate immune response at the earliest stage by targeting DCs, suggesting the therapeutic potential of Chinese herbal remedies in DC-dependent immune diseases, and may lead to the discovery of novel biological modifiers of DCs from natural sources. More mechanistic studies will be needed to elucidate the molecular basis of DC-regulatory action of TCM. DCs represent a heterogeneous population of antigen-presenting cells and species differences exist, therefore it is very crucial to characterize the action of TCM on a defined subset of human DCs. Studies aimed at documenting the stimulatory action of TCM and their components on the activation of DCs need to be carefully controlled to rule out the potential contamination of LPS in the tested samples, especially for those in which the TLR4 pathway is proposed to be involved. Furthermore, the relevant physiological or pharmacological concentrations of TCM should be used in those *in vitro* studies and an appropriate *in vivo* modeling system should be developed to verify the *in vivo* relevance of the observations. In addition to initiating the immune response, DCs are also very crucial to establish antigen specific tolerance by interacting with regulatory T cells. The potential effect of TCM on the generation of tolerogenic DCs needs much more investigative effort.

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