Journal of Neuroimmunology 216 (2009) 8–19

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review article

Role of dopamine in the physiology of T-cells and dendritic cells

Rodrigo Pacheco [a,b,c,*], Carolina E. Prado [a,b], Magaly J. Barrientos [a,b], Sebastián Bernales [a,b,c]

[a] Fundación Ciencia para la Vida, Santiago, Chile
[b] Instituto Milenio de Biología Fundamental y Aplicada, Avenida Zañartu #1482, Santiago, Chile
[c] Universidad San Sebastián, Chile

ARTICLE INFO

Article history:
Received 17 April 2009
Received in revised form 22 July 2009
Accepted 28 July 2009

Keywords:
T-cell mediated immunity
CD8+ cytotoxic T-cells
CD4+ helper T-cells
Dopamine
Dendritic cells

ABSTRACT

Dendritic cells (DCs) are responsible for priming T-cells and for promoting their differentiation from naïve T-cells into appropriate effector cells. Because of their fundamental roles in controlling immunity, DCs and T-cells require tight regulatory mechanisms. Several studies have shown that dopamine, not only mediate interactions into the nervous system, but can also contribute to the modulation of immunity. Here, we review the emerging role of this neurotransmitter as a regulator of DC and T-cell physiology and, in turn, immune response. Moreover, we discuss how alterations in the dopamine-mediated immune regulatory mechanisms could contribute to the onset of immune-related disorders.

Contents

Abbreviations: Ach, Acetylcholine; AChR, Acetylcholine-receptor; Ag, Antigen; APCs, Ag-presenting cells; BBB, Blood–brain-barrier; CNS, Central nervous system; DCs, Dendritic cells; DA, Dopamine; DARs, DA-receptors; EAE, Experimental autoimmune encephalomyelitis; Glu, Glutamate; GluR, Glu-receptor; MHC, Major histocompatibility complex; mGluR, metabotropic-GluR; MS, Multiple sclerosis; NA/A, Noradrenaline/Adrenaline; pMHC, peptide–MHC complex; 5-HT, Serotonin; 5-HTR, 5-HT-receptor; TCR, T-cell receptor; TH, Tyrosine hydroxylase; TLRs, Toll-like receptors; Tregs, T regulatory cells.

* Corresponding author. Fundación Ciencia para la Vida and Instituto Milenio de Biología Fundamental y Aplicada, Avenida Zañartu #1482, Santiago, Chile. Tel.: +56 2 3672046; fax: +56 2 2372259.
E-mail address: rodrigo.pacheco@bionova.cl (R. Pacheco).

0165-5728/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jneuroim.2009.07.018

1. Introduction

1.1. The key role of T-cells and dendritic cells in the adaptive immune response

Adaptive immune responses against foreign antigens (Ags) are orchestrated by Ag-specific T-cells. Two main T-cell populations have been described, phenotypically differentiated by expression of CD4 or CD8 on the cell surface. These molecules function as co-receptors for

the MHC molecule. CD8+ and CD4+ T-cells recognize Ags as peptides bound to class I and class II MHC molecules, respectively (Nouri-Shirazi et al., 2000). Effector CD8+ T-cells may directly recognize tumor cells or infected cells expressing foreign Ags as surface peptide–MHC complexes (pMHCs). After recognition they mediate killing of those cells by secreting cytotoxic granules (Schoenborn and Wilson, 2007). In addition, by secreting IFN-γ, cytotoxic CD8+ T-cells may also potentiate function of other immune cells, including macrophages and NK cells (Schoenborn and Wilson, 2007). Thus CD8+ T-cells are key players during adaptive immune response against intracellular pathogens and tumors (Nouri-Shirazi et al., 2000).

Effector CD4+ T-cells not only contribute to efficient activation of CD8+ T-cells (Bennett et al., 1998; Ridge et al., 1998; Schoenberger et al., 1998) and B-cells (Smith et al., 2000), but they also regulate function of several cells of the innate arm of immune system, orchestrating the immune response. Depending on the signals that dendritic cells (DCs) provide to T-cells in addition to antigenic pMHC, they can promote the differentiation of CD4+ T-cell toward distinct subsets, including T helper (Th) 1 (Th1), Th2 and Th17 (Banchereau and Steinman, 1998; Lanzavecchia and Sallusto, 2001; McGeachy and Cua, 2008). The Th1 phenotype is favoured by the secretion of IL-12 by DCs. In contrast, Th2 phenotype is induced in the absence of IL-12 secretion during Ag recognition (Watford et al., 2003). Th1 cells predominantly secrete IFN-γ to promote cellular immunity against intracellular pathogens and tumor cells. In contrast, Th2 cells primarily secrete IL-4 which facilitates responses that can be efficient at eliminating extracellular pathogens, such as helmints and extracellular bacterium (Del Prete, 1998). The Th17 phenotype, which primarily secretes IL-17, has been more recently described. Differentiation into Th17 is promoted by TGF-β and IL-6, which can be secreted by DCs during Ag-presentation. It is thought that Th17 cells protect against extracellular bacteria, particularly in the gut (Schoenborn and Wilson, 2007), however they have also been extensively associated with autoimmune diseases (McGeachy and Cua, 2008). Another type of CD4+ T-cells consists on T regulatory cells (Tregs), a phenotype favoured by the presence of TGF-β (DiPaolo et al., 2007) which mainly secrete IL-10 and TGF-β and suppress several functions of effector Ag-specific T-cells (Cosentino et al., 2007; Nouri-Shirazi et al., 2000). The success of a particular immune response depends on the polarization of specific naïve CD4+ T-cells toward appropriate functional phenotype, thereby this process is tightly regulated. In this regard, deregulation in the functional phenotype of CD4+ T-cells could results in cancer or the onset of autoimmunity.

DCs are the most potent Ag-presenting cells (APCs) specialized in initiation of adaptive immune responses by directing the activation and differentiation of naïve T lymphocytes (Banchereau and Steinman, 1998; Lanzavecchia and Sallusto, 2001). These cells can capture both self and foreign Ags in diverse tissues and migrate to secondary lymphoid organs to present captured and processed Ags on MHC molecules to T-cells (Nouri-Shirazi et al., 2000). T-cell–DC synapses can comprise a diverse range of contact modes and distinct molecular arrangements that ultimately determine the nature of the T-cell response (Davis and Dustin, 2004; Friedl et al., 2005). Thus, T-cell–DC interaction can control and regulate T-cell activation, effector function and induction of tolerance (Friedl et al., 2005). Important functional components of the immunological synapse are activating/inhibitory receptor pairs expressed either on the DC or the T-cell surface (Herrada et al., 2007; Iruretagoyena et al., 2006; Pacheco et al., 2005). In addition, the synapse recruits several modulating receptors that, upon engagement, contribute to polarization of effector T-cell responses. The main interactions in the T-cell–DC interface are TCR/pMHC, costimulatory interactions mediated by CD80/CD86–CD28 and cytokines released from DCs toward T-cells. All of these signals are integrated together to modulate the differentiation of naïve T-cell toward the appropriate effector/regulator phenotype necessary to eliminate the invading pathogen or tumor.

1.2. Emerging role of neurotransmitters on the regulation of T-cells and DCs physiology

Traditionally, it has been thought that the functions of immune cells such as T-cells and DCs are regulated by soluble protein mediators known as cytokines. However, a number of studies have more recently shown that immune system cells can be also regulated by neurotransmitters (Franco et al., 2007). Accordingly, it has been described that several receptors for neurotransmitters classically expressed in the nervous system, such as glutamate (Glu)-receptors (GluRs), acetylcholine (ACh)-receptors (AChRs), serotonin (5-HT)-receptors (5-HTRs) and DA-receptors (DARs) are also expressed on the surface of immune system cells. For instance, T-cells express GluRs (Pacheco et al., 2004, 2007), DARs (Besser et al., 2005; Saha et al., 2001b; Sarkar et al., 2006; Watanabe et al., 2006), 5-HTRs (Leon-Ponte et al., 2007), AChRs (Kawashima and Fujii, 2003), noradrenaline/adrenaline (NA/A) receptors (Elenkov et al., 2000) and γ-aminobutiric acid receptors (Tian et al., 2004). On the other hand, DCs express GluRs (Pacheco et al., 2007), DARs (Nakano et al., 2008), 5-HTRs (Katoh et al., 2006), AChRs (Kawashima et al., 2007), and NA/A receptors (Maestroni and Mazzola, 2003). The identification of these receptors on these and other immune system cells suggests that neurotransmitters play a physiological role in the regulation of the immune response and that deregulation of the activation of these receptors could contribute to the development of autoimmunity or malignancies. Furthermore, this evidence implies that different physiological or pathophysiological states of the nervous system could be involved in the regulation of immunity.

Importantly, a number of recent studies have revealed that some cells involved in adaptive and innate immune responses such as DCs, T-cells and others, are capable of synthesizing and/or capturing classical neurotransmitters. Under specific conditions, these cells may release neurotransmitters from intracellular storages thus involving autocrine, paracrine, yuxtacrine and eventually endocrine communications between different leukocytes (Franco et al., 2007). For instance, T-cells may release 5-HT (O'Connell et al., 2006), NA/A (Nishibori et al., 2003), DA (Beck et al., 2004; Cosentino et al., 2007) and ACh (Kawashima and Fujii, 2003) while DCs may release Glu (Pacheco et al., 2006), DA (Nakano et al., 2009a) and 5-HT (O'Connell et al., 2006).

Important studies in this area have shown relevant regulatory function of some neurotransmitters in the function and differentiation of T-cells and DCs. Regarding the role of Glu, it has been demonstrated that during Ag-presentation, DCs release Glu, which subsequently act over T-cells (Pacheco et al., 2007, 2006). This mediator initially stimulates metabotropic-GluR5 (mGluR5), which by coupling to adenylate cyclase, triggers inhibitory signals to impairs T-cell activation. However, when the interaction TCR-pMHC is productive, T-cell activation overcomes the inhibitory mGlu5R-induced effect and they begin to express mGluR1. Further stimulation of mGlu1R by DCs-derived Glu potentiates T-cell activation and induces increased secretion of Th1- and pro-inflammatory cytokines, thus contributing to the polarization of the functional phenotype of T-cells (Pacheco et al., 2004, 2007, 2006). Addressing the role of ACh in the regulation of adaptive immune response, interesting studies have revealed the presence of the cholinergic system in T-cells. These studies have shown that T-cells not only express nicotinic and muscarinic AChRs (Kawashima and Fujii, 2003), but they also express ACh-transporter and they are able to store ACh in intracellular vesicles (Kawashima et al., 1998; Rinner and Schauenstein, 1993). Upon TCR-stimulation, T-cells release ACh, which in an autocrine way stimulates AChRs, potentiating T-cell activation and favouring differentiation toward Th1 phenotype (Fujii and Kawashima, 2000; Fujino et al., 1997; Hallquist et al., 2000). Another example is the serotoninergic system that regulates the T-cell response. Under maturation stimuli, DCs begin to express the 5-HT-transporter, which mediates uptake of 5-HT from the extracellular

compartment to be stored into intracellular vesicles. Subsequently, when mature DCs present Ags to T-cells in lymph nodes, DCs release these 5-HT-containing vesicles on T-cells, thus stimulating 5-HTRs expressed on these cells (O'Connell et al., 2006). Actually, it has been demonstrated that, indeed, 5-HT is required for proper T-cell activation early by stimulating 5-HTR_7 (Leon-Ponte et al., 2007) and 5-HTR_3 (Khan and Hichami, 1999; Khan and Poisson, 1999) expressed on naïve T-cells, and later by stimulating 5-HTR_{1B} and 5-HTR_{2C} expressed on activating T-cells (Yin et al., 2006).

These and other examples not only suggest that neurotransmitters could mediate communication between immune cells, but also that these molecules may be involved in bidirectional cross-talk between immune and nervous system. Importantly, DA not only has a highly relevant role in the nervous system, but it has also been shown to be involved in immune-related diseases (Giorelli et al., 2005; Kavtaradze and Mosidze, 2007; Lechin et al., 1990; Saha et al., 2001a,b; Zaffaroni et al., 2008). Due to the pivotal roles of T-cells and DCs during adaptive immune responses, we have analysed and discussed recent studies relative to the contribution of DA as mediator in the function of these cells.

1.3. The dopaminergic system

DA plays an essential role as neurotransmitter and neuromodulator in the nervous system. Neurotransmission associated to DA in the brain has been related with diverse functions including movement (Cenci, 2007), drug addiction (Dayan, 2009), pain perception (Potvin et al., 2009), hormone secretion (Ben-Jonathan and Hnasko, 2001), motivation and pleasure (Wise, 2008). DA synthesis and storage involves a number of cofactors and proteins, including enzymes and transporters. For instance, the rate-limiting enzyme in DA synthesis is tyrosine hydroxylase (TH), which converts tyrosine to L-DOPA. This product subsequently is metabolized by aromatic amino acid decarboxylase (AADC) to produce DA (Weihe et al., 2006). In addition to TH, DA-transporters are also relevant markers for dopaminergic systems. In the nervous system, the plasma membrane transporter for DA (DAT) removes this neurotransmitter from the extracellular space thereby controlling half-life of DA action (Mignini et al., 2009). On the other hand, vesicular monoamine transporters (VMAT) type-1 and type-2, mediate mobilization of cytosolic DA (*de novo* synthesised or captured) toward vesicular storages (Mignini et al., 2006).

DA exerts its effects in susceptible cells by stimulating DARs expressed on the cell surface. So far, five DARs have been described (D1–D5), which are hepta-spanning membrane receptors and belong to the superfamily of G protein-coupled receptors (Strange, 1993). Whereas type I DARs (D1 and D5) are generally coupled to Gαs and subsequent stimulation of cAMP production, type II DARs (D2, D3 and D4) are often coupled to Gαi promoting inhibition of cAMP synthesis (Sibley et al., 1993). However, it has been shown that type I and type II DARs also can be coupled to other Gα proteins, thus triggering signaling pathways different to the increase or decrease of cAMP production respectively (Neve et al., 2004; Sidhu, 1998). This differential coupling of DARs allows that DA might promote distinct cellular effects in two different kinds of cells expressing the same DAR. Furthermore, differential expression of DARs on different cells also contributes to DA exerts distinct effects in those cells. According to this idea and to the fact that there is differential expression and differential coupling of DARs in distinct neurons, DA may play very different roles on the distinct zones of the nervous system (Sidhu, 1998). Due to the extensive and important role that DA plays in the nervous system, the imbalance on the capture/release of DA or DARs expression have been related with a number of neurological or psychiatric disorders such as Parkinson's disease, Huntington's disease and schizophrenia (Hoenicka et al., 2007; Strange, 1993).

Dopaminergic components have not only described in the nervous system, but they have also been found in other organs and tissues including various vascular beds, the heart, the gastrointestinal tract, and the kidney. Thereby DA may exert regulation in the functioning of those tissues and organs. For instance, whereas DARs expressed in kidney contribute to the control of renal electrolyte balance (Gildea, 2009), there is evidence involving DA as an endogenous gastroprotective element (Glavin, 1992). Importantly, during the last decade, numerous evidences showing dopaminergic components in the immune system and involving to DA as a key modulator of the immune response, have emerged. Due to the central role that DCs and T-cells play in the development of adaptive immune responses, in this review we are focused to integrate and discuss the role that DA plays in the regulation of the functioning of these cells.

2. Modulation on the function of T-cells, DCs and other immune cells by dopamine

2.1. Sources of dopamine for immune cells

By stimulating different DARs expressed on T-cells or DCs, DA from diverse sources may strongly regulate the initiation and development of immune responses. The primary source of DA for patrolling resting naïve or memory T-cells and peripheral migrating effector T-cells into the blood vessels is plasma DA, which in normal individuals reaches levels of 10 pg/ml (Saha et al., 2001a,b). Furthermore, dopaminergic innervation of primary and secondary lymphoid organs through sympathetic nerves has been described (Mignini et al., 2003), which suggests the existence of direct DA-mediated regulation by nervous system on activating T-cells, resting T-cells and DCs in lymphoid organs (Fig. 1A). Accordingly, it has recently been described that early sympathectomy of animals ameliorates the development of autoimmunity by a mechanism involving stimulation of Tregs (Harle et al., 2008). This data therefore demonstrates a pro-inflammatory role of sympathetic-derived catecholamines on the early onset of autoimmunity.

Another source of DA for activating T-cells could be autocrine and paracrine secretion of DA by immune cells in secondary lymphoid organs. Accordingly, it has recently been described that human Tregs constitutively express TH and contain substantial amounts of DA and other catecholamines, while effector T-cells only contain trace amounts (Cosentino et al., 2000; Cosentino et al., 2007). Moreover, Tregs as well as effector T-cells express VMAT-1 and -2 which allow to these cells to accumulate catecholamines into specific vesicular storages (Cosentino et al., 2007). However, only Tregs store and release physiologically relevant amounts of DA from vesicular storages (Cosentino et al., 2007) (Fig. 1A). Interestingly, an autocrine/paracrine release of this neurotransmitter by DCs during Ag-presentation to naïve CD4+ T-cells has been recently described (Nakano et al., 2009a,b) (Fig. 1A). Production and storage of DA in DCs is discussed in Section 2.3.

Depending on the context of the immune response and on the location of inflammation, another important source of DA could be the central nervous system (CNS). Due to the presence of the blood–brain-barrier (BBB) and the lack of lymphatic vessels, the entrance of immune cells into the CNS is normally avoided. However, during inflammatory processes in the CNS such as those which occur in multiple sclerosis (MS), an autoimmune disorder directed against CNS constituents, circulating immunocompetent cells readily enter the CNS (Engelhardt, 2006). In this regard, it has been shown that effector T-cells are able to cross the BBB where they may be exposed to a variety of neurotransmitters (Owens et al., 1998). Effector T-cells can cross the BBB and enter the CNS due to their expression of particular cytokines, chemokine receptors and adhesion molecules. These molecules interact in a multistep process with surface molecules expressed on the BBB, allowing entrance of T-cells (Fig. 1B). Initially, a low-affinity interaction between α4-integrins on activated T-cells and VCAM-1 on endothelial surface cells (Vajkoczy et al., 2001) and the

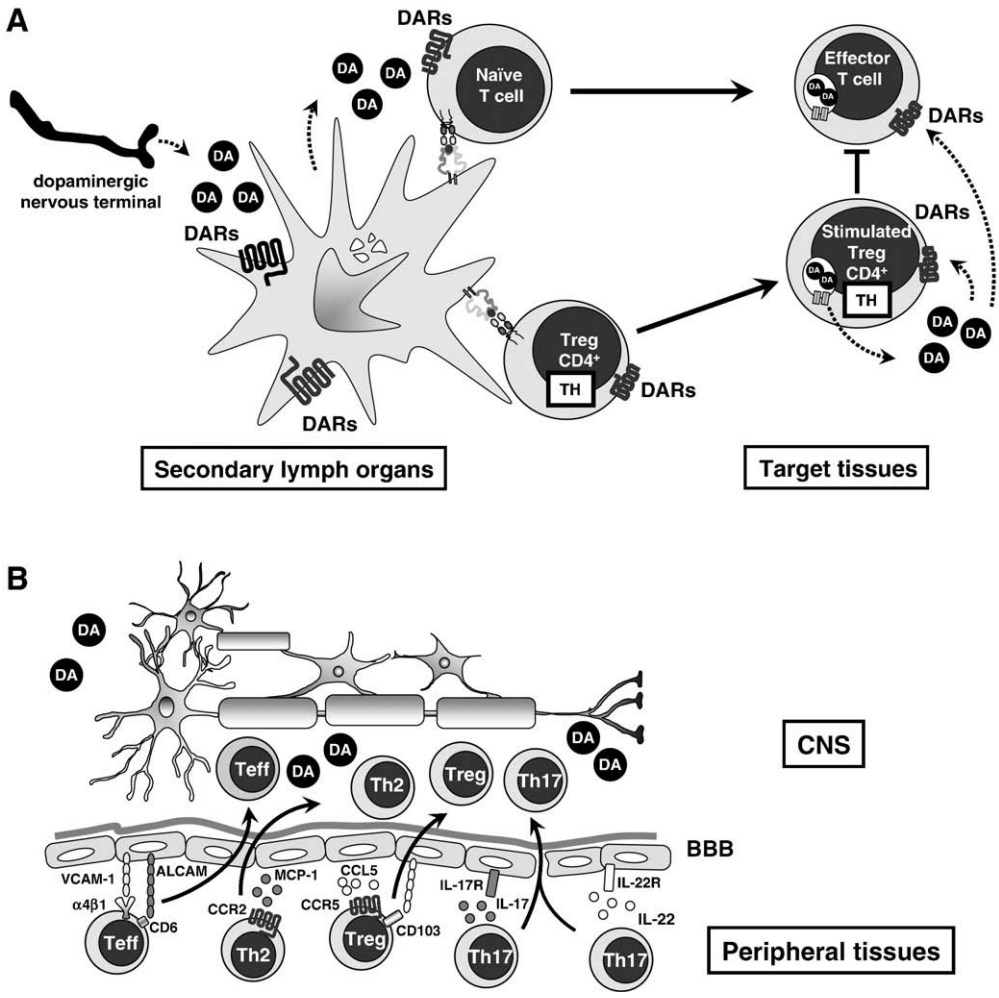


Fig. 1. Sources of DA for T-cells and DCs. A. Sources of DA in secondary lymph nodes. During Ag-presentation by DCs to T-cells into secondary lymph nodes, these cells may be stimulated by DA from dopaminergic nervous endings or by DCs-released DA. When naïve T-cells have been stimulated to differentiate into effector T-cells, they migrate toward infected/inflamed tissues (target tissues) where these cells orchestrate pathogen/tumor elimination. An important source of DA in target tissues involves the autocrine and paracrine secretion of DA by Tregs, which constitutively express tyrosine hydroxylase (TH). B. Entrance of T-cells into the CNS, another source of DA. During inflammatory processes in the CNS, stimulated effector T-cells (Teffs) and Tregs are able to cross the blood–brain-barrier (BBB) by mechanisms involving specific interactions between surface molecules of T-cells with surface molecules expressed on the BBB including specific cytokines, chemokine receptors and adhesion molecules. Solid lines represent cellular differentiation/migration while dotted lines represent DA secretion.

recently described interaction between the endothelial molecule ALCAM and the costimulatory surface molecule CD6 on T-cells (Cayrol et al., 2008), mediate the first step of T-cell/BBB interaction. Following this step, key chemokines such as CXCL9, CXCL10 or CXCL11 (Kivisakk et al., 2002), CCL19, CCL21 (Engelhardt, 2006) and MCP-1 (exclusive for Th2 cells) stimulate their respective receptors. These interactions play a crucial role in the successful recruitment of T-cells through BBB (Biernacki et al., 2001). After activation of chemokine receptors, cell surface integrins on leukocytes undergo conformational changes and engage their interactions with their receptors on the BBB surface, thus becoming high-affinity interactions and promoting strong adhesion of leukocytes to the endothelium. Subsequent to these strong interactions involving adhesion molecules such as LFA-1/ICAM-1 (Biernacki et al., 2001) takes place the extravasation of leukocytes through the BBB. Another mechanism to cross the BBB has been recently described for Th17 cells. A study performed in a model of human BBB *in vitro* has determined that IL-17R and IL-22R are up-regulated on the surface of endothelial cells of BBB in MS lesions (Kebir et al., 2007). Further action of IL-17 and IL-22 secreted by Th17 cells induces disruption of tight junctions by decreasing the expression of their constituent proteins occludin and zona occludens-1. Thus, Th17 cells perform a particular and specialized mechanism to cross the BBB (Kebir et al., 2007) (Fig. 1B). Regarding the capability of Tregs to cross the BBB, it has been described that when stimulated, they display an "activated/migratory" phenotype which is associated with high expression of CCR5 and CD103 ($\alpha E\beta 7$). By recognising and binding to their respective ligands these surface molecules have been associated with targeting Tregs toward sites of inflammation (Bagaeva et al., 2003; Glabinski et al., 2002; Huehn et al., 2004; Korn et al., 2007). The fact that Tregs from secondary lymph nodes do not express CCR5 and CD103, but selective expression of these surface molecules are found on Tregs from the CNS in mice suffering experimental autoimmune encephalomyelitis (EAE), an animal model of autoimmunity similar to MS in humans, suggests that these receptors could mediate entrance of Tregs into the CNS (Korn et al., 2007) (Fig. 1B).

2.2. Modulation of T-cell signaling and function by DARs stimulation

The TCR-pMHC interaction determines the specificity of T-cell activation and the nature of T-cell response (Carreno et al., 2006). Recognition of pMHC by the TCR is required to trigger all downstream events which occur during T-cell function. Parallel to TCR-pMHC signaling, interaction between CD86/CD80 on DCs and CD28 on the T-cell surface triggers costimulatory signals necessary for efficient T-cell activation. The signaling pathways which contribute to efficient activation of T-cells after specific Ag recognition include the PKC/Ca^{2+}

pathway and the mitogen-activated-protein-kinases (MAPK) ERKs, JNKs and p38. Together these signaling molecules promote the activation of transcriptional factors NF-κB, NF-AT and AP-1 complexes (Fig. 2A). The simultaneous efficient stimulation of all of these pathways leads to T-cell activation with expansion of Ag-specific T-cell clones and differentiation into effector and memory cells.

Type I and Type II DARs are often coupled to stimulation and inhibition of intracellular cAMP production respectively (Sibley et al., 1993). Regarding regulation of TCR-triggered signaling by cAMP in T-cells, PKA (a protein kinase activated by cAMP) as well as cAMP induce inhibition of ERKs phosphorylation (Ramstad et al., 2000) and of JNK activation (Harada et al., 1999), activate C-terminal Src kinase (Vang et al., 2001) and block NF-κB activation (Hershfield, 2005; Jimenez et al., 2001). All of these intracellular biochemical events induce a marked impairment on T-cell activation with inhibition of T-cell proliferation and of cytokine production (Aandahl et al., 2002). Thus, by stimulating DARs, DA could regulate T-cell function either negatively or positively (Fig. 2A).

Studies carried out on human and murine T-cells have demonstrated that these cells express all five DARs (D1–D5), each of which has diverse modulatory effects on the T-cell physiology (Fig. 2B and C). These studies have shown that stimulation of the D1/5 receptor impairs T-cell function by causing the rise of intracellular cAMP. Further evidence indicates that stimulation of type I DARs not only inhibits cytotoxic function of CD8+ T-cells (Saha et al., 2001b) but also impairs function and differentiation of Tregs (Cosentino et al., 2007; Kipnis et al., 2004). Moreover, stimulation of D1/5 receptors has also been involved in the polarization of naïve CD4+ T-cells toward Th17 cells (Nakano et al., 2008; Nakano et al., 2009b). Because Th17 and Treg cells are involved in autoimmunity as auto-aggressive and beneficial cells respectively, it is likely that type I DARs expressed on T-cells are involved in the interface between autoimmunity and health. Interestingly, a decreased expression of D5 in peripheral-blood-mononuclear-cells has been found in patients suffering the autoimmune disease MS (Giorelli et al., 2005). Type II DARs are also involved in modulation of T-cell physiology. Addressing the role of D2 receptor on the T-cell function, it has been demonstrated that stimulation of this receptor promotes enhanced production of IL-10, a cytokine that negatively regulates the function of effector T-cells (Besser et al., 2005). This inhibition could be involved in the polarization toward Tregs. Regarding D4 receptor stimulation, evidence indicates that this receptor triggers T-cell quiescence by up-regulating Krüppel-like factor-2 (KLF-2) expression (Buckley et al., 2001; Sarkar et al., 2006) (Fig. 2C). On the other hand, whereas D3-stimulation facilitates differentiation of naïve CD8+ T-cells into CTLs (Besser et al., 2005), it also contributes to polarization of naïve CD4+ T-cells toward Th1 effector phenotype (Ilani et al., 2004) (Fig. 2B and C). Furthermore, stimulation via D3 receptor is thought to be involved in migration and adhesion of T-cells, thus modulating the homing of these cells (Ilani et al., 2004; Kivisakk et al., 2002; Watanabe et al., 2006). An integrative scheme summarizing the involvement of DARs stimulation in the function and polarization of effector phenotype of T-cells is shown in Fig. 2B and C.

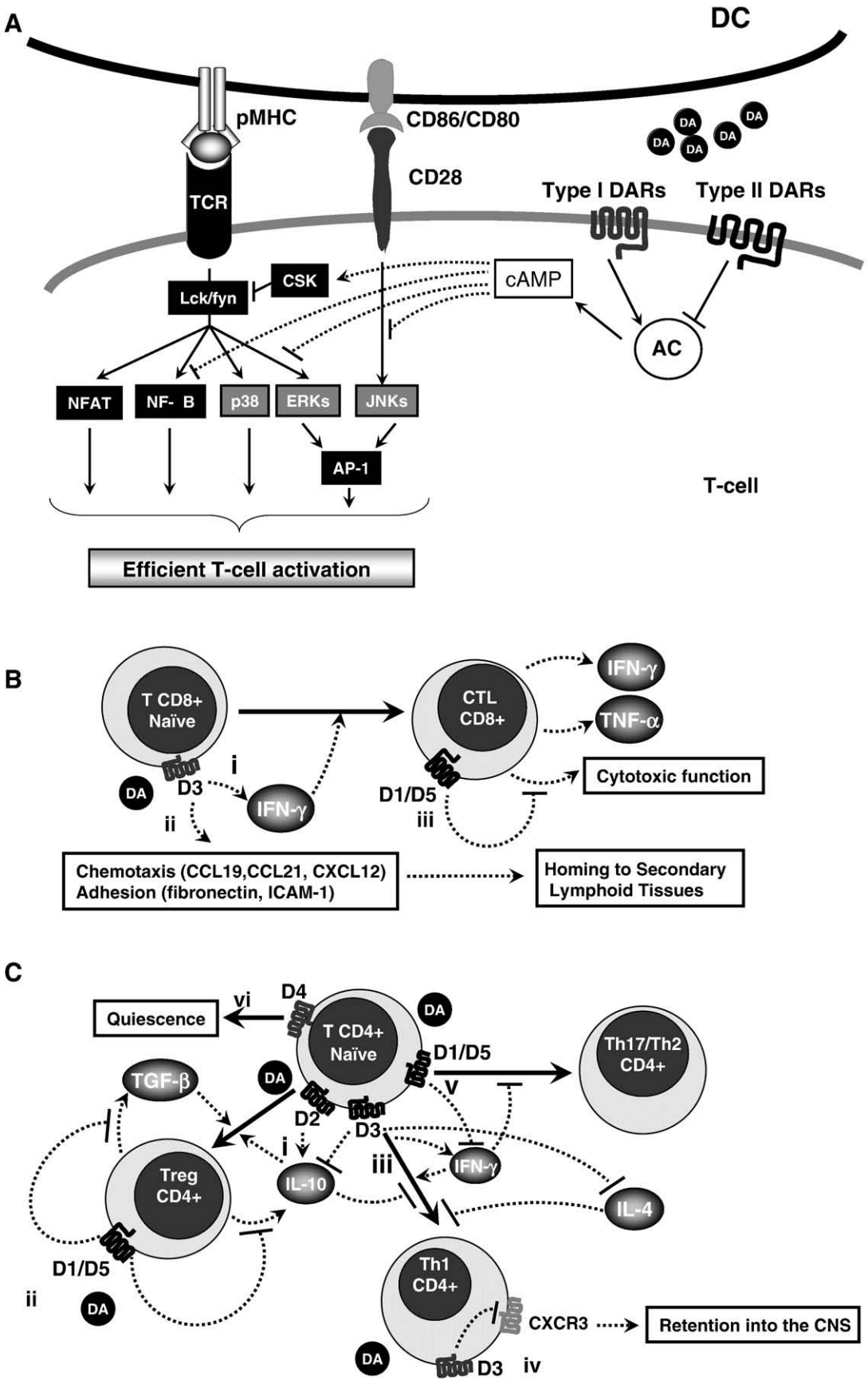
2.3. Involvement of dopamine in the function and signaling of DCs

The key role that DCs play in T-cell differentiation and development of immune responses is carried out via secretion of some regulatory cytokines and expression of specialized surface molecules during Ag-presentation. So far, among the most relevant surface molecules and regulatory cytokines in the function of DCs are costimulatory membrane-bound CD80 and CD86 molecules and soluble cytokines IL-12, IL-10 and IL-6. CD80 and CD86 (Zheng et al., 2004) are two costimulatory molecules that contribute to the immunogenicity of DCs. At the T-cell–DC synapse, CD80/CD86 can bind to CD28 on T-cells and provide activating signaling for T-cells. The presence or absence of costimulatory surface molecules allows DCs to modulate the nature of T-cell responses, promoting either immunity or tolerance, respectively (Iruretagoyena et al., 2006). Regulatory cytokines produced by DCs are IL-12, IL-10 and IL-6, among others. IL-12 favours differentiation toward Th1 and impairs Th2 and Th17 differentiation (McGeachy and Cua, 2008; Watford et al., 2003). Whereas IL-6 together with TGF-β facilitates Th17 differentiation (McGeachy and Cua, 2008), the cooperative action of IL-6 and IL-4 allow development of Th2-mediated responses (Diehl and Rincon, 2002). Because TGF-β alone promotes differentiation of naïve T-cells into Tregs, but in the presence of IL-6 induces differentiation to Th17, IL-6 plays a pivotal role in the decision of differentiation between Th17/Tregs (Dardalhon et al., 2008; McGeachy and Cua, 2008; Oukka, 2008). Interestingly, both of these phenotypes of T-cells are involved in autoimmunity, Th17 being the phenotype of pathogenic cells while Tregs perform the function of beneficial cells (Dardalhon et al., 2008; Oukka, 2008). On the other hand, by secreting the suppressive cytokine IL-10, tolerogenic DCs provide a suitable environment to stimulate function of Tregs (Gaudreau et al., 2007; Mahnke et al., 2007).

Inflammatory signals triggered in DCs by stimulation of Toll-like receptors (TLRs) or by pro-inflammatory cytokine receptors generally involve activation of several signaling pathways including NF-κB, MAPKs, PI-3K, IFN-regulatory factors (IRFs) and STATs (Makel et al., 2009). When turned on, these signaling pathways stimulate DCs maturation with consequent strong expression of costimulatory molecules CD80/CD86 and production of pro-inflammatory cytokine (Fig. 3A). Depending on the precise combination of signaling pathways triggered in the stimulation of DCs, these cells may be induced to produce and release different regulatory cytokine and to express surface molecules (Ardeshna et al., 2000; Arrighi et al., 2001; Iijima et al., 2003; Loscher et al., 2005; Makel et al., 2009; Mann et al., 2002; Nakahara et al., 2004; Usluoglu et al., 2007). Thus, the combination of signaling pathways triggered in DCs is pivotal for T-cell fate and the development of proper immune response (Fig. 3A).

With regard to the expression of DARs on DCs, type I as well as type II DARs have recently been described on these cells (Nakano et al., 2008), which are generally coupled to stimulation and inhibition of adenylate cyclase respectively (Sibley et al., 1993). Importantly, it has recently been described that adenylate cyclase stimulation potentiates LPS-induced ERKs and p38 phosphorylation. However adenylate

Fig. 2. Regulation of T-cell activation and polarization of effector phenotype by DA. A. Putative role of DARs in the T-cell signaling. Under Ag-presentation, TCR-stimulation together with costimulatory signals induce early activation of Src-kinases such as Lck and Fyn with subsequent stimulation of MAPKs pathways (p38, ERKs and JNKs), NF-κB and NF-AT. Simultaneous stimulation of these signaling pathways leads to efficient T-cell activation. Stimulation of Type I or Type II DARs by activation or inhibition of adenylate cyclase (AC) activity respectively may regulate intracellular cAMP levels. This regulation in turn induces activation of C-terminal Src Kinase (CSK) and inhibition of ERK, JNK and NF-κB pathways. Together these cAMP-mediated effects lead to an impaired state for T-cell activation. B. Functional role of DARs on CD8+ T-cells. i, By stimulating the D3 receptor, DA may facilitate differentiation of naïve CD8+ T-cells towards cytotoxic T lymphocyte (CTL). ii, In addition, stimulation of the D3 receptor on naïve CD8+ T-cells stimulates chemotaxis and also induces adhesion. iii, Furthermore, activation of type I DARs on CTLs impairs the cytotoxic effector function of these cells. C. Functional role of DARs on CD4+ T-cells. Naïve CD4+ T-cells express type I and type II DARs. i, Stimulation of the D2 receptor on these cells induces augmented secretion of IL-10, favouring differentiation toward Tregs. ii, Activation of type I DARs on differentiated Tregs triggers inhibitory signals for the function and differentiation of these cells. iii, On the other hand, stimulation of the D3 receptor on naïve CD4+ T-cells favours generation of the Th1 phenotype. iv, Activation of the D3 receptor expressed on differentiated Th1 cells stimulates down-regulation of the CXCR3, probably lowering the retention of these cells on the CNS. v, Stimulation of type I DARs on naïve CD4+ T-cells contributes to inducing further differentiation toward the Th17 or Th2 phenotype. vi, Stimulation of the D4 receptor on T-cells promotes an quiescent state. Solid arrows represent signaling pathways turned on after receptor stimulation in (A) and cell differentiation in (B and C). Whereas dotted lines represent cAMP-mediated effects in (A), they refer to secretion, production or effects in (B and C). Arrowheads represent activation/stimulation/up-regulation/secretion whereas flat heads represent inhibition/down-regulation.


A
DC
pMHC
CD86/CD80
CD28
TCR
DA
Type I DARs
Type II DARs
CSK
Lck/fyn
cAMP
AC
NFAT
NF- B
p38
ERKs
JNKs
AP-1
T-cell
Efficient T-cell activation
B
T CD8+ Naïve
i
D3
DA
IFN-γ
ii
CTL CD8+
IFN-γ
TNF-α
Cytotoxic function
D1/D5
iii
Chemotaxis (CCL19,CCL21, CXCL12)
Adhesion (fibronectin, ICAM-1)
Homing to Secondary Lymphoid Tissues
C
Quiescence
vi
D4
T CD4+ Naïve
DA
D1/D5
Th17/Th2 CD4+
v
TGF-β
DA
D2
D3
i
iii
Treg CD4+
IL-10
IFN-γ
IL-4
D1/D5
ii
DA
Th1 CD4+
CXCR3
Retention into the CNS
DA
D3
iv

cyclase stimulation can also inhibit LPS-promoted IRFs expression (Hickey et al., 2008) (Fig. 3A). In addition, there is evidence that augmented cAMP evokes inhibition of some Src-kinases with subsequent decrease on IRF-1 and c-Jun expression in LPS-treated DCs (Galgani et al., 2004). Together, these cAMP-induced effects in LPS-treated DCs stimulate strong IL-10 secretion coupled with attenuated IL-12 production by these cells (Galgani et al., 2004; Hickey et al., 2008). Nevertheless, whether activation of NF-κB is affected by elevated levels of cAMP in DCs remains controversial (Galgani et al., 2004; Jing et al., 2004; Zhou et al., 2007). Another signaling pathway modulated by increased cAMP in DCs involves PI-3K activation (Jing et al., 2004). These authors have demonstrated that by inhibiting PI-3K activity and consequently the participation of PKB and GSK3, cAMP exerts a dramatic decrease in the production of pro-inflammatory chemokines CCL3 and CCL4 (Fig. 3).

Addressing the physiological relevance of stimulation of DARs expressed on DCs in a pathological scenario, it has been demonstrated that DCs pre-treated with type I DARs-antagonists are enabled to promote amelioration of an autoimmune disease in mice (Nakano et al., 2008). This effect was possibly due to the fact that treatment with type I DARs-antagonists promotes DC-dependent inhibition of the pathogenic Th17-effector phenotype and favours Th1 differentiation in stimulated T-cells (Nakano et al., 2008) (Fig. 3B). In contrast, antagonism of type II DARs in DCs increase their capacity to promote the differentiation toward Th17 cells, whereas reducing Th1 polarization (Nakano et al., 2008). In order to elucidate the mechanism involved in DA-mediated regulation of the capability of DCs to evoke Th1 versus Th17 polarization, the same authors have described that under stimulation of type I DARs or antagonism of type II DARs, the increased cAMP induces enhanced DA production and storage by DCs (Nakano et al., 2009a,b). This effect was due to that cAMP stimulates activity of TH and thus DA synthesis (Nakano et al., 2009a). Subsequently, during Ag-presentation to specific-CD4+ T-cells, DCs release the DA secretory vesicles next to naïve CD4+ T-cells stimulating type I DARs and thus promoting polarization of these cells to the Th2/Th17 effector phenotype (Nakano et al., 2008, 2009a). Nonetheless, further efforts are necessary to identify specific DARs and more detailed mechanisms involved in DA-mediated regulation of DCs function. Similarly, more detailed studies on the mechanisms involved in DA-mediated polarization of effector phenotype of CD4+ T-cells should be considered as well. An integrative scheme for the role of DA and DARs in the physiology of DCs and on the interplay of these cells with T-cells is represented in the Fig. 3.

2.4. Modulation of other immune cells by dopamine

Components of the dopaminergic system have been identified not only in T-cells and DCs, but also in other immune cells such as B-cells or monocytes/macrophages, which — like DCs — constitute APCs for T-cells. Interestingly, evidences have shown that the involvement of DA in the functioning of these immune cells is not limited to DARs expression, but they also are capable of synthesizing and eventually release DA. Thereby, the release of DA during Ag-presentation seems to be a general feature for APCs.

Due to that reserpine induces intracellular DA depletion with concomitant increase of extracellular DA levels, it is thought that B-cells store DA in cytoplasmic vesicles (Cosentino et al., 2000). These vesicular storages of DA contains almost the same intracellular DA levels that Tregs (Cosentino et al., 2000, 2007). Although until now the physiologic stimuli triggering DA release from B-cells has not been determined, it is likely that DA release could be triggered by Ag-presentation. Thus, DA derived from B-cells could exert modulation on T-cells and perhaps on B-cell physiology. In this regard, B-cells show the greatest expression of D2, D3 and D5 receptors among leukocytes (McKenna et al., 2002; Meredith et al., 2006). However, the role of DARs stimulation on the B-cell function remains controversial. For instance, Morkawa et al., have shown that treatment of B-cells with bromocriptine, a D2 receptor agonist, inhibits proliferation and immunoglobulin production *in vitro* (Morkawa et al., 1993). Nonetheless, Tsao et al., have concluded that the treatment of these cells with D1 or D2 receptor agonists enhances B-cell proliferation *in vivo* and *in vitro* (Tsao et al., 1997).

Similarly to B-cells and DCs, it has been described that monocytes/macrophages also contain intracellular DA storages, probably in cytoplasmic vesicles (Cosentino et al., 2000). On the other hand, unlike other APCs, the presence of DARs on monocytes/macrophages has not clearly been demonstrated (Beck et al., 2004; McKenna et al., 2002). Interestingly, it has been described that DA or DARs agonists significantly attenuate production of pro-inflammatory cytokines secreted by LPS-stimulated macrophages. However, because the action of DA was partially prevented by propanolol and not influenced by DARs-antagonists, this effect is mainly mediated via β-adrenoreceptors (Hasko et al., 2002). This evidence suggests that DA also may modulate physiology of immune cells by DARs-independent mechanisms.

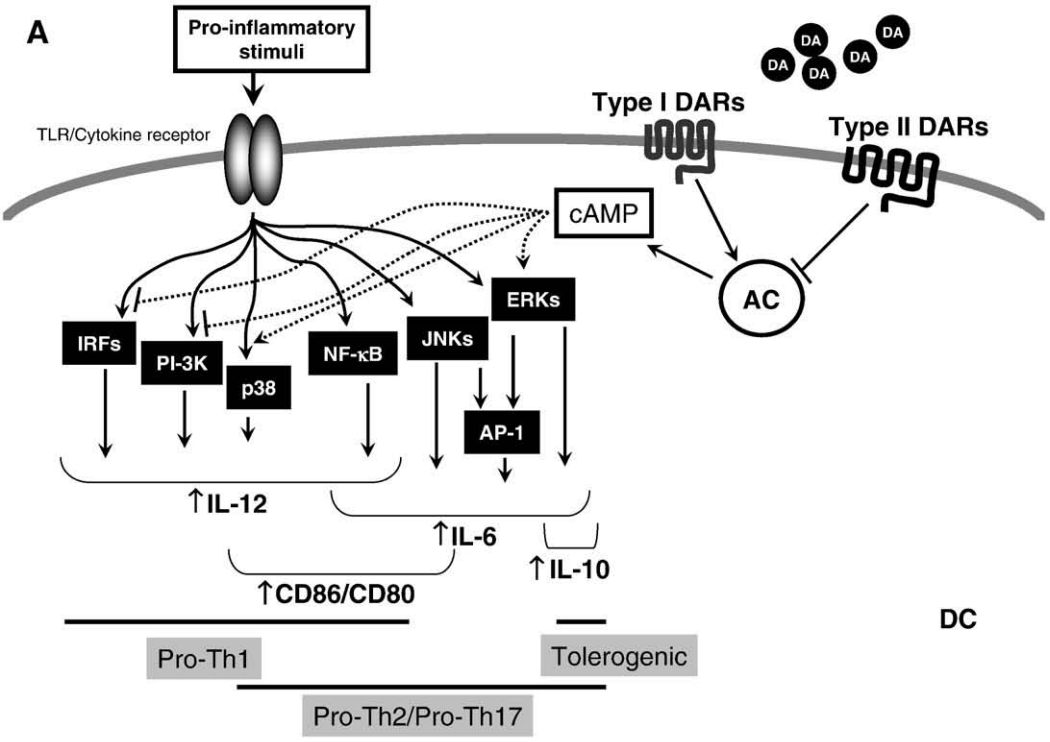
The presence of intracellular DA storages as a common feature for different kind of APCs suggests an important role of DA during Ag-presentation. However, further efforts are necessary to identify both, physiologic mechanisms triggering DA release from APCs and the relevance of these DA-mediated stimuli in the auto-regulation of APCs function and on the development of immune responses *in vivo*.

3. Alterations in DA-mediated T-cell regulation and involvement on the development of diseases

The presence of DA-mediated regulatory mechanisms involved in the modulation of the immune response suggests that deregulation of components of these mechanisms could be involved in the triggering, development or progression of immune- or neuroimmune-related diseases. Accordingly, an imbalance of plasma DA levels and deregulation of the expression of DARs on T-cells have been correlated with some disorders.

Regarding the deregulation of plasma DA levels in immune-related disorders, it seems that there is a trend in which plasma DA is increased in malignancies but decreased in autoimmunity (Table 1). It has been described that *in vitro* exposure of T-cells to DA concentrations similar to those found in the plasma of cancer-patients results in a general inhibition of T-cell proliferation and cytokine secretion (Ghosh et al., 2003; Saha et al., 2001a). It is likely that this

Fig. 3. DARs-dependent modulation of DC signaling and function. A. Putative modulation of inflammatory signaling in DCs by DARs. Pro-inflammatory agents such as pathogen-associated molecular patterns or inflammatory cytokines, by stimulating TLRs or cytokine receptors respectively, trigger activation of several signaling pathways in DCs. The production of cytokines which are key for DC function such as IL-10, IL-6 and IL-12 as well as the up-regulation of costimulatory CD80 and CD86 surface molecules on the DC surface are triggered by activation of different combinations of signaling pathways in DCs, as indicated. The capability of DCs to induce differentiation toward a specific effector phenotype in a naïve T-cell is determined by the production of regulatory cytokines and expression of costimulatory molecules, as indicated by thick lines. Stimulation of Type I or Type II DARs, by activation or inhibition of adenylate cyclase (AC) activity, may modulate cell signaling triggered by inflammatory agents in DCs. This modulation controls the capability of these cells to produce different cytokines and surface molecules and thereby alters the ability to induce a particular effector phenotype on T-cells. B. Role of DARs on the modulation of DC function. DCs express Type I and Type II DARs which are coupled to stimulation and inhibition of adenylate cyclase (AC) respectively (i). Thus, type I DARs stimulation, by cAMP accumulation, could inhibit CCL3 and CCL4 production (ii) and promote increased IL-10 and IL-6 secretion (iii) with attenuated IL-12 production (iv). cAMP also can promote DA synthesis by stimulating Tyrosine-Hydroxylase (TH) (v). During Ag-presentation by DCs to naïve T-cells in secondary lymphoid tissues, DCs release DA (vi) which subsequently stimulates different DARs expressed on T-cells, modulating T-cell differentiation. Whereas solid arrows represent signaling pathways turned on after receptor stimulation in (A), they symbolize reactions or flux in (B). Dotted lines represent cAMP-mediated effects in (A), while secretion, production or effects in (B). Arrowheads symbolize activation/stimulation/up-regulation/secretion whereas flat heads represent inhibition/down-regulation.


A
Pro-inflammatory stimuli
TLR/Cytokine receptor
DA
Type I DARs
Type II DARs
cAMP
AC
ERKs
IRFs
PI-3K
p38
NF-κB
JNKs
AP-1
↑IL-12
↑IL-6
↑IL-10
↑CD86/CD80
DC
Pro-Th1
Tolerogenic
Pro-Th2/Pro-Th17

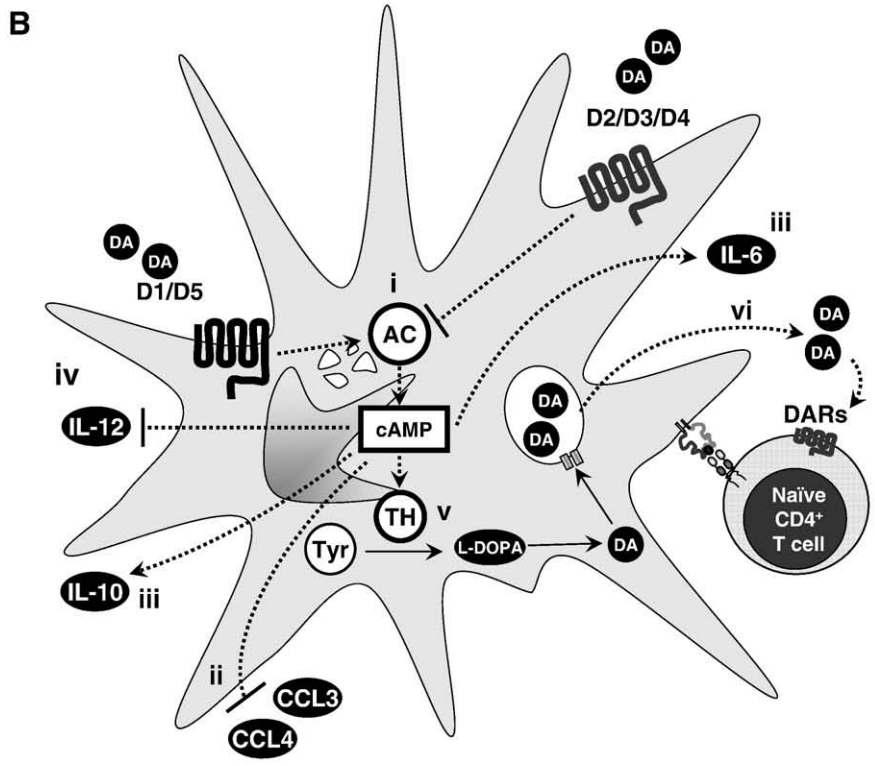

B
DA
D2/D3/D4
iii
IL-6
D1/D5
i
AC
vi
iv
IL-12
cAMP
DARs
Naïve CD4+ T cell
TH
v
Tyr
L-DOPA
IL-10
ii
CCL3
CCL4

Table 1
Deregulation of plasma DA in some neurologic disorders and immune-related pathologies.

Classification	Pathology	Increase (in-fold)[¶]	Reference
Neurologic disorders	Dementia of the Alzheimer type	1<	(Pinessi et al., 1987)
	Tension-type headache	1<	(Castillo et al., 1994)
	Stress	1.85	(LeBlanc and Ducharme, 2007)
	Stress (Males)	1.14	(Tomei et al., 2007)
	Stress (Females)	1.06	(Tomei et al., 2007)
Autoimmunity	Rheumatic diseases	0.62	(Kavtaradze and Mosidze, 2007)
Malignancies	Lung cancer	4.76	(Saha et al., 2001a)
	Advanced cancer (several types)	5.59	(Lechin et al., 1990)

[¶]Increase in plasma DA levels is expressed as the ratio of average of plasma DA concentration from patients versus average plasma DA concentration from healthy donors.

Table 2
Imbalanced expression of DARs in human T-cells in some neurological or immune-related pathologies.

Pathology	Receptors[¶]	Cells[#]	Reference
Alzheimer's disease	↓Type II DARs	PBMCs	(Barbanti et al., 2000a)
Migraine	↑D3, ↑D4, ↑D5	PBMCs	(Barbanti et al., 1996; Barbanti et al., 2000b)
Parkinson's disease	↓D3	PBMCs	(Nagai et al., 1996)
Schizophrenia	↑D3	T-cells	(Boneberg et al., 2006; Ilani et al., 2001; Kwak et al., 2001)
Schizophrenia	↓D4	CD4+ T-cells	(Boneberg et al., 2006)
Multiple sclerosis	↓D5	PBMCs	(Giorelli et al., 2005)

[¶]arrows indicate increased or decreased expression of receptors compared with control conditions from healthy individuals.
[#]PBMCs, peripheral-blood mononuclear-cells.

DA-mediated inhibition of T-cell function contributes to the depression of anti-neoplasic immune response in cancer-patients. On the other hand, low levels of plasma DA found on autoimmunity could have a role in these pathologies by allowing an exacerbated response of autoreactive T-cells. Thereby, the trend of high DA levels in malignancies and low DA levels in autoimmunity could constitute an important factor in the pathophysiology of these diseases and consequently should be taken in account for treatment and/or diagnosis. Given the imbalanced levels of plasma DA seen in diverse neurologic disorders, it may be too complex a process to establish the cause of the imbalance. Nevertheless, the effect of this imbalance on the T-cell function may sometimes results quite predictable. For instance, the pathophysiological state of stress promotes increased levels of plasma DA (Table 1), which results in the inhibition of T-cell function and therefore immunosuppression (Iagmurov and Ogurtsov, 1996; La Via et al., 1996). Indeed, it is likely that elevation of plasma DA levels found in malignancy could be due to the stress suffered by patients with this illness. These findings collectively suggest that selective stimulation of specific DARs on T-cells, which may be carried out by administration of selective agonist/antagonists, could improve T-cell response in some neurological and immune-related disorders.

Not only an imbalance of plasma levels of DA can alter T-cell function, but also the deregulation of DARs expressed on T-cells can cause similar effects. Accordingly, abnormal expression of DARs on T-cells has been described in some neurological and immune-related disorders (Table 2). For example, decreased expression of the D5 receptor, which performs an inhibitory role in T-cell function, has been described in T-cells from patients with MS, an autoimmune disorder (Giorelli et al., 2005). Furthermore, it has recently been shown that amelioration of MS by treatment with IFN-β is accompanied by restoration of levels of D5 receptor expressed on T-cells (Zaffaroni et al., 2008). DARs deregulation on T-cells has been also described in several neurological disorders (Table 2), which could have serious consequences on the function of the immune system. Indeed, some studies have suggested that the RNA levels of specific DARs subtypes expressed on T-cells could be used as peripheral markers for clinical diagnosis of these neurological and immune-related diseases (Table 2). More importantly, all of these studies suggest that the functional dialogue between DA and T-cells might be either up- or down-regulated in these diseases, playing a key element in the pathological scenario. According to this idea, it has been demonstrated that administration of an D2-agonist to mice during EAE, produces beneficial outcomes in the clinical course of development of this disease (Dijkstra et al., 1994). Another work supporting this notion has recently been performed by Nakano et al. (Nakano et al., 2008). These authors described that DCs pre-treated with type I DARs-antagonists are able to promote amelioration of EAE by impairing differentiation of naïve T-cells toward Th17 cells, the pathogenic effector phenotype in this pathology (Nakano et al., 2008). In fact, recently DA has been shown to be highly involved in the regulation of the phenotype of the effector T-cell response (Fig. 2B and C). Indeed, it has been demonstrated that the ratio IFN-γ/IL-4 in plasma is significantly higher in schizophrenic patients with early treatment or without medication than in healthy controls. The increased levels of IFN-γ/IL-4 were attenuated by effective neuroleptic treatment (Avgustin et al., 2005; Kim et al., 2004), indicating how dopaminergic regulation may influence Th1/Th2 polarization *in vivo*. Therefore, imbalanced neurotransmitter receptors expression on T-cells seems to be also an additional important factor that can be considered for the design of therapies for immune- or neuroimmune-related disorders.

4. Concluding remarks and future perspectives

The evidence presented suggests that DA and DARs play an important role in the regulation of physiology of T-cells and DCs. We have proposed that by modulating signaling pathways, DARs stimulation on DCs could modify the pattern of cytokine secretion promoted by inflammatory stimuli, thus skewing polarization of T-cell differentiation toward a particular phenotype. In addition, by modulating intracellular signals in T-cells, DARs stimulation on these cells may induce further regulation of adaptive immune responses. Thereby DA has important roles in the development and progression of immune- or neuroimmune-related diseases.

Identification of sources of DA for modulation of T-cells constitutes an important and active research field. Neurotransmitters have not only been involved in nervous-driven regulation of immunity, but also in leukocyte-driven regulation of immunity. In this regard, DCs as well as T-cells and other immune cells have been described as sources of neurotransmitters, released under particular conditions. However, target cells and physiological roles for these leukocyte-derived neurotransmitters remains, in several cases, not well defined. Further studies are still necessary to determine physiological relevance of immune-driven release of DA, its roles, both individual and synergistic with other mediators, and their mechanism of action. In this direction, the role of leukocyte-derived DA on the physiology of nervous system should be explored as well. These studies would allow elucidation of bidirectional mechanisms of DA-mediated neuro-immune communication, which could give a better understanding of physiological mechanisms or those operating in pathologies involving leukocyte infiltration into the brain such as occurs in MS.

Further insight into DA-mediated regulation of immune function is critical to understanding its role in imbalanced immune responses, including autoimmunity, immunodeficiency and tumor growth. The relevant involvement of DA-mediated regulation in the immune response is evidenced by deregulation of DARs expressed on T-cells and alteration of plasma DA levels, both conditions found as part of the

pathophysiological scenario in some immune-related and neurological disorders. In this regard, deregulation of DARs expression and plasma DA levels follow a trend geared toward exacerbate the imbalance of immune response. For instance, plasma DA levels, which in general inhibit T-cell function, are increased in malignancies, but decreased on autoimmune disorders. The precise knowledge of the deregulation of plasma DA concentration and DARs expression on T-cells under different pathophysiological conditions, together with an understanding of the precise role of stimulation of each DARs subtype on T-cell physiology could facilitate to the design of therapies for the treatment of autoimmunity, immunodeficiency and cancer.

Acknowledgements

We would like to thank Britta Hult for critically reading this manuscript. This work was supported by grants FONDECYT 1095114 and CONICYT PFB-16. CEP is a CONICYT fellow.

References

Aandahl, E.M., Moretto, W.J., Haslett, P.A., Vang, T., Bryn, T., Tasken, K., Nixon, D.F., 2002. Inhibition of antigen-specific T cell proliferation and cytokine production by protein kinase A type I. J. Immunol. 169, 802–808.

Ardeshna, K.M., Pizzey, A.R., Devereux, S., Khwaja, A., 2000. The PI3 kinase, p38 SAP kinase, and NF-kappaB signal transduction pathways are involved in the survival and maturation of lipopolysaccharide-stimulated human monocyte-derived dendritic cells. Blood 96, 1039–1046.

Arrighi, J.F., Rebsamen, M., Rousset, F., Kindler, V., Hauser, C., 2001. A critical role for p38 mitogen-activated protein kinase in the maturation of human blood-derived dendritic cells induced by lipopolysaccharide, TNF-alpha, and contact sensitizers. J. Immunol. 166, 3837–3845.

Avgustin, B., Wraber, B., Tavcar, R., 2005. Increased Th1 and Th2 immune reactivity with relative Th2 dominance in patients with acute exacerbation of schizophrenia. Croat. Med. J. 46, 268–274.

Bagaeva, L.V., Williams, L.P., Segal, B.M., 2003. IL-12 dependent/IFN gamma independent expression of CCR5 by myelin-reactive T cells correlates with encephalitogenicity. J. Neuroimmunol. 137, 109–116.

Banchereau, J., Steinman, R.M., 1998. Dendritic cells and the control of immunity. Nature 392, 245–252.

Barbanti, P., Bronzetti, E., Ricci, A., Cerbo, R., Fabbrini, G., Buzzi, M.G., Amenta, F., Lenzi, G.L., 1996. Increased density of dopamine D5 receptor in peripheral blood lymphocytes of migraineurs: a marker for migraine? Neurosci. Lett. 207, 73–76.

Barbanti, P., Fabbrini, G., Ricci, A., Bruno, G., Cerbo, R., Bronzetti, E., Amenta, F., Luigi Lenzi, G., 2000a. Reduced density of dopamine D2-like receptors on peripheral blood lymphocytes in Alzheimer's disease. Mech. Ageing Dev. 120, 65–75.

Barbanti, P., Fabbrini, G., Ricci, A., Pascali, M.P., Bronzetti, E., Amenta, F., Lenzi, G.L., Cerbo, R., 2000b. Migraine patients show an increased density of dopamine D3 and D4 receptors on lymphocytes. Cephalalgia 20, 15–19.

Beck, G., Brinkkoetter, P., Hanusch, C., Schulte, J., van Ackern, K., van der Woude, F.J., Yard, B.A., 2004. Clinical review: immunomodulatory effects of dopamine in general inflammation. Crit. Care 8, 485–491.

Ben-Jonathan, N., Hnasko, R., 2001. Dopamine as a prolactin (PRL) inhibitor. Endocr. Rev. 22, 724–763.

Bennett, S.R., Carbone, F.R., Karamalis, F., Flavell, R.A., Miller, J.F., Heath, W.R., 1998. Help for cytotoxic-T-cell responses is mediated by CD40 signalling. Nature 393, 478–480.

Besser, M.J., Ganor, Y., Levite, M., 2005. Dopamine by itself activates either D2, D3 or D1/D5 dopaminergic receptors in normal human T-cells and triggers the selective secretion of either IL-10, TNFalpha or both. J. Neuroimmunol. 169, 161–171.

Biernacki, K., Prat, A., Blain, M., Antel, J.P., 2001. Regulation of Th1 and Th2 lymphocyte migration by human adult brain endothelial cells. J. Neuropathol. Exp. Neurol. 60, 1127–1136.

Boneberg, E.M., von Seydlitz, E., Propster, K., Watzl, H., Rockstroh, B., Illges, H., 2006. D3 dopamine receptor mRNA is elevated in T cells of schizophrenic patients whereas D4 dopamine receptor mRNA is reduced in CD4+ -T cells. J. Neuroimmunol. 173, 180–187.

Buckley, A.F., Kuo, C.T., Leiden, J.M., 2001. Transcription factor LKLF is sufficient to program T cell quiescence via a c-Myc-dependent pathway. Nat. Immunol. 2, 698–704.

Carreno, L.J., Gonzalez, P.A., Kalergis, A.M., 2006. Modulation of T cell function by TCR/pMHC binding kinetics. Immunobiology 211, 47–64.

Castillo, J., Martinez, F., Leira, R., Lema, M., Noya, M., 1994. Plasma monoamines in tension-type headache. Headache 34, 531–535.

Cayrol, R., Wosik, K., Berard, J.L., Dodelet-Devillers, A., Ifergan, I., Kebir, H., Haqqani, A.S., Kreymborg, K., Krug, S., Moumdjian, R., Bouthillier, A., Becher, B., Arbour, N., David, S., Stanimirovic, D., Prat, A., 2008. Activated leukocyte cell adhesion molecule promotes leukocyte trafficking into the central nervous system. Nat. Immunol. 9, 137–145.

Cenci, M.A., 2007. Dopamine dysregulation of movement control in L-DOPA-induced dyskinesia. Trends Neurosci. 30, 236–243.

Cosentino, M., Bombelli, R., Ferrari, M., Marino, F., Rasini, E., Maestroni, G.J., Conti, A., Boveri, M., Lecchini, S., Frigo, G., 2000. HPLC-ED measurement of endogenous catecholamines in human immune cells and hematopoietic cell lines. Life Sci. 68, 283–295.

Cosentino, M., Fietta, A.M., Ferrari, M., Rasini, E., Bombelli, R., Carcano, E., Saporiti, F., Meloni, F., Marino, F., Lecchini, S., 2007. Human CD4+CD25+ regulatory T cells selectively express tyrosine hydroxylase and contain endogenous catecholamines subserving an autocrine/paracrine inhibitory functional loop. Blood 109, 632–642.

Dardalhon, V., Korn, T., Kuchroo, V.K., Anderson, A.C., 2008. Role of Th1 and Th17 cells in organ-specific autoimmunity. J. Autoimmun. 31, 252–256.

Davis, D.M., Dustin, M.L., 2004. What is the importance of the immunological synapse? Trends Immunol. 25, 323–327.

Dayan, P., 2009. Dopamine, reinforcement learning, and addiction. Pharmacopsychiatry 42 (1), S56–S65.

Del Prete, G., 1998. The concept of type-1 and type-2 helper T cells and their cytokines in humans. Int. Rev. Immunol. 16, 427–455.

Diehl, S., Rincon, M., 2002. The two faces of IL-6 on Th1/Th2 differentiation. Mol. Immunol. 39, 531–536.

Dijkstra, C.D., van der Voort, E.R., De Groot, C.J., Huitinga, I., Uitdehaag, B.M., Polman, C.H., Berkenbosch, F., 1994. Therapeutic effect of the D2-dopamine agonist bromocriptine on acute and relapsing experimental allergic encephalomyelitis. Psychoneuroendocrinology 19, 135–142.

DiPaolo, R.J., Brinster, C., Davidson, T.S., Andersson, J., Glass, D., Shevach, E.M., 2007. Autoantigen-specific TGFbeta-induced Foxp3+ regulatory T cells prevent autoimmunity by inhibiting dendritic cells from activating autoreactive T cells. J. Immunol. 179, 4685–4693.

Elenkov, I.J., Wilder, R.L., Chrousos, G.P., Vizi, E.S., 2000. The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. Pharmacol. Rev. 52, 595–638.

Engelhardt, B., 2006. Molecular mechanisms involved in T cell migration across the blood–brain barrier. J. Neural. Transm. 113, 477–485.

Franco, R., Pacheco, R., Lluis, C., Ahern, G.P., O Connell, P.J., 2007. The emergence of neurotransmitters as immune modulators. Trends Immunol. 28, 400–407.

Friedl, P., den Boer, A.T., Gunzer, M., 2005. Tuning immune responses: diversity and adaptation of the immunological synapse. Nat. Rev. Immunol. 5, 532–545.

Fujii, T., Kawashima, K., 2000. Calcium signaling and c-Fos gene expression via M3 muscarinic acetylcholine receptors in human T- and B-cells. Jpn. J. Pharmacol. 84, 124–132.

Fujino, H., Kitamura, Y., Yada, T., Uehara, T., Nomura, Y., 1997. Stimulatory roles of muscarinic acetylcholine receptors on T cell antigen receptor/CD3 complex-mediated interleukin-2 production in human peripheral blood lymphocytes. Mol. Pharmacol. 51, 1007–1014.

Galgani, M., De Rosa, V., De Simone, S., Leonardi, A., D Oro, U., Napolitani, G., Masci, A.M., Zappacosta, S., Racioppi, L., 2004. Cyclic AMP modulates the functional plasticity of immature dendritic cells by inhibiting Src-like kinases through protein kinase A-mediated signaling. J. Biol. Chem. 279, 32507–32514.

Gaudreau, S., Guindi, C., Menard, M., Besin, G., Dupuis, G., Amrani, A., 2007. Granulocyte-macrophage colony-stimulating factor prevents diabetes development in NOD mice by inducing tolerogenic dendritic cells that sustain the suppressive function of CD4+CD25+ regulatory T cells. J. Immunol. 179, 3638–3647.

Ghosh, M.C., Mondal, A.C., Basu, S., Banerjee, S., Majumder, J., Bhattacharya, D., Dasgupta, P.S., 2003. Dopamine inhibits cytokine release and expression of tyrosine kinases, Lck and Fyn in activated T cells. Int. Immunopharmacol. 3, 1019–1026.

Gildea, J.J., 2009. Dopamine and angiotensin as renal counterregulatory systems controlling sodium balance. Curr. Opin. Nephrol. Hypertens. 18, 28–32.

Giorelli, M., Livrea, P., Trojano, M., 2005. Dopamine fails to regulate activation of peripheral blood lymphocytes from multiple sclerosis patients: effects of IFN-beta. J. Interferon Cytokine. Res. 25, 395–406.

Glabinski, A.R., Bielecki, B., O Bryant, S., Selmaj, K., Ransohoff, R.M., 2002. Experimental autoimmune encephalomyelitis: CC chemokine receptor expression by trafficking cells. J. Autoimmun. 19, 175–181.

Glavin, G.B., 1992. Dopamine: a stress modulator in the brain and gut. Gen. Pharmacol. 23, 1023–1026.

Hallquist, N., Hakki, A., Wecker, L., Friedman, H., Pross, S., 2000. Differential effects of nicotine and aging on splenocyte proliferation and the production of Th1- versus Th2-type cytokines. Proc. Soc. Exp. Biol. Med. 224, 141–146.

Harada, Y., Miyatake, S., Arai, K., Watanabe, S., 1999. Cyclic AMP inhibits the activity of c-Jun N-terminal kinase (JNKp46) but not JNKp55 and ERK2 in human helper T lymphocytes. Biochem. Biophys. Res. Commun. 266, 129–134.

Harle, P., Pongratz, G., Albrecht, J., Tarner, I.H., Straub, R.H., 2008. An early sympathetic nervous system influence exacerbates collagen-induced arthritis via CD4+CD25+ cells. Arthritis Rheum. 58, 2347–2355.

Hasko, G., Szabo, C., Nemeth, Z.H., Deitch, E.A., 2002. Dopamine suppresses IL-12 p40 production by lipopolysaccharide-stimulated macrophages via a beta-adrenoceptor-mediated mechanism. J. Neuroimmunol. 122, 34–39.

Herrada, A.A., Contreras, F.J., Tobar, J.A., Pacheco, R., Kalergis, A.M., 2007. Immune complex-induced enhancement of bacterial antigen presentation requires Fcgamma receptor III expression on dendritic cells. Proc. Natl. Acad. Sci. U. S. A. 104, 13402–13407.

Hershfield, M.S., 2005. New insights into adenosine-receptor-mediated immunosuppression and the role of adenosine in causing the immunodeficiency associated with adenosine deaminase deficiency. Eur. J. Immunol. 35, 25–30.

Hickey, F.B., Brereton, C.F., Mills, K.H., 2008. Adenylate cycalse toxin of *Bordetella pertussis* inhibits TLR-induced IRF-1 and IRF-8 activation and IL-12 production and enhances IL-10 through MAPK activation in dendritic cells. J. Leukoc. Biol. 84, 234–243.

Hoenicka, J., Aragues, M., Ponce, G., Rodriguez-Jimenez, R., Jimenez-Arriero, M.A., Palomo, T., 2007. From dopaminergic genes to psychiatric disorders. Neurotox. Res. 11, 61–72.

Huehn, J., Siegmund, K., Lehmann, J.C., Siewert, C., Haubold, U., Feuerer, M., Debes, G.F., Lauber, J., Frey, O., Przybylski, G.K., Niesner, U., de la Rosa, M., Schmidt, C.A., Brauer,

R., Buer, J., Scheffold, A., Hamann, A., 2004. Developmental stage, phenotype, and migration distinguish naive- and effector/memory-like CD4+ regulatory T cells. J. Exp. Med. 199, 303–313.
Iagmurov, O.D., Ogurtsov, R.P., 1996. [Functional activity of spleen and peripheral blood lymphocytes during stress-induced immunodepression]. Biull. Eksp. Biol. Med. 122, 64–68.
Iijima, N., Yanagawa, Y., Onoe, K., 2003. Role of early- or late-phase activation of p38 mitogen-activated protein kinase induced by tumour necrosis factor-alpha or 2,4-dinitrochlorobenzene during maturation of murine dendritic cells. Immunology 110, 322–328.
Ilani, T., Ben-Shachar, D., Strous, R.D., Mazor, M., Sheinkman, A., Kotler, M., Fuchs, S., 2001. A peripheral marker for schizophrenia: increased levels of D3 dopamine receptor mRNA in blood lymphocytes. Proc. Natl. Acad. Sci. U. S. A. 98, 625–628.
Ilani, T., Strous, R.D., Fuchs, S., 2004. Dopaminergic regulation of immune cells via D3 dopamine receptor: a pathway mediated by activated T cells. Faseb J. 18, 1600–1602.
Iruretagoyena, M.I., Wiesendanger, M., Kalergis, A.M., 2006. The dendritic cell-T cell synapse as a determinant of autoimmune pathogenesis. Curr. Pharm. Des. 12, 131–147.
Jimenez, J.L., Punzon, C., Navarro, J., Munoz-Fernandez, M.A., Fresno, M., 2001. Phosphodiesterase 4 inhibitors prevent cytokine secretion by T lymphocytes by inhibiting nuclear factor-kappaB and nuclear factor of activated T cells activation. J. Pharmacol. Exp. Ther. 299, 753–759.
Jing, H., Yen, J.H., Ganea, D., 2004. A novel signaling pathway mediates the inhibition of CCL3/4 expression by prostaglandin E2. J. Biol. Chem. 279, 55176–55186.
Katoh, N., Soga, F., Nara, T., Tamagawa-Mineoka, R., Nin, M., Kotani, H., Masuda, K., Kishimoto, S., 2006. Effect of serotonin on the differentiation of human monocytes into dendritic cells. Clin. Exp. Immunol. 146, 354–361.
Kavtaradze, S., Mosidze, T., 2007. Neuro-endocrinal regulation and disorders of intracranial hemocirculation in rheumatic diseases in children. Georgian Med. News 32–35.
Kawashima, K., Fujii, T., 2003. The lymphocytic cholinergic system and its contribution to the regulation of immune activity. Life Sci. 74, 675–696.
Kawashima, K., Fujii, T., Watanabe, Y., Misawa, H., 1998. Acetylcholine synthesis and muscarinic receptor subtype mRNA expression in T-lymphocytes. Life Sci. 62, 1701–1705.
Kawashima, K., Yoshikawa, K., Fujii, Y.X., Moriwaki, Y., Misawa, H., 2007. Expression and function of genes encoding cholinergic components in murine immune cells. Life Sci. 80, 2314–2319.
Kebir, H., Kreymborg, K., Ifergan, I., Dodelet-Devillers, A., Cayrol, R., Bernard, M., Giuliani, F., Arbour, N., Becher, B., Prat, A., 2007. Human TH17 lymphocytes promote blood–brain barrier disruption and central nervous system inflammation. Nat. Med. 13, 1173–1175.
Khan, N.A., Hichami, A., 1999. Ionotrophic 5-hydroxytryptamine type 3 receptor activates the protein kinase C-dependent phospholipase D pathway in human T-cells. Biochem. J. 344 (1), 199–204.
Khan, N.A., Poisson, J.P., 1999. 5-HT3 receptor-channels coupled with Na+ influx in human T cells: role in T cell activation. J. Neuroimmunol. 99, 53–60.
Kim, Y.K., Myint, A.M., Lee, B.H., Han, C.S., Lee, H.J., Kim, D.J., Leonard, B.E., 2004. Th1, Th2 and Th3 cytokine alteration in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry. 28, 1129–1134.
Kipnis, J., Cardon, M., Avidan, H., Lewitus, G.M., Mordechay, S., Rolls, A., Shani, Y., Schwartz, M., 2004. Dopamine, through the extracellular signal-regulated kinase pathway, downregulates CD4+CD25+ regulatory T-cell activity: implications for neurodegeneration. J. Neurosci. 24, 6133–6143.
Kivisakk, P., Trebst, C., Liu, Z., Tucky, B.H., Sorensen, T.L., Rudick, R.A., Mack, M., Ransohoff, R.M., 2002. T-cells in the cerebrospinal fluid express a similar repertoire of inflammatory chemokine receptors in the absence or presence of CNS inflammation: implications for CNS trafficking. Clin. Exp. Immunol. 129, 510–518.
Korn, T., Reddy, J., Gao, W., Bettelli, E., Awasthi, A., Petersen, T.R., Backstrom, B.T., Sobel, R.A., Wucherpfennig, K.W., Strom, T.B., Oukka, M., Kuchroo, V.K., 2007. Myelin-specific regulatory T cells accumulate in the CNS but fail to control autoimmune inflammation. Nat. Med. 13, 423–431.
Kwak, Y.T., Koo, M.S., Choi, C.H., Sunwoo, I., 2001. Change of dopamine receptor mRNA expression in lymphocyte of schizophrenic patients. BMC. Med. Genet. 2, 3.
La Via, M.F., Munno, I., Lydiard, R.B., Workman, E.W., Hubbard, J.R., Michel, Y., Paulling, E., 1996. The influence of stress intrusion on immunodepression in generalized anxiety disorder patients and controls. Psychosom. Med. 58, 138–142.
Lanzavecchia, A., Sallusto, F., 2001. Regulation of T cell immunity by dendritic cells. Cell 106, 263–266.
LeBlanc, J., Ducharme, M.B., 2007. Plasma dopamine and noradrenaline variations in response to stress. Physiol. Behav. 91, 208–211.
Lechin, F., van der Dijs, B., Vitelli-Florez, G., Lechin-Baez, S., Azocar, J., Cabrera, A., Lechin, A., Jara, H., Lechin, M., Gomez, F., 1990. Psychoneuroendocrinological and immunological parameters in cancer patients: involvement of stress and depression. Psychoneuroendocrinology 15, 435–451.
Leon-Ponte, M., Ahern, G.P., O Connell, P.J., 2007. Serotonin provides an accessory signal to enhance T-cell activation by signaling through the 5-HT7 receptor. Blood 109, 3139–3146.
Loscher, C.E., Draper, E., Leavy, O., Kelleher, D., Mills, K.H., Roche, H.M., 2005. Conjugated linoleic acid suppresses NF-kappa B activation and IL-12 production in dendritic cells through ERK-mediated IL-10 induction. J. Immunol. 175, 4990–4998.
Maestroni, G.J., Mazzola, P., 2003. Langerhans cells beta 2-adrenoceptors: role in migration, cytokine production, Th priming and contact hypersensitivity. J. Neuroimmunol. 144, 91–99.
Mahnke, K., Johnson, T.S., Ring, S., Enk, A.H., 2007. Tolerogenic dendritic cells and regulatory T cells: a two-way relationship. J. Dermatol. Sci. 46, 159–167.
Makel, S.M., Strengell, M., Pietila, T.E., Osterlund, P., Julkunen, I., 2009. Multiple signaling pathways contribute to synergistic TLR ligand-dependent cytokine gene expression in human monocyte-derived macrophages and dendritic cells. J. Leukoc. Biol. 85 (4), 664–672.
Mann, J., Oakley, F., Johnson, P.W., Mann, D.A., 2002. CD40 induces interleukin-6 gene transcription in dendritic cells: regulation by TRAF2, AP-1, NF-kappa B, AND CBF1. J. Biol. Chem. 277, 17125–17138.
McGeachy, M.J., Cua, D.J., 2008. Th17 cell differentiation: the long and winding road. Immunity 28, 445–453.
McKenna, F., McLaughlin, P.J., Lewis, B.J., Sibbring, G.C., Cummerson, J.A., Bowen-Jones, D., Moots, R.J., 2002. Dopamine receptor expression on human T- and B-lymphocytes, monocytes, neutrophils, eosinophils and NK cells: a flow cytometric study. J. Neuroimmunol. 132, 34–40.
Meredith, E.J., Holder, M.J., Rosen, A., Lee, A.D., Dyer, M.J., Barnes, N.M., Gordon, J., 2006. Dopamine targets cycling B cells independent of receptors/transporter for oxidative attack: Implications for non-Hodgkin's lymphoma. Proc. Natl. Acad. Sci. U. S. A. 103, 13485–13490.
Mignini, F., Streccioni, V., Amenta, F., 2003. Autonomic innervation of immune organs and neuroimmune modulation. Auton. Autacoid. Pharmacol. 23, 1–25.
Mignini, F., Tomassoni, D., Traini, E., Amenta, F., 2009. Dopamine, vesicular transporters and dopamine receptor expression and localization in rat thymus and spleen. J. Neuroimmunol. 206, 5–13.
Mignini, F., Traini, E., Tomassoni, D., Amenta, F., 2006. Dopamine plasma membrane transporter (DAT) in rat thymus and spleen: an immunochemical and immunohistochemical study. Auton. Autacoid. Pharmacol. 26, 183–189.
Morkawa, K., Oseko, F., Morikawa, S., 1993. Immunosuppressive property of bromocriptine on human B lymphocyte function in vitro. Clin. Exp. Immunol. 93, 200–205.
Nagai, Y., Ueno, S., Saeki, Y., Soga, F., Hirano, M., Yanagihara, T., 1996. Decrease of the D3 dopamine receptor mRNA expression in lymphocytes from patients with Parkinson's disease. Neurology 46, 791–795.
Nakahara, T., Uchi, H., Urabe, K., Chen, Q., Furue, M., Moroi, Y., 2004. Role of c-Jun N-terminal kinase on lipopolysaccharide induced maturation of human monocyte-derived dendritic cells. Int. Immunol. 16, 1701–1709.
Nakano, K., Higashi, T., Hashimoto, K., Takagi, R., Tanaka, Y., Matsushita, S., 2008. Antagonizing dopamine D1-like receptor inhibits Th17 cell differentiation: preventive and therapeutic effects on experimental autoimmune encephalomyelitis. Biochem. Biophys. Res. Commun. 373, 286–291.
Nakano, K., Higashi, T., Takagi, R., Hashimoto, K., Tanaka, Y., Matsushita, S., 2009a. Dopamine released by dendritic cells polarizes Th2 differentiation. Int. Immunol. 21 (6), 645–654.
Nakano, K., Matsushita, S., Saito, K., Yamaoka, K., Tanaka, Y., 2009b. [Dopamine as an immune-modulator between dendritic cells and T cells and the role of dopamine in the pathogenesis of rheumatoid arthritis]. Nihon Rinsho Meneki Gakkai Kaishi 32, 1–6.
Neve, K.A., Seamans, J.K., Trantham-Davidson, H., 2004. Dopamine receptor signaling. J. Recept. Signal Transduct. Res. 24, 165–205.
Nishibori, M., Takahashi, H.K., Mori, S., 2003. The regulation of ICAM-1 and LFA-1 interaction by autacoids and statins: a novel strategy for controlling inflammation and immune responses. J. Pharmacol. Sci. 92, 7–12.
Nouri-Shirazi, M., Banchereau, J., Fay, J., Palucka, K., 2000. Dendritic cell based tumor vaccines. Immunol. Lett. 74, 5–10.
O'Connell, P.J., Wang, X., Leon-Ponte, M., Griffiths, C., Pingle, S.C., Ahern, G.P., 2006. A novel form of immune signaling revealed by transmission of the inflammatory mediator serotonin between dendritic cells and T cells. Blood 107, 1010–1017.
Oukka, M., 2008. Th17 cells in immunity and autoimmunity. Ann. Rheum. Dis. 67 (3), iii26–iii29.
Owens, T., Tran, E., Hassan-Zahraee, M., Krakowski, M., 1998. Immune cell entry to the CNS—a focus for immunoregulation of EAE. Res. Immunol. 149, 781–789 discussion 844–786, 855–760.
Pacheco, R., Ciruela, F., Casado, V., Mallol, J., Gallart, T., Lluis, C., Franco, R., 2004. Group I metabotropic glutamate receptors mediate a dual role of glutamate in T cell activation. J. Biol. Chem. 279, 33352–33358.
Pacheco, R., Gallart, T., Lluis, C., Franco, R., 2007. Role of glutamate on T-cell mediated immunity. J. Neuroimmunol. 185, 9–19.
Pacheco, R., Martinez-Navio, J.M., Lejeune, M., Climent, N., Oliva, H., Gatell, J.M., Gallart, T., Mallol, J., Lluis, C., Franco, R., 2005. CD26, adenosine deaminase, and adenosine receptors mediate costimulatory signals in the immunological synapse. Proc. Natl. Acad. Sci. U. S. A. 102, 9583–9588.
Pacheco, R., Oliva, H., Martinez-Navio, J.M., Climent, N., Ciruela, F., Gatell, J.M., Gallart, T., Mallol, J., Lluis, C., Franco, R., 2006. Glutamate released by dendritic cells as a novel modulator of T cell activation. J. Immunol. 177, 6695–6704.
Pinessi, L., Rainero, I., De Gennaro, T., Gentile, S., Portaleone, P., Bergamasco, B., 1987. Biogenic amines in cerebrospinal fluid and plasma of patients with dementia of Alzheimer type. Funct. Neurology 2, 51–58.
Potvin, S., Grignon, S., Marchand, S., 2009. Human evidence of a supra-spinal modulating role of dopamine on pain perception. Synapse 63, 390–402.
Ramstad, C., Sundvold, V., Johansen, H.K., Lea, T., 2000. cAMP-dependent protein kinase (PKA) inhibits T cell activation by phosphorylating ser-43 of raf-1 in the MAPK/ERK pathway. Cell. Signal. 12, 557–563.
Ridge, J.P., Di Rosa, F., Matzinger, P., 1998. A conditioned dendritic cell can be a temporal bridge between a CD4+ T-helper and a T-killer cell. Nature 393, 474–478.
Rinner, I., Schauenstein, K., 1993. Detection of choline-acetyltransferase activity in lymphocytes. J. Neurosci. Res. 35, 188–191.
Saha, B., Mondal, A.C., Basu, S., Dasgupta, P.S., 2001a. Circulating dopamine level, in lung carcinoma patients, inhibits proliferation and cytotoxicity of CD4+ and CD8+ T cells by D1 dopamine receptors: an in vitro analysis. Int. Immunopharmacol. 1, 1363–1374.

Saha, B., Mondal, A.C., Majumder, J., Basu, S., Dasgupta, P.S., 2001b. Physiological concentrations of dopamine inhibit the proliferation and cytotoxicity of human CD4+ and CD8+ T cells in vitro: a receptor-mediated mechanism. Neuroimmunomodulation 9, 23–33.

Sarkar, C., Das, S., Chakroborty, D., Chowdhury, U.R., Basu, B., Dasgupta, P.S., Basu, S., 2006. Cutting edge: stimulation of dopamine D4 receptors induce T cell quiescence by up-regulating Kruppel-like factor-2 expression through inhibition of ERK1/ERK2 phosphorylation. J. Immunol. 177, 7525–7529.

Schoenberger, S.P., Toes, R.E., van der Voort, E.I., Offringa, R., Melief, C.J., 1998. T-cell help for cytotoxic T lymphocytes is mediated by CD40–CD40L interactions. Nature 393, 480–483.

Schoenborn, J.R., Wilson, C.B., 2007. Regulation of interferon-gamma during innate and adaptive immune responses. Adv. Immunol. 96, 41–101.

Sibley, D.R., Monsma Jr., F.J., Shen, Y., 1993. Molecular neurobiology of dopaminergic receptors. Int. Rev. Neurobiol. 35, 391–415.

Sidhu, A., 1998. Coupling of D1 and D5 dopamine receptors to multiple G proteins: implications for understanding the diversity in receptor-G protein coupling. Mol. Neurobiol. 16, 125–134.

Smith, K.M., Pottage, L., Thomas, E.R., Leishman, A.J., Doig, T.N., Xu, D., Liew, F.Y., Garside, P., 2000. Th1 and Th2 CD4+ T cells provide help for B cell clonal expansion and antibody synthesis in a similar manner in vivo. J. Immunol. 165, 3136–3144.

Strange, P.G., 1993. New insights into dopamine receptors in the central nervous system. Neurochem. Int. 22, 223–236.

Tian, J., Lu, Y., Zhang, H., Chau, C.H., Dang, H.N., Kaufman, D.L., 2004. Gamma-aminobutyric acid inhibits T cell autoimmunity and the development of inflammatory responses in a mouse type 1 diabetes model. J. Immunol. 173, 5298–5304.

Tomei, G., Capozzella, A., Ciarrocca, M., Fiore, P., Rosati, M.V., Fiaschetti, M., Casale, T., Anzelmo, V., Tomei, F., Monti, C., 2007. Plasma dopamine in workers exposed to urban stressor. Toxicol. Ind. Health 23, 421–427.

Tsao, C.W., Lin, Y.S., Cheng, J.T., 1997. Effect of dopamine on immune cell proliferation in mice. Life Sci. 61, PL 361–371.

Usluoglu, N., Pavlovic, J., Moelling, K., Radziwill, G., 2007. RIP2 mediates LPS-induced p38 and IkappaBalpha signaling including IL-12 p40 expression in human monocyte-derived dendritic cells. Eur. J. Immunol. 37, 2317–2325.

Vajkoczy, P., Laschinger, M., Engelhardt, B., 2001. Alpha4-integrin-VCAM-1 binding mediates G protein-independent capture of encephalitogenic T cell blasts to CNS white matter microvessels. J. Clin. Invest. 108, 557–565.

Vang, T., Torgersen, K.M., Sundvold, V., Saxena, M., Levy, F.O., Skalhegg, B.S., Hansson, V., Mustelin, T., Tasken, K., 2001. Activation of the COOH-terminal Src kinase (Csk) by cAMP-dependent protein kinase inhibits signaling through the T cell receptor. J. Exp. Med. 193, 497–507.

Watanabe, Y., Nakayama, T., Nagakubo, D., Hieshima, K., Jin, Z., Katou, F., Hashimoto, K., Yoshie, O., 2006. Dopamine selectively induces migration and homing of naive CD8+ T cells via dopamine receptor D3. J. Immunol. 176, 848–856.

Watford, W.T., Moriguchi, M., Morinobu, A., O Shea, J.J., 2003. The biology of IL-12: coordinating innate and adaptive immune responses. Cytokine Growth Factor Rev. 14, 361–368.

Weihe, E., Depboylu, C., Schutz, B., Schafer, M.K., Eiden, L.E., 2006. Three types of tyrosine hydroxylase-positive CNS neurons distinguished by dopa decarboxylase and VMAT2 co-expression. Cell. Mol. Neurobiol. 26, 659–678.

Wise, R.A., 2008. Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotox. Res. 14, 169–183.

Yin, J., Albert, R.H., Tretiakova, A.P., Jameson, B.A., 2006. 5-HT(1B) receptors play a prominent role in the proliferation of T-lymphocytes. J. Neuroimmunol. 181, 68–81.

Zaffaroni, M., Marino, F., Bombelli, R., Rasini, E., Monti, M., Ferrari, M., Ghezzi, A., Comi, G., Lecchini, S., Cosentino, M., 2008. Therapy with interferon-beta modulates endogenous catecholamines in lymphocytes of patients with multiple sclerosis. Exp. Neurol. 214, 315–321.

Zheng, Y., Manzotti, C.N., Liu, M., Burke, F., Mead, K.I., Sansom, D.M., 2004. CD86 and CD80 differentially modulate the suppressive function of human regulatory T cells. J. Immunol. 172, 2778–2784.

Zhou, W., Hashimoto, K., Goleniewska, K., O Neal, J.F., Ji, S., Blackwell, T.S., Fitzgerald, G.A., Egan, K.M., Geraci, M.W., Peebles Jr., R.S., 2007. Prostaglandin I2 analogs inhibit proinflammatory cytokine production and T cell stimulatory function of dendritic cells. J. Immunol. 178, 702–710.