Review

The adenosinergic system: a potential player in the pathogenesis of ANCA-associated vasculitis?

L. Kling, B.K. Krämer, B.A. Yard, A.-I. Kälsch

V^th Department of Medicine (Nephrology/Endocrinology/Rheumatology), University Medical Centre Mannheim, University of Heidelberg, Germany.

Lovis Kling
Bernhard K. Krämer, Prof. Dr. med.
Benito A. Yard, Prof. Dr. rer. nat.
Anna-Isabelle Kälsch, PD Dr. med.

Please address correspondence to:
Dr Anna-Isabelle Kälsch,
Theodor-Kutzer-Ufer 1-3,
68167 Mannheim, Germany.
E-mail: anna-isabelle.kaelsch@umm.de

Received on October 26, 2017; accepted in revised form on February 1, 2018.

Clin Exp Rheumatol 2018; 36 (Suppl. 111): S143-S151.

Key words: ANCA-associated vasculitis, adenosine, CD73 antigen, CD26 antigen, purinergic effects

Competing interests: none declared.

ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a potentially lethal autoimmune disease whose pathology comprises disturbed T cell differentiation and functionality accompanied by dysfunctional autoreactive immunoglobulin development, culminating in destructive innate immune response as well. Purines, adenine nucleotides and adenosine in particular, have been elucidated as potent extracellular mediators for fine adjustment of these pivotal processes establishing human immunity. Therefore, the extracellular purinergic microenvironment is under control of ectonucleotidases CD39 and CD73 degrading pro-inflammatory adenosine triphosphate (ATP) to anti-inflammatory adenosine as well as adenosine deaminase bound to CD26 deactivating adenosine. Accordingly, the ATP $P2X_7$ receptor was elicited to be responsible for promotion of inflammation, while predominantly the adenosine A_{2A} receptor demonstrated the opposite. Recent reports pointed at the adenosinergic system to be crucially involved in AAV pathogenesis. Here, experimental evidence on ecto-enzymes controlling extracellular adenine nucleotide concentrations and purinergic signalling in the immune system with respect to its contribution to the AAV pathomechanism is reviewed besides unsolved problems being identified that require further investigation in order to develop new treatment strategies for AAV.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is defined as small vessel vasculitis highly associated with presumably pathogenic auto-antibodies detectable in patients' peripheral blood (1). It is a life-threatening disease potentially affecting all organs (2), but necrotising vasculitis is most commonly found in the respiratory tract and the kidneys (as reviewed previously) (3). Its pathogenesis is not completely elucidated yet, but increasing experimental evidence and understanding of the disease resulted in the current pathogenetic model summarised by the extended ANCA-cytokine sequence theory (4, 5). In short, AAV patients present with disturbed adaptive immunity forming dysfunctional lymphocyte populations (for example persistently activated T cell subsets, impaired regulatory T lymphocytes, autoreactive Th17 as well as B cells) and producing ANCA which are able to trigger neutrophil driven inflammation of the vessel walls by binding their epitopes (mainly proteinase 3 (PR3) or myeloperoxidase (MPO)) expressed on the activated neutrophil cell surface. Subsequently, released cytokines and chemokines (*e.g.*, TNF-α, IL-6, IL-8, C5a, monocyte chemoattractant protein 1/CCL2) (6) cause other immune cells including lymphocytes to migrate to the damaged vessel wall, thus, maintaining the inflammatory destruction of vascular tissue and surrounding parenchyma.

More recently, purinergic signalling was recognised as a key player involved in homeostasis of immunity. Specifically, adenosine triphosphate (ATP) is generally perceived to enhance inflammation, while adenosine demonstrated the opposite. This review focuses on ecto-enzymes controlling extracellular concentrations of indispensable adenine nucleotides for purinergic signalling (such as ATP, ADP, AMP, NAD and the nucleoside adenosine) and both their contribution to pathogenic processes in AAV.

The extracellular adenosine microenvironment: CD39, CD73, CD26

The fate of extracellular adenine derivatives including ATP, ADP, AMP and adenosine is determined by the local expression of ectonucleotidases CD39 and CD73 degrading nucleotides, adenosine deaminase metabolising adenosine as well as receptors binding - thus capture - the different purine molecules mentioned with various affinity (7, 8). The intracellular location of ATP is well established and its involvement in cellular energy supply is undoubted (9). However, compelling evidence describing different mechanisms of ATP transport into the extracellular compartment including exocytosis and secretion was discussed in the literature. Moreover, data on its extracellular presence and function in intercellular signalling is available (9, 10).

CD39 belongs to the group of ectonucleoside triphosphate diphosphohydrolases (E-NTPDases) with different names used in the literature, *e.g.*, ectoapyrase, ecto ATP diphosphohydrolase or NTPDase1 (11). CD39 is able to hydrolyze ATP to adenosine diphosphate (ADP) and subsequently to adenosine monophosphate (AMP) with a resulting product ratio of 1:10 (ADP:AMP) (11). Several pro-inflammatory cytokines (*e.g.*, TGFβ, IL-6 (12)), oxidative stress and hypoxia, involving transcription factors STAT3 and Sp1, control CD39 expression (12, 13). CD39 expression has been widely observed, including the endothelium (14) and lymphocytic populations (15).

CD73, or ecto-5'-nucleotidase, also belongs to the group of ectonucleotidases (16). Its enzymatic activity dephosphorises AMP to adenosine (17). Its expression is reduced by pro-inflammatory cytokines like IL-6, IFNγ and IL-12, but enhanced by TGFβ (18). Expressional increase was demonstrated upon hypoxia involving oxygen-sensitive transcription factor hypoxia-inducible factor-1α (HIF-1α) (19) in addition to cyclic AMP response element binding protein (CREB) (19, 20). Various tissues including human lymphocytes and endothelial cells are described to express CD73 (15, 21).

CD26 is an exopeptidase, also known as dipeptidyl peptidase-4 (DPP-4), which cleaves dipeptides from proteins that contain alanine or proline in the second last N-terminal position (22). Its transcriptional regulation is influenced by inter alia hepatocyte nuclear factor 1 alpha (HNF-1α) (23). Considerable CD26 expression is known in human epithelial (24) and endothelial cells (25) as well as lymphocytes (26) with regards to CD26 serving as a potent co-stimulatory receptor in the activation of T cells (27). Although CD26 has no related enzymatic activity to nucleotides, it strongly binds adenosine deaminase and therefore is pivotal for purine metabolism (28). Adenosine deaminase is ubiquitously expressed in the cytoplasm with its primary structure lacking a transmembranous domain. However, its ecto-enzyme activity degrading adenosine to inosine and ammonia has been detected repeatedly (29). Consistently, membrane bound CD26 has previously been used as surrogate parameter for the presence and enzymatic activity of adenosine deaminase as it is considered to be an adenosine deaminase receptor (as also expressed by its other name adenosine deaminase-binding protein) (29, 30).

Alternative sources of extracellular adenosine: CD38, CD157, CD203a

In addition, extracellular adenosine can also be synthesised from nicotinamide dinucleotide (NAD^+) by the concerted action of CD38 and CD203a (also known as plasma cell membrane glycoprotein (31)/PC-1 (32), NPPase (33), NPPγ (34), major aFGF stimulated protein/MAFP (35)) together with CD73 (36). Evidence from *in vitro* experiments with canine and murine vessel and bladder specimen suggests NAD^+ is constitutively released into the extracellular space (37). Data supports NAD^+ first is converted to adenosine diphosphate ribose (ADPR) - with nicotinamide as side product - by CD38 which subsequently is digested into AMP and pyrophosphate by activity of CD203a (36). Furthermore, NAD^+ was demonstrated to be also a direct substrate for CD203a, which is able to cleave it into AMP and nicotinamide mononucleotide (NMN) as well (36). Belonging to the same gene family as CD38, CD157 (also known as bone marrow stromal cell antigen 1/BST-1) (38) metabolises extracellular NAD^+ to either ADP ribose (ADPR) or cyclic ADP ribose (cADPR) as well (39-41). CD38, formerly referred to as T10 molecule (thymic cell surface antigen) (42), is expressed on human thymocytes and lymphocytes (43). In contrast to CD38, CD157 is reported not to be expressed on lymphocytes, eosinophils and dendritic cells (44), but on human monocytes and neutrophils, synovial as well as follicular dendritic cells (44) besides human endothelium (45). Conceivably, purine metabolism in the extracellular compartment shapes the immune response since activation of the different purinergic receptors heavily depends on the enzymatic activity of CD39, CD73, adenosine deaminase bound to CD26 (29), CD38/CD157 and CD203a (36, 46) determining ligand concentrations.

Purinergic receptors and their expression in the immune system

Purinergic receptors are categorised in two families by their activating ligands: P1 or adenosine receptors and P2 receptors recognising purine and pyrimidine nucleotides, inter alia ATP, ADP, uridine triphosphate (UTP) and uridine diphosphate (UDP). The P2 receptor group comprises of diverse ionotropic P2X and metabotropic P2Y receptors. To date, the P1 family contains four different adenosine receptors (A_1, A_{2A}, A_{2B} and A_3) which were reported to be expressed in different tissues and almost all cells of the immune system. The majority of cells express more than one subtype of the P1 and P2 receptors simultaneously (47). Expression of the immunomodulatory A_{2A} receptor (48, 49) was reported in human endothelial cells (50, 51), neutrophils (52, 53), monocytes (54), platelets (55), T cells (56), B cells (56, 57) and dendritic cells (58). IFNγ was found to downregulate A_{2A} receptor expression, while TNF-α and IL-1 stimulation were described to enhance it (48). The lower affinity A_{2B} and the A_3 receptor were detected in dendritic cells (59, 60), T cells (61, 62), monocytes (54, 62) and human neutrophils (62, 63). Expression of the

fourth member of the P1 family, the A_1 receptor, was found in neutrophils (64), peripheral blood mononuclear cells (PBMC) (65) and dendritic cells (58). Ionotropic as well as metabotropic ATP receptors from the P2 family also are expressed in various immune cell types. For example, there is data available on neutrophils, monocytes and lymphocytes expressing the $P2X_1$, $P2X_4$, $P2X_5$, $P2X_7$ and $P2Y_{11}$ subtypes (as reviewed in (7)).

The co-expression of a myriad of different receptor subtypes from the P1 and P2 family on immune cells implies the high complexity of purinergic signal transduction. In conclusion, the intracellular signal resulting from extracellular stimuli originating from extracellular ATP depends not only on expression of purinergic ecto-enzymes controlling concentrations of the different receptor ligands, but also on the co-expression and density of the individual purinergic receptors showing different affinities to their ligands (7). In systemic inflammation, *e.g.* as found in AAV and other rheumatologic disorders or sepsis (49), cytokines modify both the expressional level of purinergic receptors and ectonucleotidases providing purinergic ligands. Hence, complexity of the extracellular purinergic microenvironment even increases and is prone to pathologic alteration.

Adenosine inhibits pivotal processes of immunity

Adenosinergic signalling is believed to represent a potent negative feedback mechanism protecting tissue from further inflammatory damage highlighted by its anti-inflammatory characteristics as demonstrated by inhibition of activated immune cells (47) and upregulation of A_{2A} receptor on murine T cells upon T cell receptor activation (66, 67). Consistently, the A_{2A} receptor currently is suspected to be predominantly responsible for anti-inflammatory transduction on immune cells (68, 69). However, involvement of AAV pathomechanism is not only restricted to lymphocytes, but also encompasses compartments of innate immunity which all dramatically respond to purinergic signalling as depicted in the following sections.

Adenosine guarding the blood-vascular-tissue barrier

Different scientific approaches allowed to conclude adenosine is involved in the very first onset of inflammation due to its immunosuppressive effect not only on infiltrating immune cells characterising the peak of inflammatory conditions (as elaborated on below) (70), but also on the endothelium which is able to trigger local as well as systemic inflammatory response. Specifically, cultured human umbilical vein endothelial cells demonstrated a reduced vascular cell adhesion molecule-1 induction and endothelial release of pro-inflammatory IL-6 and IL-8 upon stimulation when treated with adenosine (71). Moreover, adenosine limited diapedesis by mainly acting on the A_{2A} and A_{2B} receptors (72), correspondingly, promoting the tightness of the endothelial barrier (73) and decreasing neutrophil adhesion to endothelial cells as well as neutrophil damage to the endothelium *in vitro* (74). An airpouch mice model underscored this concept of adenosine invigorating vascular integrity, since it reduced the accumulation of inflammatory cells at the inflamed tissue site (72). Therefore, endothelial cells are able to produce adenosine themselves (75) in order to protect them from inflammatory damage as adenosine was found to inhibit the oxidative burst in human neutrophils (74-76). Thus, adenosine additionally interferes during the initial phase of inflammation representing a negative feedback mechanism also on innate immunity directly at the vascular interface. Explicitly, our group was able to demonstrate production of reactive oxygen species (ROS) was reduced by extrinsic adenosinergic stimulation of activated neutrophils not only from healthy controls, but also from AAV patients highlighting local ectonucleotidase expression determining adenosine generating capacity to be pivotal for adenosinergic hindrance of inadequate inflammatory response in AAV rather than neutrophil adenosine receptor responsiveness (76). Furthermore, ROS produced by neutrophils are known to be indispensable for NETosis (77). Hence, adenosine might also prevent NETosis, which has been just recently presumed to drive the pathogenesis of AAV (78). In addition, adenosine potentially decreases formation of granulomatous tissue, a core aspect of granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA) pathology, given that A_{2A} antagonists added to cultured human monocytes during stimulation increased formation of giant cell like macrophages (79).

Adaptive immunity under control of adenosine

Adenosinergic signalling is probably best investigated in the context of adaptive immunity. Several studies concluded CD39 and CD73 expression of lymphocytes (*e.g.* $CD8^+$ cells (80-82), regulatory T cells (80) and B cells (83)) were responsible for the generation of adenosine, thus its mediatory effects (84, 85) such as reducing the functionality of antigen-presenting cells like dendritic cells (58, 86). In murine dendritic cells, the activation of the A_{2A} receptor resulted in tolerogenic dendritic cells with decreased secretion of IL-6 and IL-12 (87). Consistent with this finding, mature dendritic cells from human donors shifted to an anti-inflammatory phenotype under A_{2A} activation upon stimulation showing enhanced IL-10, diminished IL-12 (88) and reduced TNF-α production (86). Thus, environmental adenosine was observed to limit Th1 differentiation of T cells in co-culture with mature dendritic cells (86). In addition, direct stimulation of the A_{2A} receptor expressed on T cells inhibited both Th1 and Th2 T cell differentiation and proliferation by reducing production of IL-4, IL-5, IL-10 and IFNγ under the appropriate stimulating conditions in order to skew towards a Th1 or Th2 phenotype (66, 67, 89). Both these Th subpopulations seem to be involved in the pathology of AAV as analysis of granulomas and peripheral T cells from GPA and MPA patients indicated predominance of a Th1 cytokine profile (90, 91) accompanied with elevated counts of the Th1 phenotype in peripheral blood of GPA patients (92). Nonetheless, GPA patients also disclosed a Th2 phenotype (as defined by expression of surface marker ST2L) among the effector memory T cell population (92).

Transcription of IL-2 (93) and TNFα production in human T cells were both inhibited via the A_{2A} receptor in HIV positive patients (93). Adenosine and its analogs additionally impeded CD25 upregulation due to stimulation of murine T cell receptors (94). Thus, adenosine prohibited expansion of T cell clones upon activation by reducing levels of IL-2 as well as its receptor CD25 (95). By contrast, AAV patients showed a lymphocytic phenotype indicative of persistent T cell activation evident by high frequency of CD25 expression as well as decreased naïve T cells which also was associated with a more severe course of AAV (96).

A_{2A} receptor activation was also shown to reduce Th17 differentiation of naïve T cells (97). Instead, *in vivo* A_{2A} receptor stimulation in a C3HA mice model demonstrated differentiation of T lymphocytes predominantly towards a regulatory T cell phenotype (97). Interestingly, Th17 cells were suggested to be pathogenic in AAV (98) as GPA patients disclosed higher frequencies of Th17 cells than healthy controls in the peripheral circulation (98, 99) as well as PR3-specific Th17 cells in PR3-ANCA positive patients implicating the pivotal involvement of Th17 cells also in formation of ANCA (100). Accordingly, levels of IL-17 (produced by Th17 cells) and IL-23 (stimulating the differentiation and activity of Th17 cells) were found elevated in AAV patients with active disease as well as in remission (98) supporting the idea of Th17 cells maintaining AAV. This is also supported by an animal model of MPO-ANCA glomerulonephritis using C57BL/6 mice knocked out for the IL-17A gene (C57BL/6 IL-17A$^{-/-}$), since it revealed the knockout mice had been protected from renal injury (101).

Prolonged A_{2A} receptor stimulation of murine CD4$^+$ cells led to expansion of regulatory T cells and an increase of their immunosuppressive capacity while it impaired CD8$^+$ cell stimulation and activation (102). A_{2A} activation of murine CD4$^+$ and CD8$^+$ T cells resulted in upregulation of both immunosuppressive surface proteins CTLA-4 and programmed death-1 (PD-1) (103). Underlying these findings, selective activation of murine regulatory T cells accompanied by active A_{2A} receptor transduction caused expansion of these regulatory T cells and enhanced their immunosuppressive activity, too (104). Murine regulatory T cells were elicited to express CD39 and CD73, thus produce adenosine in order to suppress effector T cells in mice (85). Subsequently, it was shown adenosine also was an immunosuppressive mediator produced by regulatory T cells isolated from healthy humans (105). Intriguingly, AAV patients (GPA specifically) were demonstrated with both altered relations of T helper and regulatory T cells in the peripheral blood (106) as well as functional deficiencies of regulatory T cells. However, evidence providing an underlying mechanism explicating this intrinsic regulatory T cell defect remained lacking (107, 108). Nonetheless, our group lately discovered impaired lymphocytic adenosine generating capacity in AAV patients due to downregulation of CD39 and CD73 combined with upregulation of CD26, most imposing in CD4$^-$ lymphocytic subsets (109). Enthrallingly, this pattern of ectonucleotidase expression in our AAV cohort is in line with previous studies reporting altered Th17 and regulatory T cell populations in AAV, as both subsets were unveiled to be responsive to adenosinergic signalling. Moreover, our study implied disrupted ectonucleotidase expression contributed not only to the pathogenesis, but also to the clinical picture of AAV as it was independent from disease activity, but linked to decreased renal function and systemic inflammation.

Further details underscoring adenosine as an immunosuppressive agent itself were given by investigations on T cell anergy. In patients with follicular lymphoma, adenosine was produced in the extracellular space by subsequent activity of CD39 and CD73 from ATP and was reported to suppress cytokine production of T cells infiltrating the malignant tissue (110). Similarly, A_{2A} receptor activation during stimulation of a A.E7 CD4$^+$ T cell line resulted in hyporesponsiveness of these cells resembling features of T cell anergy as assessed by stimulation assays using their designated antigen (97).

Antibody formation involves adenosinergic signalling

Animal studies unveiled purines were fundamentally involved in formation of immunoglobulins, too. Murine B cells were found to express CD39 and CD73, thus were able to generate adenosine from ATP released into the extracellular space upon B cell stimulation in culture (83). Thus, adenosine was found to influence class switch of antibody subtype produced by the investigated B cells. Namely, CD73$^+$ B cells tended to produce rather IgG and IgA immunoglobulins compared to CD73$^-$ subpopulations (83). Furthermore, in a human cohort of patients with combined immunodeficiency syndrome, a lack of CD73 expression on B cells combined with decreased production of IgG and IgA immunoglobulins was measured (83). In AAV, antibody class switch is reported to be pivotal as ANCA can also be detected in healthy individuals without clinical evidence of AAV (often referred to as natural auto-antibodies). Surprisingly, these clinically irrelevant ANCA showed lower avidity and preferentially belonged to the IgG_1 subclass (111) whereas PR3-ANCA of active patients were most abundant in the IgG_3 fraction (112).

Cytokine secretion responds to adenosinergic signalling

The influence of adenosine on lymphocytic cytokine production has already been described above. Nevertheless, cytokine release of other immune compartments was reported to be responsive to adenosine as well. In detail, adenosine reduced leukotriene B4 synthesis in neutrophils (113), TNF-α secretion (114), transcription and release of chemokines CXCL2, CCL3, CCL4 and CCL20 (114) implying adenosine is able to reduce recruitment of immune cells to sites of inflammatory lesion, hence limiting not only the onset, but also the maintenance of inflammation. Similar results were obtained in BALB/c mice with adenosine receptor agonists decreasing peripheral TNF-α levels and enhancing secretion of anti-inflammatory IL-10 after intraperitoneal LPS application (115). Not only adenosinergic inhibition of TNF-α and

IL-12 release in murine macrophages (116), but also enhancement of IL-10 synthesis in these cells and in a RAW264.7 macrophage cell line was elicited (116-118). Direct, functional effects of adenosinergic signalling were shown in *in vitro* experiments as well: unselective A_2 receptor agonists and adenosine impaired phagocytic activity of human monocytes cultured for more than 48 hours (119).

ATP as promotor of inflammation

In general, ATP can be perceived as the antipode of adenosine, and A_{2A} activation respectively, being an extracellular pro-inflammatory mediator (84) with well described effects on lymphocytes and cytokine secretion. Specifically, its $P2X_7$ receptor was found to transduce induction of pro-inflammatory cytokines, chemokines and leukotrienes (120, 121). Moreover, extracellular ATP activating the $P2X_7$ receptor induced lytic cell death in murine T cells with regulatory T cell subsets being more susceptible to this treatment than other lymphocyte subtypes as a key finding (122). Consistently, mice knocked out for the $P2X_7$ gene disclosed higher regulatory T cell frequencies in lymphatic tissue as well as peripheral blood than wild-type mice (122). Investigating $P2X_7$ knockout mice in a model of inflammatory bowel disease, the control group was observed with higher neutrophil infiltration and mast cell activation in the bowel (120). Involving its other receptors $P2X_1$ and $P2X_4$, ATP was also reported to act as a co-stimulatory molecule on T cells (123, 124) with T cells showing active ATP release at the immune synapse themselves in order to amplify T cell activation in an autocrine manner (124). In contrast to the A_{2A} receptor, this specific receptor activation also coded for enhancement of IL-2 transcription during T cell activation (124). Furthermore, ATP was described not only to enhance T cell activation, but also driving T cell differentiation fate. Exposure to ATP, thus $P2X_7$ receptor activation resulted in IL-17 synthesis in human T cells and subsequent induction of a Th17 resembling phenotype (125) while regulatory T cell function was suppressed, but could be overcome by $P2X_7$ receptor blockade (125). Accordingly, ATP was shown to induce Th17 differentiation of murine T cells *in vitro* (126) and *in vivo* using a germ-free mice model for peritoneal and rectal treatment with non-degradable ATP derivatives (126). In systemic lupus erythematosus, the literature recently supported the hypothesis that ATP activating the $P2X_7$ receptor seems likely to contribute dually to the promotion of this inflammatory disease by leading to pyroptotic cell death on the one hand, and directly stimulating the inflammasome on the other (127).

Prospects of adenosinergic signalling in the context of AAV

Although primary data on adenosinergic signalling in AAV specifically still has to be judged scarce in general (and mainly is focused on regulatory T cells), reports on purinergic effects on key players of the immune system, which are known to be involved in AAV pathogenesis, is strongly suggestive of dysfunctional adenosinergic signalling in AAV. This is further underscored by a CD73 knockout ($CD73^{-/-}$) mice model that presented with typical findings of AAV pathology including glomerular and peritubular capillaritis, deposition of IgG and complement as well as proteinuria besides features of autoimmunity (128). Purinergic signalling and adenosine producing capacity through ecto-enzyme activity has already been linked to other autoimmune diseases, for example Sjögren's syndrome (121, 129) and systemic lupus erythematosus with decreased lymphocytic CD39 (130) and CD73 levels (131). This suggests alterations of the adenosinergic system are possibly a common feature of autoimmunity in general. However, this review identified several complex relationships between AAV pathogenesis and adenosinergic signalling. Our group hypothesises the intercellular microenvironment in AAV patients demonstrates an adenosine deficit caused by defective extracellular adenosine metabolism which is likely to enable expansion of autoreactive dendritic cells and in consequence, T and B lymphocytes as well. Additionally, AAV patients seem to fail in terminating autoreactive lymphocytes in the state of anergy which is reported to depend at least partially on extracellular adenosine. By contrast, we suggest the disrupted adenosinergic negative feedback mechanism promotes continuous, therefore persistent, activation of T lymphocytes and pathologic $CD4^-$, Th1, Th2, Th17 or regulatory T cell differentiation. Besides, the adenosinergic negative feedback appears to be of particular interest in AAV as the blood-vascular-tissue-barrier cannot be maintained in the phase of disease onset and during the chronically maintained vasculitic process (for example showing granuloma in GPA and EGPA). On the contrary, absence of adenosine might prolong vasculitis due to unresisted cytokine release. Nonetheless, these hypotheses not only require further investigation, but also impose on other questions: Ecto-enzyme expression enabling adenosinergic signalling may also contribute to better understanding of organ selectivity in AAV syndromes which frequently affect *e.g.* renal and pulmonary vessels. Our own data implied AAV patients potentially benefit from treatment targeting their disrupted adenosinergic system as lymphocytic CD73 expression was associated with renal function and systemic inflammation (109). Fortunately, a myriad of substances engaging in adenosinergic signalling became a matter of interest for drug developers more recently. Specific adenosine receptor agonists and antagonists have been and are currently studied in registered clinical trials, albeit these do not study the agents in the context of AAV. However, one study investigating the anti-inflammatory effect of $P2Y_{12}$ antagonist ticagrelor in methotrexate refractory patients with rheumatoid arthritis on disease activity has been launched lately (NCT02874092). Our study group is convinced further investigation of adenosinergic signalling in AAV is imperative on the means to launch clinical studies developing future therapies of the disease. Finally, if purinergic signalling is pathogenic in AAV, it still remains to elucidate its aetiology with prospects to evolve adequate measures to prevent pathogenic alteration.

References

1. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65: 1-11.
2. FLOSSMANN O, BERDEN A, DE GROOT K *et al*.: Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; 70: 488-94.
3. MILLET A, PEDERZOLI-RIBEIL M, GUILLEVIN L, WITKO-SARSAT V, MOUTHON L: Antineutrophil cytoplasmic antibody-associated vasculitides: is it time to split up the group? *Ann Rheum Dis* 2013; 72: 1273-9.
4. KALLENBERG CG, STEGEMAN CA, ABDULAHAD WH, HEERINGA P: Pathogenesis of ANCA-associated vasculitis: new possibilities for intervention. *Am J Kidney Dis* 2013; 62: 1176-87.
5. CSERNOK E, MULLER A, GROSS WL: Immunopathology of ANCA-associated vasculitis. *Intern Med* 1999; 38: 759-65.
6. XIAO H, HU P, FALK RJ, JENNETTE JC: Overview of the Pathogenesis of ANCA-Associated Vasculitis. *Kidney Dis* 2016; 1: 205-15.
7. BOURS MJ, SWENNEN EL, DI VIRGILIO F, CRONSTEIN BN, DAGNELIE PC: Adenosine 5'-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. *Pharmacol Ther* 2006; 112: 358-404.
8. LASLEY RD, HEGGE JO, NOBLE MA, MENTZER RM: Evidence that cytosolic and ecto 5'-nucleotidases contribute equally to increased interstitial adenosine concentration during porcine myocardial ischemia. *Basic Res Cardiol* 1999; 94: 199-207.
9. BODIN P, BURNSTOCK G: Purinergic signalling: ATP release. *Neurochem Res* 2001; 26: 959-69.
10. ELTZSCHIG HK, MACMANUS CF, COLGAN SP: Neutrophils as sources of extracellular nucleotides: functional consequences at the vascular interface. *Trends Cardiovasc Med* 2008; 18: 103-7.
11. HEINE P, BRAUN N, SEVIGNY J, ROBSON SC, SERVOS J, ZIMMERMANN H: The C-terminal cysteine-rich region dictates specific catalytic properties in chimeras of the ecto-nucleotidases NTPDase1 and NTPDase2. *Eur J Biochem* 2001; 268: 364-73.
12. CHALMIN F, MIGNOT G, BRUCHARD M *et al*.: Stat3 and Gfi-1 transcription factors control Th17 cell immunosuppressive activity via the regulation of ectonucleotidase expression. *Immunity* 2012; 36: 362-73.
13. ELTZSCHIG HK, KOHLER D, ECKLE T, KONG T, ROBSON SC, COLGAN SP: Central role of Sp1-regulated CD39 in hypoxia/ischemia protection. *Blood* 2009; 113: 224-32.
14. KANEIDER NC, EGGER P, DUNZENDORFER S *et al*.: Reversal of thrombin-induced deactivation of CD39/ATPDase in endothelial cells by HMG-CoA reductase inhibition: effects on Rho-GTPase and adenosine nucleotide metabolism. *Arterioscler Thromb Vasc Biol* 2002; 22: 894-900.
15. ZHANG HY, YAN KX, HUANG Q, MA Y, FANG X, HAN L: Target tissue ectoenzyme CD39/CD73-expressing Foxp3^{+} regulatory T cells in patients with psoriasis. *Clin Exp Dermatol* 2015; 40: 182-91.
16. STRATER N: Ecto-5'-nucleotidase: Structure function relationships. *Purinergic Signal* 2006; 2: 343-50.
17. KNOFEL T, STRATER N: X-ray structure of the Escherichia coli periplasmic 5'-nucleotidase containing a dimetal catalytic site. *Nat Struct Biol* 1999; 6: 448-53.
18. REGATEIRO FS, HOWIE D, NOLAN KF *et al*.: Generation of anti-inflammatory adenosine by leukocytes is regulated by TGF-beta. *Eur J Immunol* 2011; 41: 2955-65.
19. SYNNESTVEDT K, FURUTA GT, COMERFORD KM *et al*.: Ecto-5'-nucleotidase (CD73) regulation by hypoxia-inducible factor-1 mediates permeability changes in intestinal epithelia. *J Clin Invest* 2002; 110: 993-1002.
20. HANSEN KR, RESTA R, WEBB CF, THOMPSON LF: Isolation and characterization of the promoter of the human 5'-nucleotidase (CD73)-encoding gene. *Gene* 1995; 167: 307-12.
21. AIRAS L, JALKANEN S: CD73 mediates adhesion of B cells to follicular dendritic cells. *Blood* 1996; 88: 1755-64.
22. ABBOTT CA, YU DM, WOOLLATT E, SUTHERLAND GR, MCCAUGHAN GW, GORRELL MD: Cloning, expression and chromosomal localization of a novel human dipeptidyl peptidase (DPP) IV homolog, DPP8. *Eur J Biochem* 2000; 267: 6140-50.
23. GU N, TSUDA M, MATSUNAGA T *et al*.: Glucose regulation of dipeptidyl peptidase IV gene expression is mediated by hepatocyte nuclear factor-1alpha in epithelial intestinal cells. *Clin Exp Pharmacol Physiol* 2008; 35: 1433-9.
24. DARMOUL D, VOISIN T, COUVINEAU A *et al*.: Regional Expression of Epithelial Dipeptidyl Peptidase IV in the Human Intestines. *Biochem Biophys Res Commun* 1994; 203: 1224-9.
25. GHERSI G, CHEN W, LEE EW, ZUKOWSKA Z: Critical role of dipeptidyl peptidase IV in neuropeptide Y-mediated endothelial cell migration in response to wounding. *Peptides* 2001; 22: 453-8.
26. HATANO R, OHNUMA K, YAMAMOTO J, DANG NH, MORIMOTO C: CD26-mediated co-stimulation in human CD8$^{(+)}$ T cells provokes effector function via pro-inflammatory cytokine production. *Immunology* 2013; 138: 165-72.
27. HATANO R, OHNUMA K, OTSUKA H *et al*.: CD26-mediated induction of EGR2 and IL-10 as potential regulatory mechanism for CD26 costimulatory pathway. *J Immunol* 2015; 194: 960-72.
28. MORRISON ME, VIJAYASARADHI S, ENGELSTEIN D, ALBINO AP, HOUGHTON AN: A marker for neoplastic progression of human melanocytes is a cell surface ectopeptidase. *J Exp Med* 1993; 177: 1135-43.
29. HASHIKAWA T, HOOKER SW, MAJ JG *et al*.: Regulation of adenosine receptor engagement by ecto-adenosine deaminase. *FASEB J* 2004; 18: 131-3.
30. XU S, SHAO QQ, SUN JT *et al*.: Synergy between the ectoenzymes CD39 and CD73 contributes to adenosinergic immunosuppression in human malignant gliomas. *Neuro Oncol* 2013; 15: 1160-72.
31. BUCKLEY M, LOVELAND K, MCKINSTRY W, GARSON O, GODING J: Plasma cell membrane glycoprotein PC-1. cDNA cloning of the human molecule, amino acid sequence, and chromosomal location. *J Biol Chem* 1990; 265: 17506-11.
32. BELLO V, GODING JW, GREENGRASS V *et al*.: Characterization of a di-leucine-based signal in the cytoplasmic tail of the nucleotide-pyrophosphatase NPP1 that mediates basolateral targeting but not endocytosis. *Mol Biol Cell* 2001; 12: 3004-15.
33. FUNAKOSHI I, KATO H, HORIE K *et al*.: Molecular cloning of cDNAs for human fibroblast nucleotide pyrophosphatase. *Arch Biochem Biophys* 1992; 295: 180-7.
34. STEFAN C, GIJSBERS R, STALMANS W, BOLLEN M: Differential regulation of the expression of nucleotide pyrophosphatases/phosphodiesterases in rat liver. *Biochim Biophys Acta* 1999; 1450: 45-52.
35. ODA Y, KUO M-D, HUANG SS, HUANG J: The plasma cell membrane glycoprotein, PC-1, is a threonine-specific protein kinase stimulated by acidic fibroblast growth factor. *J Biol Chem* 1991; 266: 16791-5.
36. HORENSTEIN AL, CHILLEMI A, ZACCARELLO G *et al*.: A CD38/CD203a/CD73 ectoenzymatic pathway independent of CD39 drives a novel adenosinergic loop in human T lymphocytes. *Oncoimmunology* 2013; 2: e26246.
37. SMYTH LM, BOBALOVA J, MENDOZA MG, LEW C, MUTAFOVA-YAMBOLIEVA VN: Release of β-nicotinamide adenine dinucleotide upon stimulation of postganglionic nerve terminals in blood vessels and urinary bladder. *J BiolChem* 2004; 279: 48893-903.
38. KATZ F, POVEY S, PARKAR M *et al*.: Chromosome assignment of monoclonal antibody-defined determinants on human leukemic cells. *Eur J Immunol* 1983; 13: 1008-13.
39. ISHIHARA K, HIRANO T: BST-1/CD157 regulates the humoral immune responses *in vivo*. *Chem Immunol* 2000; 75: 235-55.
40. LUND FE, SANTOS-ARGUMEDO L, PARKHOUSE R, WALSETH TF, LEE HC: Formation and hydrolysis of cyclic ADP-ribose catalyzed by lymphocyte antigen CD38. *Nature* 1991; 353: 726.
41. HIRATA Y, KIMURA N, SATO K *et al*.: ADP ribosyl cyclase activity of a novel bone marrow stromal cell surface molecule, BST-1. *FEBS Lett* 1994; 356: 244-8.
42. TERHORST C, VAN AGTHOVEN A, LECLAIR K, SNOW P, REINHERZ E, SCHLOSSMAN S: Biochemical studies of the human thymocyte cell-surface antigens T6, T9 and T10. *Cell* 1981; 23: 771-80.
43. JACKSON DG, BELL JI: Isolation of a cDNA encoding the human CD38 (T10) molecule, a cell surface glycoprotein with an unusual discontinuous pattern of expression during lymphocyte differentiation. *J Immunol* 1990; 144: 2811-5.
44. HERNANDEZ-CAMPO PM, ALMEIDA J, SANCHEZ ML, MALVEZZI M, ORFAO A: Normal patterns of expression of glycosylphosphatidylinositol-anchored proteins on different subsets of peripheral blood cells: a frame of reference for the diagnosis

of paroxysmal nocturnal hemoglobinuria. *Cytometry B Clin Cytom* 2006; 70: 71-81.
45. ORTOLAN E, TIBALDI EV, FERRANTI B *et al*.: CD157 plays a pivotal role in neutrophil transendothelial migration. *Blood* 2006; 108: 4214-22.
46. HORENSTEIN AL, QUARONA V, TOSCANI D *et al*.: Adenosine Generated in the Bone Marrow Niche Through a CD38-Mediated Pathway Correlates with Progression of Human Myeloma. *Mol Med* 2016; 22.
47. SITKOVSKY MV, LUKASHEV D, APASOV S *et al*.: Physiological control of immune response and inflammatory tissue damage by hypoxia-inducible factors and adenosine A2A receptors. *Annu Rev Immunol* 2004; 22: 657-82.
48. KHOA ND, MONTESINOS MC, REISS AB, DELANO D, AWADALLAH N, CRONSTEIN BN: Inflammatory cytokines regulate function and expression of adenosine A(2A) receptors in human monocytic THP-1 cells. *J Immunol* 2001; 167: 4026-32.
49. THIEL M, CALDWELL CC, SITKOVSKY MV: The critical role of adenosine A2A receptors in downregulation of inflammation and immunity in the pathogenesis of infectious diseases. *Microbes Infect* 2003; 5: 515-26.
50. LI J, FENTON RA, WHEELER HB *et al*.: Adenosine A2a receptors increase arterial endothelial cell nitric oxide. *J Surg Res* 1998; 80: 357-64.
51. NGUYEN DK, MONTESINOS MC, WILLIAMS AJ, KELLY M, CRONSTEIN BN: Th1 cytokines regulate adenosine receptors and their downstream signaling elements in human microvascular endothelial cells. *J Immunol* 2003; 171: 3991-8.
52. HEYN J, LEDDEROSE C, HINSKE LC *et al*.: Adenosine A2A receptor upregulation in human PMNs is controlled by miRNA-214, miRNA-15, and miRNA-16. *Shock* 2012; 37: 156-63.
53. SULLIVAN GW, RIEGER JM, SCHELD WM, MACDONALD TL, LINDEN J: Cyclic AMP-dependent inhibition of human neutrophil oxidative activity by substituted 2-propynylcyclohexyl adenosine A(2A) receptor agonists. *Br J Pharmacol* 2001; 132: 1017-26.
54. THIELE A, KRONSTEIN R, WETZEL A, GERTH A, NIEBER K, HAUSCHILDT S: Regulation of adenosine receptor subtypes during cultivation of human monocytes: role of receptors in preventing lipopolysaccharide-triggered respiratory burst. *Infect Immun* 2004; 72: 1349-57.
55. VARANI K, GESSI S, DALPIAZ A, BOREA PA: Pharmacological and biochemical characterization of purified A2a adenosine receptors in human platelet membranes by [3H]-CGS 21680 binding. *Br J Pharmacol* 1996; 117: 1693-701.
56. KOSHIBA M, ROSIN DL, HAYASHI N, LINDEN J, SITKOVSKY MV: Patterns of A2A extracellular adenosine receptor expression in different functional subsets of human peripheral T cells. Flow cytometry studies with anti-A2A receptor monoclonal antibodies. *Mol Pharmacol* 1999; 55: 614-24.
57. SAZE Z, SCHULER PJ, HONG CS, CHENG D, JACKSON EK, WHITESIDE TL: Adenosine production by human B cells and B cell-mediated suppression of activated T cells. *Blood* 2013; 122: 9-18.
58. SCHNURR M, TOY T, SHIN A *et al*.: Role of adenosine receptors in regulating chemotaxis and cytokine production of plasmacytoid dendritic cells. *Blood* 2004; 103: 1391-7.
59. FOSSETTA J, JACKSON J, DENO G *et al*.: Pharmacological analysis of calcium responses mediated by the human A3 adenosine receptor in monocyte-derived dendritic cells and recombinant cells. *Mol Pharmacol* 2003; 63: 342-50.
60. WILSON JM, ROSS WG, AGBAI ON *et al*.: The A2B adenosine receptor impairs the maturation and immunogenicity of dendritic cells. *J Immunol* 2009; 182: 4616-23.
61. GESSI S, VARANI K, MERIGHI S *et al*.: Expression of A3 adenosine receptors in human lymphocytes: up-regulation in T cell activation. *Mol Pharmacol* 2004; 65: 711-9.
62. GESSI S, VARANI K, MERIGHI S *et al*.: Expression, pharmacological profile, and functional coupling of A2B receptors in a recombinant system and in peripheral blood cells using a novel selective antagonist radioligand, [3H]MRE 2029-F20. *Mol Pharmacol* 2005; 67: 2137-47.
63. CHEN Y, CORRIDEN R, INOUE Y *et al*.: ATP release guides neutrophil chemotaxis via P2Y2 and A3 receptors. *Science* 2006; 314: 1792-5.
64. CRONSTEIN BN, DAGUMA L, NICHOLS D, HUTCHISON AJ, WILLIAMS M: The adenosine/neutrophil paradox resolved: human neutrophils possess both A1 and A2 receptors that promote chemotaxis and inhibit O2 generation, respectively. *J Clin Invest* 1990; 85: 1150-7.
65. MAYNE M, SHEPEL PN, JIANG Y, GEIGER JD, POWER C: Dysregulation of adenosine A1 receptor-mediated cytokine expression in peripheral blood mononuclear cells from multiple sclerosis patients. *Ann Neurol* 1999; 45: 633-9.
66. LAPPAS CM, RIEGER JM, LINDEN J: A2A adenosine receptor induction inhibits IFN-gamma production in murine CD4+ T cells. *J Immunol* 2005; 174: 1073-80.
67. CSOKA B, HIMER L, SELMECZY Z *et al*.: Adenosine A2A receptor activation inhibits T helper 1 and T helper 2 cell development and effector function. *FASEB J* 2008; 22: 3491-9.
68. HASKO G, PACHER P: A2A receptors in inflammation and injury: lessons learned from transgenic animals. *J Leukoc Biol* 2008; 83: 447-55.
69. HASKO G, LINDEN J, CRONSTEIN B, PACHER P: Adenosine receptors: therapeutic aspects for inflammatory and immune diseases. *Nat Rev Drug Discov* 2008; 7: 759-70.
70. JENNETTE JC, FALK RJ: The role of pathology in the diagnosis of systemic vasculitis. *Clin Exp Rheumatol* 2007; 25 (Suppl. 44): S52-6.
71. BOUMA MG, VAN DEN WILDENBERG FA, BUURMAN WA: Adenosine inhibits cytokine release and expression of adhesion molecules by activated human endothelial cells. *Am J Physiol* 1996; 270: C522-529.
72. ELTZSCHIG HK, THOMPSON LF, KARHAUSEN J *et al*.: Endogenous adenosine produced during hypoxia attenuates neutrophil accumulation: coordination by extracellular nucleotide metabolism. *Blood* 2004; 104: 3986-92.
73. ELTZSCHIG HK, IBLA JC, FURUTA GT *et al*.: Coordinated adenine nucleotide phosphohydrolysis and nucleoside signaling in posthypoxic endothelium: role of ectonucleotidases and adenosine A2B receptors. *J Exp Med* 2003; 198: 783-96.
74. CRONSTEIN BN, LEVIN RI, BELANOFF J, WEISSMANN G, HIRSCHHORN R: Adenosine: an endogenous inhibitor of neutrophil-mediated injury to endothelial cells. *J Clin Invest* 1986; 78: 760-70.
75. LU X, GARFIELD A, RAINGER GE, SAVAGE CO, NASH GB: Mediation of endothelial cell damage by serine proteases, but not superoxide, released from antineutrophil cytoplasmic antibody-stimulated neutrophils. *Arthritis Rheum* 2006; 54: 1619-28.
76. AL LAHAM F, KALSCH AI, HEINRICH L *et al*.: Inhibition of neutrophil-mediated production of reactive oxygen species (ROS) by endothelial cells is not impaired in anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis patients. *Clin Exp Immunol* 2010; 161: 268-75.
77. FUCHS TA, ABED U, GOOSMANN C *et al*.: Novel cell death program leads to neutrophil extracellular traps. *J Cell Biol* 2007; 176: 231-41.
78. NAKAZAWA D, TOMARU U, SUZUKI A *et al*.: Abnormal conformation and impaired degradation of propylthiouracil-induced neutrophil extracellular traps: implications of disordered neutrophil extracellular traps in a rat model of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2012; 64: 3779-87.
79. MERRILL JT, SHEN C, SCHREIBMAN D *et al*.: Adenosine A1 receptor promotion of multinucleated giant cell formation by human monocytes: a mechanism for methotrexate-induced nodulosis in rheumatoid arthritis. *Arthritis Rheum* 1997; 40: 1308-15.
80. MONCRIEFFE H, NISTALA K, KAMHIEH Y *et al*.: High expression of the ectonucleotidase CD39 on T cells from the inflamed site identifies two distinct populations, one regulatory and one memory T cell population. *J Immunol* 2010; 185: 134-43.
81. GOUTTEFANGEAS C, MANSUR I, SCHMID M *et al*.: The CD39 molecule defines distinct cytotoxic subsets within alloactivated human CD8-positive cells. *Eur J Immunol* 1992; 22: 2681-5.
82. TOTH I, LE AQ, HARTJEN P *et al*.: Decreased frequency of CD73+CD8+ T cells of HIV-infected patients correlates with immune activation and T cell exhaustion. *J Leukoc Biol* 2013; 94: 551-61.
83. SCHENA F, VOLPI S, FALITI CE *et al*.: Dependence of immunoglobulin class switch recombination in B cells on vesicular release of ATP and CD73 ectonucleotidase activity. *Cell Rep* 2013; 3: 1824-31.
84. FRANCOIS V, SHEHADE H, ACOLTY V *et al*.: Intestinal immunopathology is associated with decreased CD73-generated adenosine during lethal infection. *Mucosal Immunol* 2015; 8: 773-84.

85. DEAGLIO S, DWYER KM, GAO W *et al*.: Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. *J Exp Med* 2007; 204: 1257-65.
86. PANTHER E, CORINTI S, IDZKO M *et al*.: Adenosine affects expression of membrane molecules, cytokine and chemokine release, and the T-cell stimulatory capacity of human dendritic cells. *Blood* 2003; 101: 3985-90.
87. LI L, HUANG L, YE H *et al*.: Dendritic cells tolerized with adenosine A(2)AR agonist attenuate acute kidney injury. *J Clin Invest* 2012; 122: 3931-42.
88. PANTHER E, IDZKO M, HEROUY Y *et al*.: Expression and function of adenosine receptors in human dendritic cells. *FASEB J* 2001; 15: 1963-70.
89. NAGANUMA M, WIZNEROWICZ EB, LAPPAS CM, LINDEN J, WORTHINGTON MT, ERNST PB: Cutting edge: Critical role for A2A adenosine receptors in the T cell-mediated regulation of colitis. *J Immunol* 2006; 177: 2765-9.
90. CSERNOK E, TRABANDT A, MULLER A *et al*.: Cytokine profiles in Wegener's granulomatosis: predominance of type 1 (Th1) in the granulomatous inflammation. *Arthritis Rheum* 1999; 42: 742-50.
91. SETA N, KOBAYASHI S, HASHIMOTO H, KUWANA M: Characterization of autoreactive T-cell clones to myeloperoxidase in patients with microscopic polyangiitis and healthy individuals. *Clin Exp Rheumatol* 2009; 27: 826-9.
92. ABDULAHAD WH, VAN DER GELD YM, STEGEMAN CA, KALLENBERG CG: Persistent expansion of $CD4^+$ effector memory T cells in Wegener's granulomatosis. *Kidney Int* 2006; 70: 938-47.
93. JENABIAN MA, SEDDIKI N, YATIM A *et al*.: Regulatory T cells negatively affect IL-2 production of effector T cells through CD39/adenosine pathway in HIV infection. *PLoS Pathog* 2013; 9: e1003319.
94. HUANG S, APASOV S, KOSHIBA M, SITKOVSKY M: Role of A2a extracellular adenosine receptor-mediated signaling in adenosine-mediated inhibition of T-cell activation and expansion. *Blood* 1997; 90: 1600-10.
95. ERDMANN AA, GAO ZG, JUNG U *et al*.: Activation of Th1 and Tc1 cell adenosine A2A receptors directly inhibits IL-2 secretion *in vitro* and IL-2-driven expansion *in vivo*. *Blood* 2005; 105: 4707-14.
96. MARINAKI S, KALSCH AI, GRIMMINGER P *et al*.: Persistent T-cell activation and clinical correlations in patients with ANCA-associated systemic vasculitis. *Nephrol Dial Transplant* 2006; 21: 1825-32.
97. ZAREK PE, HUANG CT, LUTZ ER *et al*.: A2A receptor signaling promotes peripheral tolerance by inducing T-cell anergy and the generation of adaptive regulatory T cells. *Blood* 2008; 111: 251-9.
98. NOGUEIRA E, HAMOUR S, SAWANT D *et al*.: Serum IL-17 and IL-23 levels and autoantigen-specific Th17 cells are elevated in patients with ANCA-associated vasculitis. *Nephrol Dial Transplant* 2010; 25: 2209-17.
99. SAITO H, TSURIKISAWA N, TSUBURAI T, OSHIKATA C, AKIYAMA K: Cytokine production profile of $CD4^+$ T cells from patients with active Churg-Strauss syndrome tends toward Th17. *Int Arch Allergy Immunol* 2009; 149 (Suppl. 1): 61-5.
100. ABDULAHAD WH, STEGEMAN CA, LIMBURG PC, KALLENBERG CG: Skewed distribution of Th17 lymphocytes in patients with Wegener's granulomatosis in remission. *Arthritis Rheum* 2008; 58: 2196-205.
101. GAN PY, STEINMETZ OM, TAN DS *et al*.: Th17 cells promote autoimmune anti-myeloperoxidase glomerulonephritis. *J Am Soc Nephrol* 2010; 21: 925-31.
102. OHTA A, KINI R, OHTA A, SUBRAMANIAN M, MADASU M, SITKOVSKY M: The development and immunosuppressive functions of $CD4^{(+)}$ $CD25^{(+)}$ $FoxP3^{(+)}$ regulatory T cells are under influence of the adenosine-A2A adenosine receptor pathway. *Front Immunol* 2012; 3: 190.
103. SEVIGNY CP, LI L, AWAD AS *et al*.: Activation of adenosine 2A receptors attenuates allograft rejection and alloantigen recognition. *J Immunol* 2007; 178: 4240-9.
104. OHTA A, GORELIK E, PRASAD SJ *et al*.: A2A adenosine receptor protects tumors from antitumor T cells. *Proc Natl Acad Sci USA* 2006; 103: 13132-7.
105. SCHULER PJ, SAZE Z, HONG CS *et al*.: Human $CD4^+$ $CD39^+$ regulatory T cells produce adenosine upon co-expression of surface CD73 or contact with $CD73^+$ exosomes or $CD73^+$ cells. *Clin Exp Immunol* 2014; 177: 531-43.
106. ZHAO Y, LUTALO PM, THOMAS JE *et al*.: Circulating T follicular helper cell and regulatory T cell frequencies are influenced by B cell depletion in patients with granulomatosis with polyangiitis. *Rheumatology* (Oxford) 2014; 53: 621-30.
107. RIMBERT M, HAMIDOU M, BRAUDEAU C *et al*.: Decreased numbers of blood dendritic cells and defective function of regulatory T cells in antineutrophil cytoplasmic antibody-associated vasculitis. *PLoS One* 2011; 6: e18734.
108. ABDULAHAD WH, STEGEMAN CA, VAN DER GELD YM, DOORNBOS-VAN DER MEER B, LIMBURG PC, KALLENBERG CG: Functional defect of circulating regulatory $CD4^+$ T cells in patients with Wegener's granulomatosis in remission. *Arthritis Rheum* 2007; 56: 2080-91.
109. KLING L, BENCK U, BREEDIJK A *et al*.: Changes in CD73, CD39 and CD26 expression on T-lymphocytes of ANCA-associated vasculitis patients suggest impairment in adenosine generation and turn-over. *Scientific Reports* 2017; 7: s41598-41017.
110. HILCHEY SP, KOBIE JJ, COCHRAN MR *et al*.: Human follicular lymphoma $CD39^+$-infiltrating T cells contribute to adenosine-mediated T cell hyporesponsiveness. *J Immunol* 2009; 183: 6157-66.
111. XU PC, CUI Z, CHEN M, HELLMARK T, ZHAO MH: Comparison of characteristics of natural autoantibodies against myeloperoxidase and anti-myeloperoxidase autoantibodies from patients with microscopic polyangiitis. *Rheumatology* (Oxford) 2011; 50: 1236-43.
112. JAYNE DR, WEETMAN AP, LOCKWOOD CM: IgG subclass distribution of autoantibodies to neutrophil cytoplasmic antigens in systemic vasculitis. *Clin Exp Immunol* 1991; 84: 476-81.
113. SURETTE ME, KRUMP E, PICARD S, BORGEAT P: Activation of leukotriene synthesis in human neutrophils by exogenous arachidonic acid: inhibition by adenosine A(2a) receptor agonists and crucial role of autocrine activation by leukotriene B(4). *Mol Pharmacol* 1999; 56: 1055-62.
114. MCCOLL SR, ST-ONGE M, DUSSAULT AA *et al*.: Immunomodulatory impact of the A2A adenosine receptor on the profile of chemokines produced by neutrophils. *FASEB J* 2006; 20: 187-9.
115. HASKO G, SZABO C, NEMETH ZH, KVETAN V, PASTORES SM, VIZI ES: Adenosine receptor agonists differentially regulate IL-10, TNF-alpha, and nitric oxide production in RAW 264.7 macrophages and in endotoxemic mice. *J Immunol* 1996; 157: 4634-40.
116. HASKO G, KUHEL DG, CHEN JF *et al*.: Adenosine inhibits IL-12 and TNF-[alpha] production via adenosine A2a receptor-dependent and independent mechanisms. *FASEB J* 2000; 14: 2065-74.
117. NEMETH ZH, LUTZ CS, CSOKA B *et al*.: Adenosine augments IL-10 production by macrophages through an A2B receptor-mediated posttranscriptional mechanism. *J Immunol* 2005; 175: 8260-70.
118. CSOKA B, NEMETH ZH, VIRAG L *et al*.: A2A adenosine receptors and C/EBPbeta are crucially required for IL-10 production by macrophages exposed to Escherichia coli. *Blood* 2007; 110: 2685-95.
119. EPPELL BA, NEWELL AM, BROWN EJ: Adenosine receptors are expressed during differentiation of monocytes to macrophages *in vitro*. Implications for regulation of phagocytosis. *J Immunol* 1989; 143: 4141-5.
120. KURASHIMA Y, AMIYA T, NOCHI T *et al*.: Extracellular ATP mediates mast cell-dependent intestinal inflammation through P2X7 purinoceptors. *Nat Commun* 2012; 3: 1034.
121. KHALAFALLA MG, WOODS LT, CAMDEN JM *et al*.: P2X7 receptor antagonism prevents IL-1beta release from salivary epithelial cells and reduces inflammation in a mouse model of autoimmune exocrinopathy. *J Biol Chem* 2017; 292: 16626-37.
122. ASWAD F, KAWAMURA H, DENNERT G: High sensitivity of $CD4^+CD25^+$ regulatory T cells to extracellular metabolites nicotinamide adenine dinucleotide and ATP: a role for P2X7 receptors. *J Immunol* 2005; 175: 3075-83.
123. SCHENK U, WESTENDORF AM, RADAELLI E *et al*.: Purinergic control of T cell activation by ATP released through pannexin-1 hemichannels. *Sci Signal* 2008; 1: ra6.
124. WOEHRLE T, YIP L, ELKHAL A *et al*.: Pannexin-1 hemichannel-mediated ATP release together with P2X1 and P2X4 receptors regulate T-cell activation at the immune synapse. *Blood* 2010; 116: 3475-84.
125. SCHENK U, FRASCOLI M, PROIETTI M *et al*.:

ATP inhibits the generation and function of regulatory T cells through the activation of purinergic P2X receptors. *Sci Signal* 2011; 4: ra12.

126. ATARASHI K, NISHIMURA J, SHIMA T *et al*.: ATP drives lamina propria T(H)17 cell differentiation. *Nature* 2008; 455: 808-12.
127. DI VIRGILIO F, GIULIANI AL: Purinergic signalling in autoimmunity: A role for the P2X7R in systemic lupus erythematosus? *Biomed J* 2016; 39: 326-38.
128. BLUME C, FELIX A, SHUSHAKOVA N *et al*.: Autoimmunity in CD73/Ecto-5'-nucleotidase deficient mice induces renal injury. *PLoS One* 2012; 7: e37100.
129. XIE B, CHEN Y, ZHANG S *et al*.: The expression of P2X7 receptors on peripheral blood mononuclear cells in patients with primary Sjögren's syndrome and its correlation with anxiety and depression. *Clin Exp Rheumatol* 2014; 32: 354-60.
130. LI DM, LI XP, LI XM *et al*.: [Expression of FOXP3 in $CD4^+$ $CD39^+$ T cells of patients with systemic lupus erythematosus and dynamic observation of treatment with glucocorticoid]. *Zhonghua Yi Xue Za Zhi* 2009; 89: 1636-8.
131. LI DM, LI XP, ZHANG JH *et al*.: [The expression of CD73 in $CD4^+$ regulatory T cells in patients with new-onset systemic lupus erythematosus]. *Zhonghua Nei Ke Za Zhi*. 2010; 49: 772-775.