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ORIGINAL ARTICLE

P2 receptors and platelet function

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Abstract Following vessel wall injury, platelets adhere to the exposed subendothelium, become activated and release mediators such as TXA_2 and nucleotides stored at very high concentration in the so-called dense granules. Released nucleotides and other soluble agents act in a positive feedback mechanism to cause further platelet activation and amplify platelet responses induced by agents such as thrombin or collagen. Adenine nucleotides act on platelets through three distinct P2 receptors: two are G protein-coupled ADP receptors, namely the $P2Y_1$ and $P2Y_{12}$ receptor subtypes, while the $P2X_1$ receptor ligand-gated cation channel is activated by ATP. The $P2Y_1$ receptor initiates platelet aggregation but is not sufficient for a full platelet aggregation in response to ADP, while the $P2Y_{12}$ receptor is responsible for completion of the aggregation to ADP. The latter receptor, the molecular target of the antithrombotic drugs clopidogrel, prasugrel and ticagrelor, is responsible for most of the potentiating effects of ADP when platelets are stimulated by agents such as thrombin, collagen or immune complexes. The $P2X_1$ receptor is involved in platelet shape change and in activation by collagen under shear conditions. Each of these receptors is coupled to specific signal transduction pathways in response to ADP or ATP and is differentially involved in all the sequential events involved in platelet function and haemostasis. As such, they represent potential targets for antithrombotic drugs.

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Introduction

The main role of blood platelets is to ensure primary haemostasis, which means the maintenance of blood vessel integrity and the rapid cessation of bleeding in the event of loss of vascular integrity. They are also responsible for the formation of pathogenic thrombi at sites of rupture or erosion of an atherosclerotic plaque, promoting atherothrombotic diseases including acute coronary syndromes, ischaemic stroke and peripheral artery disease [1]. Platelets also play an important role in inflammation and can influence the phenotype of other blood and vascular cells, thereby contributing to many other non-haemostatic disorders, from cystic fibrosis and arthritis to diabetes, atherosclerosis and cancer [2–7].

Extracellular nucleotides and their receptors are important components of the cardiovascular system and regulate a broad range of physiological processes like the control of vascular tone, smooth muscle cell proliferation and platelet activation [8]. Adenosine 5′-disphosphate (ADP) plays crucial roles in the physiological process of haemostasis and in the development and extension of arterial thrombosis [9]. As compared to strong agonists such as thrombin or collagen, ADP is, by itself, a weak agonist of platelet aggregation inducing only reversible responses. However, ADP, stored at a very high concentration in platelet dense granules and released upon activation at sites of vascular injury, constitutes an important so-called secondary agonist, which greatly amplifies most of the platelet responses and contributes to the stabilization of the thrombus.

Addition of ADP to washed platelets results in shape change, reversible aggregation at physiological concentrations of calcium (2 mM) and finally desensitization [10, 11]. Transduction of the ADP signal involves a transient rise in free cytoplasmic calcium, due to mobilization of internal stores, secondary store-mediated influx and a concomitant inhibition of adenylyl cyclase activity [12]. ATP induces an extremely rapid influx of calcium from the extracellular medium associated to platelet shape change [13, 14].

Starting from the concept of a unique P2T receptor (T for thrombocyte) originally postulated on the basis of pharmacological data [15], a model of three platelet P2 receptors progressively emerged [16]. These are the $P2X_1$ cation channel, which is activated by ATP and two G protein-coupled receptors, $P2Y_1$ and $P2Y_{12}$, both activated by ADP. Each of these receptors has a specific function during platelet activation and aggregation, which naturally has implications for their involvement in thrombosis.

The respective roles of the three platelet P2 receptors during platelet activation

The $P2Y_1$ receptor

The $P2Y_1$ receptor is widely distributed in many tissues including heart, blood vessels and blood cells, neural tissue, testis, prostate and ovary (Fig. 1) [17]. About 150 $P2Y_1$ receptor-binding sites are expressed per platelet [18, 19], which is very low as compared for instance to the TP receptors or the thrombin receptor PAR-1 (1,000 to 2,000 sites per platelet). As it is coupled to Gαq, the $P2Y_1$ receptor triggers the mobilization of calcium from internal stores, which results in platelet shape change and weak, transient aggregation in response to ADP [20–22]. The $P2Y_1$ receptor is absolutely required for ADP-induced platelet aggregation. Its pharmacological inhibition or genetic deficiency results in complete absence of platelet aggregation and shape change in response to ADP. As a consequence, at the intracellular level, the calcium signal is abolished, while the ability of ADP to inhibit cAMP formation is preserved [20, 23]. The $P2Y_1$ receptor also participates in the aggregation response to collagen and plays a key role in collagen-induced shape change when TXA_2 formation is prevented [23, 24]. Overall, the $P2Y_1$ receptor mediates weak responses to ADP but is nevertheless a crucial factor in the initiation of the platelet activation induced by ADP or collagen.

Several selective antagonists of this receptor have been described [25], namely the adenine nucleotide analogues A2P5P, A3P5P or A3P5PS [26]; MRS2179 (N^6-methyl-2′-deoxyadenosine-3′,5′-bisphosphate) [18, 27–30]; MRS2279 [31] and MRS2500 (2-iodo-N^6-methyl-(*N*)-methanocarba-2′-deoxyadenosine-3′,5′-bisphosphate) [19, 29, 32]. The latter displays the highest affinity for $P2Y_1$ and constitutes to date the most valuable tool to investigate the role of the $P2Y_1$ receptor in platelet function (for review, please see Kenneth A. Jacobson, same issue).

Besides platelets, the $P2Y_1$ receptor is also expressed on endothelial cells, where it contributes to nucleotide-induced relaxation [33, 34], and was recently shown to be involved

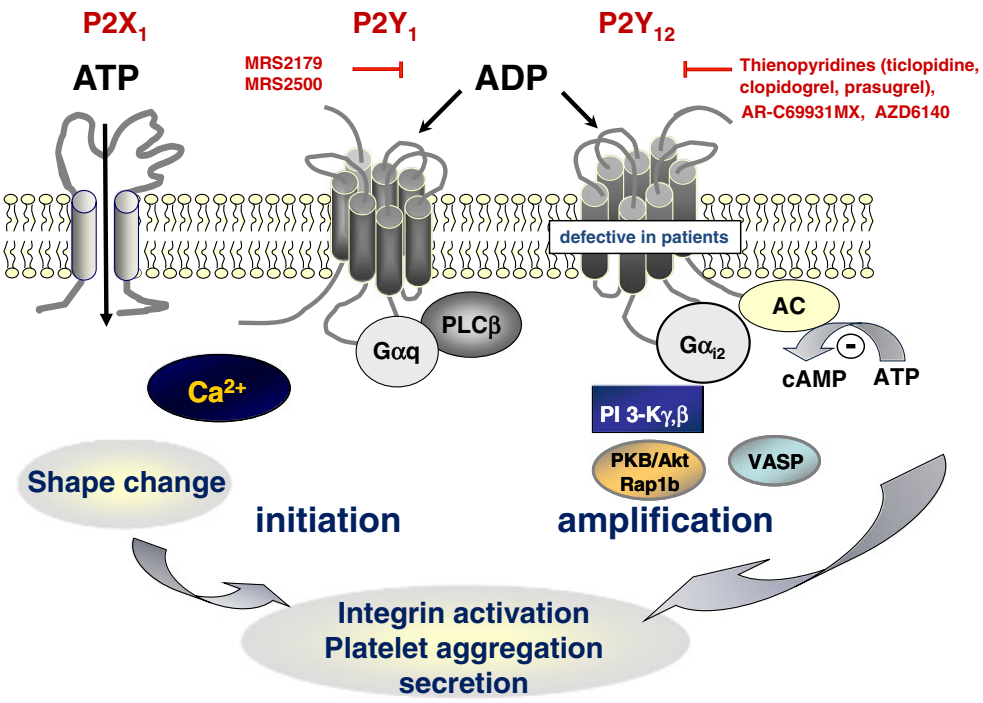

Fig. 1 Schematic representation of the current model of platelet activation induced by adenine nucleotides (ATP and ADP)

in endothelial cell migration [35]. It is also expressed on leukocytes, where its role is less well established, although a role in the phagocytic activity of macrophages has recently been highlighted [36].

The $P2Y_{12}$ receptor

The $P2Y_{12}$ receptor, despite being well known and characterized on the basis of both pharmacological and genetic evidence, was the last platelet P2 receptor to be cloned [37, 38]. Its tissue distribution is very limited, although not entirely restricted to platelets as it is also present in brain [37], glial cells [39] and possibly in vascular smooth muscle cells, where it could contribute to vessel contraction [40, 41]. This receptor is defective in patients with selective defects in platelet activation by ADP [42] (for review, please see Marco Cattaneo, same issue). ADP is the natural agonist of this receptor, while ATP and a wide range of its triphosphate analogues behave as antagonists [43, 44]. It is the molecular target of the antiplatelet drugs clopidogrel and prasugrel, two thienopyridine compounds that covalently bind to the receptor, and of ticagrelor (AZD6140), cangrelor (AR-C69931MX) and elinogrel (PRT060128), which are competitive antagonists of the receptor [42, 45]. The $P2Y_{12}$ receptor is responsible for completion of the platelet aggregation response to ADP initiated by $P2Y_1$ [46] and for the ADP-dependent amplification of platelet aggregation induced by other agents such as G_q-coupled serotonin receptors [22], G_q and $G_{12/13}$-coupled TXA_2 and PAR-1 receptors [47, 48], immune complexes [49, 50] or when platelets are activated by collagen through GPVI/tyrosine kinase/PLCγ2 pathway [51]. The $P2Y_{12}$ receptor is also responsible for the ability of ADP to restore collagen-induced aggregation in $G_{\alpha q}$-deficient mouse platelets [52]. The $P2Y_{12}$ receptor is also involved in potentiation of platelet secretion independently of TXA_2 generation and macroaggregate formation [53, 54] and mediates the stabilization of platelet aggregates induced by thrombin [55–57] or TXA_2 [58]. The requirement of this receptor for completion of aggregation in response to ADP but also for the ADP-dependent amplification of aggregation induced by other agents was confirmed in $P2Y_{12}^{-/-}$ mice [37, 59]. The bleeding time is markedly prolonged in these mice [37, 59], as it is in patients with severe $P2Y_{12}$ deficiency [42], as well as in animals treated with high doses of clopidogrel or other $P2Y_{12}$ antagonists.

The $P2Y_{12}$ receptor is coupled to inhibition of adenylyl cyclase activity through activation of a $G_{\alpha i2}$ G protein subtype [60, 61], which is a critical component of the signalling pathway for integrin αIIbβ3 activation [61, 62]. However, adenylyl cyclase inhibition and lowering cAMP levels are not sufficient to cause platelet aggregation [63–65]; thus, other signalling events are required for full activation of the αIIbβ3 integrin and subsequent aggregation [66]. One important intracellular pathway which regulates G_i-dependent integrin αIIbβ3 activation is constituted by phosphoinositide 3-kinase (PI 3-K) [56, 67–70]. PI 3-K isoform p110β regulates integrin activation through a classical lipid kinase-dependent mechanism, involving the small GTPase Rap1 and/or the serine-threonine protein kinase B/Akt (PKB/Akt) [71–76], whereas p110γ appears to regulate integrin principally through a non-catalytic signalling mechanism [77, 78]. Whether other PI3K class I isoforms such as the p110α or PI3K class II or III isoforms, which are highly expressed in blood platelets, play a role in integrin αIIbβ3 activation remains to be determined. Another way by which $P2Y_{12}$ could contribute to modulate aggregation through $G\alpha_{i2}$ may involve inhibition of the cAMP-dependent protein kinase (PKA)-mediated phosphorylation of the vasodilator-stimulated phosphoprotein (VASP), an intracellular actin regulatory protein that is a negative modulator of αIIbβ3 integrin activation [79].

Co-activation of the $P2Y_1$ and $P2Y_{12}$ receptors is necessary for normal ADP-induced platelet aggregation since separate inhibition of either of them with selective antagonists results in a dramatic decrease in aggregation [22, 46, 80]. The $P2Y_1$ and $P2Y_{12}$ receptors are differentially involved in platelet aggregation induced by other agonists, with the $P2Y_1$ playing only a minor role, except in the case of collagen-induced activation, while $P2Y_{12}$ supports amplification of these responses. This is also the case in the procoagulant activity of platelets. While both receptors are indirectly involved through their role in platelet P-selectin exposure and in the formation of platelet-leukocyte conjugates leading to leukocyte tissue factor exposure [81, 82], the $P2Y_{12}$ receptor is also directly implicated in the exposure of phosphatidylserine at the surface of platelets [81, 83, 84].

The $P2X_1$ receptor

The third component of the platelet P2 receptors is $P2X_1$, a ligand-gated cation channel responsible for a fast calcium entry induced by ATP [14, 85]. Although unable to trigger platelet aggregation by itself, the $P2X_1$ receptor induces transient shape change [13] and participates in collagen- and shear-induced aggregation [86–88]. A comprehensive review of its role in platelet function is provided by Martyn Mahaut-Smith (this issue).

Desensitization

An important phenomenon in controlling thrombus growth is the regulation of platelet reactivity after stimulation, and

receptor desensitization is one general mechanism used by cells to adapt their responsiveness. It has long been known that after being exposed to ADP, platelets become unresponsive to a second stimulation with ADP with a resultant loss of shape change and aggregation. This so-called refractory state of platelets to ADP is transient and, depending on the experimental conditions, lasts 15 to 30 min provided an enzymatic system degrades ADP in the medium. In the absence of such a system, platelets do not recover responsiveness to ADP. The molecular mechanisms of this phenomenon have been studied in detail, but consensus has not been reached, and two different views have not yet been reconciled. On the one hand, it is thought that the phenomenon of platelet refractoriness to ADP is due to selective desensitization and internalization of the $P2Y_1$ receptor, while the $P2Y_{12}$ receptor remains functional with the ability of ADP to induce amplification of the platelet aggregation induced by other agonists [89–91]. Desensitization of the $P2Y_1$ receptor has been shown to be dependent on receptor C-terminal phosphorylation sites, β-arrestin-2 interaction and protein kinase C (PKC) activity [92, 93]. The in vivo consequence is that under conditions of platelets refractory to stimulation by ADP, the $P2Y_{12}$ receptor remains functional and able to promote their reactivity at sites of injury, thus preventing loss of haemostatic function. On the other hand, it is reported that both $P2Y_1$ and $P2Y_{12}$ receptors undergo desensitization, and that $P2Y_{12}$ desensitization is mediated by G protein-coupled receptor kinases (GRK) [93, 94]. Further studies are required to solve the apparent contradiction of these reports.

Finally, the $P2X_1$ receptor is also desensitized, and this occurs very quickly and requires lower concentrations of nucleotides than for the metabotropic receptor $P2Y_1$ [95, 96]. The physiological implications of $P2X_1$ desensitization are still not well understood but might be related to the need to confine thrombus growth to the site of a lesion and prevent uncontrolled extension of the platelet aggregates.

Genetic polymorphisms of the P2Y receptors

Apart from the $P2Y_{12}$ receptor defects in patients with mild to severe haemorrhagic diathesis (reviewed by Marco Cattaneo, this issue), $P2Y_1$ and $P2Y_{12}$ have been shown to display gene sequence variations, which have been proposed to be associated with increased platelet responsiveness to ADP. In $P2Y_{12}$, the polymorphisms are in the intronic part of the gene and have no obvious impact on the coding sequence. Two haplotypes have been identified, designated as H1 and H2, the latter being proposed to be linked to enhanced platelet reactivity to ADP [97] and to a diminished response to clopidogrel [98] and associated with increased risks for peripheral arterial disease [99] and coronary artery disease [100]. However, these results were not confirmed in latter studies [101–103]. It thus appears that polymorphisms of the non-coding region of the $P2Y_{12}$ receptor gene do not have any impact on the receptor function nor on the individual responsiveness to clopidogrel. Concerning the $P2Y_1$ receptor, a silent polymorphism was identified at position 1622 (A/G) of the coding sequence, which led to increased platelet aggregation in response to a low concentration of ADP (0.1 μM) in subjects carrying the G allele [104]. Again, these results were not confirmed in a large population of CAD patients treated with clopidogrel [105]. Overall, whether polymorphism of the $P2Y_1$ and $P2Y_{12}$ receptors exists, which have an impact on the platelet physiology or in clinical pharmacology, probably requires further studies.

The platelet P2 receptors as molecular targets for antithrombotic drugs

The $P2Y_{12}$ receptor

Long before its molecular cloning, the pharmacological importance of this receptor in haemostasis and thrombosis was well recognized. This was due to the fact that the potent antithrombotic thienopyridine compounds ticlopidine and clopidogrel, of which an active liver metabolite selectively and irreversibly targets the $P2Y_{12}$ receptor, were used as molecular tools to characterize platelet responses to ADP and the role of the latter in thrombosis [106]. The thienopyridine compounds are prodrugs which have to be metabolized by the liver in order to generate active metabolites. The active metabolite of clopidogrel [107] covalently binds cysteine residues of the $P2Y_{12}$ receptor, thus precluding the binding of ADP [108–110]. Moreover, it has been recently reported that clopidogrel's active metabolite disrupts homopolymers of the $P2Y_{12}$ receptor expressed in lipid rafts and partitions them out of lipid rafts [111], pointing to the importance of oligomerization and membrane localization on the function of this receptor. Further studies are however required to confirm these findings.

Clopidogrel treatment leads to a dose-dependent inhibition of platelet aggregation in response to ADP with conserved shape change and transient weak aggregation driven by $P2Y_1$. At the intracellular level, $P2Y_{12}$ blockade results in the inhibition of the ability of ADP to inhibit cyclic AMP production while calcium signalling is preserved [46]. Platelet aggregation in response to strong activators is also strongly inhibited through the effect on released ADP.

Large-scale clinical trials have demonstrated the beneficial effects of thienopyridines in the prevention of major cardiac events after coronary artery stent insertion and in

the secondary prevention of major vascular events in patients with a history of cerebrovascular, coronary or peripheral artery disease [106, 112].

Prasugrel (CS-747, LY640315) is a third-generation thienopyridine compound which has higher efficacy and faster onset of action than clopidogrel. This is due to a slightly different metabolic pathway and better rate of active metabolite generation as compared to clopidogrel [113]. A large-scale clinical trial, TRITON-TIMI 38, including 13,609 patients planed for percutaneous coronary intervention (PCI) demonstrated the overall superiority of prasugrel (60 mg loading dose followed by 10 mg maintenance dose) in comparison to clopidogrel (300 mg loading dose, 75 mg maintenance dose) with a total of 19% reduction of ischemic events with, particularly, 52% decreased stent thrombosis [114], but with a 32% increase of major bleeding, including fatal bleeding. Although not really surprising, these results had an important impact in the practises of interventional cardiologists [115].

Competitive $P2Y_{12}$ antagonists cangrelor (AR-C69931MX) and ticagrelor (AZD6140) are in various phases of development, the latter being orally active while cangrelor requires intravenous administration [45, 116, 117]. Theoretically, use of such molecules would have an advantage mainly in acute situations like myocardial infarction, where fast blockade of the ADP receptor should be beneficial as compared to the delayed action of thienopyridine compounds. The rapid cessation of activity would also be beneficial in terms of safety. A second theoretical advantage of using competitive $P2Y_{12}$ antagonists could be if there is less inter-individual variability in the response to the treatment. Cangrelor underwent two phase III trials (CHAMPION-PCI and CHAMPION-PLATFORM) which were stopped early for lack of efficacy over placebo or clopidogrel, respectively, in patients undergoing PCI. Cangrelor is still being studied as a bridge for patients on clopidogrel who need to go off of drug to undergo surgery [118]. Ticagrelor was in a phase III trial (PLATO) assessing whether this agent has clinical efficacy superior to clopidogrel in the management of ACS. Ticagrelor demonstrated improved cardiovascular outcomes, including a reduction in myocardial infarctions and vascular events as compared to clopidogrel. The main adverse events with ticagrelor are bleeding and dyspnoea, the latter of which is of unclear aetiology and of unknown long-term clinical concern [119, 120]. For a complete review, please see Collet et al. (this issue).

The $P2Y_1$ receptor as a target for new antiplatelet compounds

A consideration of the role of $P2Y_1$ in platelet aggregation and experimental thrombosis provides the rational for suggesting this receptor to be a relevant target for new antiplatelet compounds. $P2Y_1$ knockout mice display resistance in various models of thrombosis such as the systemic thromboembolism induced by infusion of a mixture of collagen and adrenaline [23, 121] or of tissue factor [84] or in localized thrombosis after ferric chloride- or laser-induced injury of mouse mesenteric arteries [122]. Similar protection is observed in animals treated with selective $P2Y_1$ antagonists such as the adenine nucleotide analogues MRS2179 [18, 27, 84] or MRS2500 [123]. However, due to their limited bioavailability for long-term treatment, new $P2Y_1$ receptor antagonists with improved pharmacokinetic profile will need to be developed. Several non-nucleotide antagonists of this receptor have been described such as tetrahydro-quinolinamine inhibitors [124], aryl-urea inhibitors [125] and benzofuran-substituted urea derivatives [126] which display however lower affinity for the receptor. Whether these compounds fulfil these latter criteria and are effective in vivo remain to be investigated.

Moreover, a combination of $P2Y_1$ deficiency or inhibition and clopidogrel treatment has been found to confer better thromboresistance than either condition alone, suggesting that a combination of P2 receptor antagonists could improve antithrombotic strategies [122, 123]. It is worthy to note that inhibition of the $P2Y_1$ receptor results in only moderate prolongation of the bleeding time, which could be advantageous in terms of safety. Additional advantages of targeting the $P2Y_1$ receptor rely on its role in vascular inflammation [127] and in atherosclerosis [128] (see below). As a consequence, this receptor could represent an attractive and original target for drugs with multiple sites of action in atherothrombosis and beyond in other inflammatory diseases.

The $P2X_1$ receptor as a target for new antiplatelet compounds

$P2X_1$-deficient mice have in fact no prolongation of their bleeding time as compared to the wild type, indicating that they conserve normal haemostasis. In contrast, they display resistance to the systemic thromboembolism induced by injection of a mixture of collagen and adrenaline and to localized laser-induced injury of the vessel wall of mesenteric arteries [88]. Since in vitro the $P2X_1$ receptor plays an important role in thrombus formation only under high shear conditions, it might represent the ideal target for an antithrombotic drug. Conversely, increased systemic thrombosis has been reported in mice overexpressing the human $P2X_1$ receptor [129]. Moreover, the $P2X_1$ antagonist NF449 [130] has an inhibitory effect on platelet activation ex vivo and thrombosis in vivo [131]. These results clearly indicate that the $P2X_1$ receptor should also be considered as

a potential target for antiplatelet strategies, with the interesting feature that $P2X_1$ antagonists should be effective only at sites of severe stenosis where shear forces are very high, without having a deleterious effect on normal haemostasis. However, further work is required to conclusively establish this point.

The platelet P2 receptors beyond haemostasis (Fig. 2)

Vascular inflammation plays a central role in both the progressive and acute components of atherothrombotic disease. It is now appreciated that activated platelets contribute to inflammation since platelets are an important source of inflammatory mediators, compounds with trophic activity such as PDGF, expose P-selectin, CD40 and CD40 ligand (CD40L) which allow interaction with leukocytes and subsequent leukocyte activation and release of a range of inflammatory cytokines and exposure of tissue factor [4]. Thus, the clinical efficacy of antiplatelet drugs might also be related to blockade of the contribution of platelets to inflammation [132]. The role of the $P2Y_{12}$ receptor not only in platelet aggregation but also in the activation of multiple inflammatory and trophic processes may be expected to result in its direct involvement in the progression of atherosclerosis and restenosis, which has been reported recently in rabbit and in mice [133–137].

Concerning $P2Y_1$, its role in platelet function and its presence in all cell types and tissues involved in inflammation and atherosclerosis questioned its involvement in these diseases [138, 139]. Using $P2Y_1^{-/-}$ mice crossed with $ApoE^{-/-}$ mice, a role of the $P2Y_1$ receptor in the development of atherosclerosis was demonstrated [128]. Interestingly, bone marrow transplantation experiments showed that the platelet receptor is not involved in this process, suggesting a possible role of the $P2Y_1$ receptor expressed in endothelial cells [128]. We recently reported that the $P2Y_1$ receptor contributes to the upregulation of adhesion molecule (P-selectin, VCAM-1 and ICAM-1) exposure in TNFα-stimulated ECs by a mechanism involving p38 MAP kinase signalling pathway, which in turn facilitates recruitment of monocytes and their transmigration. In addition, we found that the endothelial $P2Y_1$ receptor contributes to TNFα-induced leukocyte recruitment in experimentally inflamed arteries in a mouse model in vivo [127]. Thus, the $P2Y_1$ receptor might be an original target for new anti-inflammatory strategies.

In addition to vascular inflammation, through their capability of interacting with many other cells, platelets are involved in many physiological and pathological processes which we will not all cover here but will just point some of these. Platelets play a role in allergic asthma [140]. They are necessary for lung leukocyte recruitment in a murine model of allergic inflammation, and platelet-leukocyte aggregates are formed in circulating blood of patients with asthma after allergen exposure [141]. It has been reported that the $P2Y_{12}$ receptor is required for proinflammatory actions of the stable abundant mediator LTE4 in allergic asthma and has been suggested to be a novel potential therapeutic target for asthma [142]. The specific contribution of the platelet P2 receptors in this disease warrants further studies as the $P2Y_1$ receptor has also been proposed to have a role in airways inflammation [143].

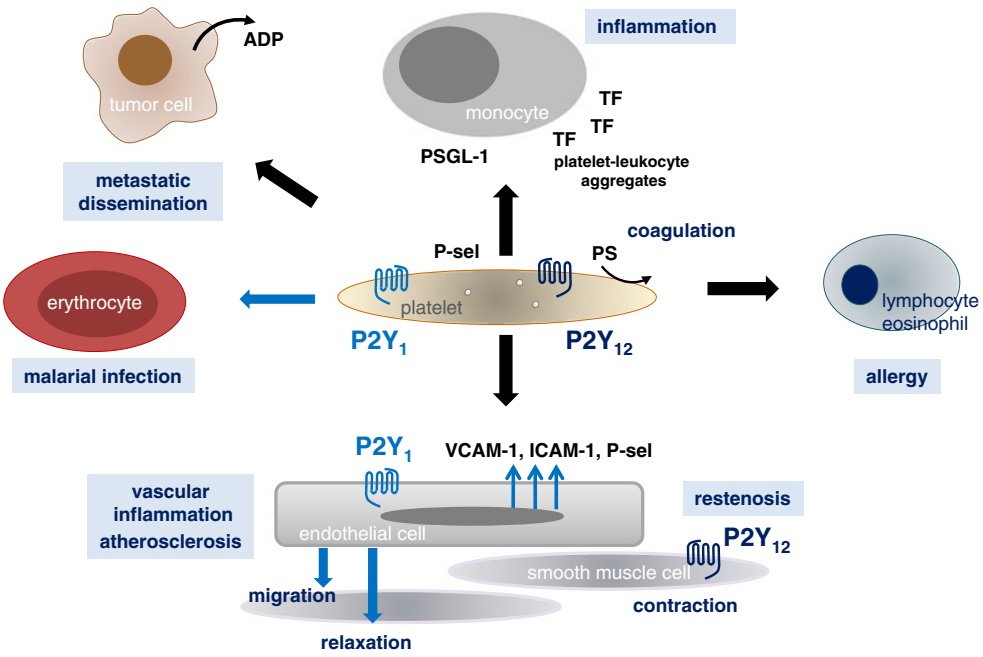

Fig. 2 Role of $P2Y_1$ and $P2Y_{12}$ receptors beyond haemostasis

Platelets are strongly involved in cancer and especially in metastatic dissemination [144, 145] through complex mechanisms including the ability to mask tumour cells to the immune system and to contribute to tumoural angiogenesis. In particular, tumour cells release nucleotides which, among other stimuli, activate platelets. Here too, animal models and clinical trials should be undertaken to evaluate existing P2 receptor targeting drugs as adjuvant anticancer therapies.

Finally, platelets are also involved in innate immunity [146, 147]. In particular, platelets play a critical role in the pathogenesis of malarial infections. However, recent work suggests that they are also involved in protection against this infection and that killing of parasite-infected erythrocytes was dependent on platelet activation via the $P2Y_1$ receptor, but not $P2Y_{12}$ [148]. Whether the platelet P2 receptors display specific roles in diseases where platelets are involved requires further studies.

Conclusions

All the effects of nucleotides on platelets appear to lay on three distinct receptors, namely two ADP receptors $P2Y_1$ and $P2Y_{12}$, and one ATP receptor $P2X_1$. They mediate selective transduction pathways responsible for the different function of platelets. Each of these receptors plays also a role in thrombosis. The $P2Y_{12}$ receptor is an established target for antithrombotic drugs. The challenge for the future will be to determine whether the two other nucleotide receptors $P2Y_1$ and $P2X_1$ constitute solely or in combination with $P2Y_{12}$, attractive target for new antithrombotic drugs. Roles of blood platelets beyond haemostasis also involve the platelet P2 receptors, which should now be studied in more details.

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