Purinergic Signaling and Vascular Cell Proliferation and Death

Geoffrey Burnstock

Abstract—Evidence for the role of purinergic signaling (via P1 and P2Y receptors) in the proliferation of vascular smooth muscle and endothelial cells is reviewed. The involvement of the mitogen-activated protein kinase second-messenger cascade in this action is clearly implicated, although details of the precise intracellular pathways involved still remain to be determined. Synergistic actions of purines and pyrimidines with growth factors occur in promoting cell proliferation. Interaction between purinergic signaling for vascular cell proliferation and cell death mediated by P2X7 receptors is discussed. There is evidence of the release of ATP from endothelial cells, platelets, and sympathetic nerves as well as from damaged cells in atherosclerosis, hypertension, restenosis, and ischemia; furthermore, there is evidence that vascular smooth muscle and endothelial cells proliferate in these pathological conditions. Thus, the involvement of ATP and its breakdown product, adenosine, is implicated; it is hoped that with the development of selective P1 (A2) and P2Y receptor agonists and antagonists, new therapeutic strategies will be explored. (Arterioscler Thromb Vasc Biol. 2002;22:364-373.)

Key Words: ATP ■ apoptosis ■ purinergic signaling ■ proliferation ■ atherosclerosis

The roles of nucleotides and nucleosides as extracellular signaling molecules are now well established.1,2 P1 receptors for adenosine, of which four subtypes (A1, A2A, A2B, and A3) have been identified, have been distinguished from P2 receptors for ATP/ADP/UTP,3 and P2 receptors have been divided into P2X ligand-gated ion channel and P2Y G protein–coupled receptor families. Seven subtypes of P2X receptors and 6 subtypes of P2Y receptors have been cloned and characterized.4 The majority of studies involving purinergic signaling have been concerned with short-term events, such as neurotransmission or secretion. However, there is growing interest in the long-term trophic actions of extracellular nucleotides and nucleosides on cell growth, proliferation, and death.5–9

In the vascular system, short-term purinergic signaling events associated with the control of vascular tone by ATP released from nerves and endothelial cells have been clearly demonstrated.10–15 However, the migration, proliferation, and death of vascular smooth muscle and endothelial cells play an important role in the development of intimal thickening during arterial diseases, such as atherosclerosis and restenosis after angioplasty, and in the growth of new vessels that takes place during wound healing and in tumors.16–18 Studies indicating that ATP, ADP, UTP, and adenosine play pivotal signaling roles in these long-term events will be discussed in the present review.19–21

Purines and Smooth Muscle Cell Proliferation

Adenosine (P1) Receptors

An early study reported that adenosine produces changes in cAMP and DNA synthesis in cultured arterial smooth muscle cells and suggested that this might result in the regulation of cell proliferation.22 The authors speculated that adenosine could be one of several regulatory factors in the development of atherosclerosis and might also regulate the release of a smooth muscle mitogen, platelet-derived growth factor (PDGF), from platelets. There is now good evidence that adenosine, an ectoenzymatic breakdown product of ATP, does regulate smooth muscle cell proliferation, but as will be discussed, its properties differ from those for ATP and ADP.

Adenosine inhibits vascular smooth muscle cell proliferation by A2 receptor activation via the elevation of cAMP,22,23 and a selective A2 receptor agonist, 2-octynyladenosine, reduced neointimal thickening in a rat femoral artery injury model.24 Indeed, cAMP is a known pathway involved in smooth muscle cell growth arrest and in the maintenance of the contractile phenotype.25 The possibility that a defect in local adenosine production within the vessel wall could contribute to vascular thickening and neointimal formation was explored,23 and it was proposed that adenosine inhibits the growth of human aortic smooth muscle cells via A2B receptors.26 Later, it was demonstrated that adenosine, acting through A3 receptors, inhibits collagen synthesis by smooth muscle cells, and it was suggested that drugs that modulate adenosine levels may protect against vaso-occlusive disorders by attenuating extracellular matrix synthesis and the cellular hypertrophy of smooth muscle cells.27 It seems surprising that this role is not shared by A2A adenosine receptors, which are coupled to the elevation of cAMP and are expressed on vascular smooth muscle, but it may be that the levels of expression of the A2A receptors are low relative to A2B...
receptors in those smooth muscle cells in which the trophic effects of adenosine were investigated. Other inhibitory pathways also exist, inasmuch as sodium butyrate (a small, naturally occurring molecule with demonstrated activity on cell growth and differentiation) and its more stable in vivo analogue, tributyrin, are potent DNA synthesis and cell proliferation inhibitors of vascular smooth muscle by a mechanism not mediated by an elevation of cAMP.

P2 Receptors

ATP and ADP stimulate DNA synthesis and cell proliferation of cultured porcine artery vascular smooth muscle cells, an action that was shown to be mediated by P2Y receptors. It was speculated that this mechanism was involved in the regulation of vascular smooth muscle cell proliferation during embryonic and early postnatal development, after injury, and in arteriosclerosis. It was further suggested that the ATP released from endothelial cells causes not only autocrine mitogenic stimulation of the endothelial cells themselves but also paracrine stimulation of the smooth muscle cells that migrate to the intima after injury. The mitogenic actions of ATP (but not those produced by adenosine) were reduced by indomethacin (indicating that part of the mechanism involves ATP-induced prostaglandin synthesis, as first proposed by Needleman et al., 1974, by downregulation of protein kinase C [PKC], by long-term exposure to phorbol dibutyrate, and by the PKC inhibitor staurosporine). These results suggest that there is a dual mechanism involved in the trophic mitogenic actions of ATP and ADP, namely, arachidonic acid metabolism and PKC.

Exogenous ATP also appears to induce a limited cell cycle progression in arterial smooth muscle cells. It was shown that stimulation of cultured, quiescent, smooth muscle cells induced chronological activation not only of immediate-early fos mRNA but also of delayed-early cell cycle–dependent genes. In contrast, ATP did not increase late G1 gene mRNA. An increase in c-fos mRNA was also induced by ADP but not by AMP or adenosine. The fact that 2-methylthio-ATP but not ATP (but not those produced by adenosine) were reduced by

ADP contributes significantly in synergy with the peptide growth factors PDGF, epidermal growth factor, and transforming growth factor-β, to the platelet-induced proliferation of vascular smooth muscle. The mitogenic effect of ATP on vascular smooth muscle cells was synergistic with other mitogens, including insulin and insulin-like growth factor-1. It is interesting in this respect that amiloride, which is known to inhibit the actions of several growth factors, also inhibited ATP-induced mitogenesis. ATP has also been shown to be a mitogen for human vascular smooth muscle cells. The molecular mechanisms underlying ATP and insulin synergistic stimulation of coronary artery smooth muscle proliferation have been examined. ATP and insulin individually stimulated DNA synthesis 4- and 2-fold, respectively; however, they acted synergistically to stimulate a 17-fold increase. A similar synergistic stimulation of extracellular signal–regulated kinase (ERK) was demonstrated, whereas ATP dramatically reduced the insulin-stimulated AKT (also known as kinase B) activation. The authors concluded that their results were consistent with the relieving (by ATP) of insulin-induced AKT-dependent inhibitory effect on the ERK signaling pathway, leading to synergistic stimulation of coronary artery smooth muscle cell proliferation.

In a study of the mechanisms involved in ATP-induced proliferation of vascular smooth muscle cells, it was shown that P2Y receptor activation of smooth muscle was coupled to a pertussis toxin–insensitive Gi protein, triggering phosphoinositide hydrolysis and subsequent activation of PKC, Raf 1, and MAPK. Both 42- and 44-kDa MAPKs were activated, and tyrosine was phosphorylated. Western blot analysis, with the use of PKC isozyme–specific antibodies, indicated that the vascular smooth muscle cells express PKC-α and PKC-δ. P2Y receptor stimulation also caused synthesis of c-fos and c-myc mRNAs; Reactive blue 2 (a P2Y-selective antagonist) and staurosporine blocked this effect. A later study presented evidence indicating that ATP-stimulated vascular smooth muscle cell proliferation requires independent ERK and phosphatidylinositol 3-kinase–signaling pathways. Tyrophostin, a specific inhibitor of tyrosine kinase, inhibited DNA synthesis, Fox-protein expression, and cell proliferation of vascular smooth muscle cells but not ATP-induced Ca2+.
influx or inositol phosphate production.\textsuperscript{54} Stimulation of cultured aortic myocytes with P2Y agonists produced an increase in the amount of membrane-bound small GTPases of the RhoA family and stimulated actin cytoskeleton organization.\textsuperscript{65} Cell proliferation and migration are also known to be induced by RhoA activation.\textsuperscript{55,56}

There are 2 phenotypes of smooth muscle: the contractile phenotype and the synthetic (proliferative) phenotype.\textsuperscript{57} In a study of cultures expressing these 2 phenotypes using quantitative reverse transcription–polymerase chain reaction, it was shown that P2X\textsubscript{k} receptors were strongly expressed in the contractile phenotype. In the synthetic phenotype, the mitogenic P2Y\textsubscript{1} and P2Y\textsubscript{2} receptor transcripts were upregulated 342- and 8-fold, respectively, whereas the contractile P2X\textsubscript{k} receptor was totally downregulated, and the P2Y\textsubscript{2} and P2Y\textsubscript{6} receptors were unchanged.\textsuperscript{42} Furthermore, MAPK kinase–dependent growth factor induced the upregulation of P2Y\textsubscript{2} receptors in vascular smooth muscle cells, which the authors suggested may be of importance in atherosclerosis and neointimal formation after balloon angioplasty.\textsuperscript{43} In a later study, this group showed that inflammatory cytokines, known to be released in atherosclerosis, upregulated P2Y\textsubscript{2} receptors through PKC and cyclooxygenase (but not cAMP), ERK-1 and -2, or P38-dependent pathways.\textsuperscript{58} When the endothelial cells of the central ear artery were injured \(\approx 2\) times, the smooth muscle cells of the media migrated into the intima and proliferated there between 1 and 3 weeks after the last injury, despite restoration of the endothelium.\textsuperscript{59} In rabbits pretreated with diprydamole, an adenosine-uptake inhibitor, proliferation was limited.

**Purines and Vascular Endothelial Cell Proliferation**

**Adenosine (P1) Receptors**

Adenosine has been claimed to be an angiogenesis factor in chick chorioallantoic membrane and embryos.\textsuperscript{60,61} In other early studies, long-term administration of adenosine was reported to induce capillary proliferation in the heart, although it was recognized that this effect might be secondary to mechanical factors resulting from an increased blood flow stimulating capillary growth.\textsuperscript{62} We know from later studies that ATP is released from endothelial cells during the shear stress produced by changes in blood flow\textsuperscript{54,48,63,64} and that there is an ectoenzymatic breakdown of ATP to adenosine. Electrical stimulation of skeletal muscle also resulted in capillary proliferation, as did long-term administration of adenosine.\textsuperscript{62} Long-term local application of adenosine induces an increase of capillary diameter in skeletal muscle of anesthetized rabbits.\textsuperscript{65} Adenosine has also been shown to induce dose-dependent proliferation of endothelial cells obtained from the aorta,\textsuperscript{66} from coronary vessels,\textsuperscript{67} and from human umbilical veins,\textsuperscript{68} and it has been shown to stimulate canine retinal microvascular endothelial cell migration and tube formation.\textsuperscript{69}

The action of adenosine in mediating endothelial cell proliferation is mediated by A\textsubscript{2A} and A\textsubscript{2B} receptors, although an action independent of adenosine receptors has also been suggested. It has been claimed by Sexl et al\textsuperscript{70} that the adenosine receptor mediating endothelial cell proliferation of the human umbilical vein is an A\textsubscript{2A} subtype acting via a mechanism that is independent of G\textsubscript{i} and G\textsubscript{i}. This group went on to show that stimulation of the A\textsubscript{2A} receptor activates MAPK on these endothelial cells.\textsuperscript{71} An investigation was carried out involving adenosine stimulation of DNA synthesis in endothelial cells by measuring [H]thymidine incorporation in cultures derived from human umbilical veins.\textsuperscript{72} The authors concluded that the results suggest that Na\textsuperscript{+}/H\textsuperscript{+} exchange and phospholipase A\textsubscript{2} are involved in adenosine-induced DNA synthesis independently of adenosine receptor, protein kinase A, or PKC activation. An 8-phenyltheophylline–resistant mitogenic action of adenosine, which was not mimicked by A\textsubscript{1}- and A\textsubscript{2}-selective agonists, was also described in bovine aortic endothelial cells.\textsuperscript{66} An intracellular action of adenosine is possible.

Some of the mitogenic effects of adenosine are mediated via the modulation of vascular endothelial growth factor (VEGF) signaling via A\textsubscript{2A} and A\textsubscript{2B} receptors. Adenosine mediates growth factor expression through the A\textsubscript{2B} receptor in human retinal endothelial cells.\textsuperscript{73} A\textsubscript{2B} activation results in sequential expression of VEGF mRNA, supporting a role for adenosine in initiating the autocrine production of a cascade of growth factors that facilitate new blood vessel formation. The addition of an antisense oligonucleotide complementary to the A\textsubscript{2B} receptor mRNA inhibited VEGF production. Augmentation by adenosine of the expression of VEGF has been described in cerebral\textsuperscript{74} and retinal\textsuperscript{75} microvascular endothelial cells. In the retinal endothelial cells, this involved A\textsubscript{2A} receptor activation of the cAMP-dependent protein kinase A pathway.\textsuperscript{76} The initial decline in mRNA of receptors for VEGF and of VEGF binding sites during hypoxia was also shown to be antagonized by A\textsubscript{2} receptor blockade.\textsuperscript{76} In the most recent study from Grant et al,\textsuperscript{77} the selective A\textsubscript{2B} receptor antagonists enprofylline and 3-isobuty1-8-pyrrolidinoxanthaline inhibited 5’-(N-ethylcarboxamido)-adenosine (NECA)–stimulated proliferation of human retinal endothelial cells, ERK activation, cell migration, and capillary tube formation. The authors suggested that this may provide a novel approach to the treatment of diseases associated with aberrant neovascularization, such as diabetic retinopathy and the retinopathy of prematurity.

Hypoxia is a potent stimulus to vascular growth and adenosine, and the pyridine metabolite nicotinamide mimics these effects.\textsuperscript{78,79} The P1 (adenosine) antagonist 8-phenyltheophylline prevented stimulation of the proliferation of bovine aortic and coronary vascular endothelial cells caused by hypoxia-conditioned medium or adenosine.\textsuperscript{78} The proliferative response of endothelial cells to adenosine has been shown to depend on an increase in cAMP: consistent with actions of adenosine at A\textsubscript{2} receptors, pretreatment of endothelial cells with pertussis toxin blocked adenosine-induced proliferation, indicating that a G protein might be involved in the mechanism.\textsuperscript{80}

**P2 Receptors**

ADP was shown to be one of several agonists that induced cultured endothelial cell migration and proliferation.\textsuperscript{81} Angiogenesis (or neovascularization) begins with the migration of endothelial cells, originating from capillaries, into the tissue being vascularized. ADP and, to a lesser extent, adenosine and adene showed strong chemotactic activity and were postulated to be angiogenesis factors in vivo.\textsuperscript{82}
Adenine nucleotides were shown to have a mitogenic action on aortic endothelial cells, probably via P2Y receptors; adenosine, inosine, and hypoxanthine also had mitogenic actions, but apparently they were not via A₁ or A₂ purinoceptor subtypes. ATP has also been shown to produce proliferation of cultured bovine corneal endothelial cells. The source of the purines involved in these trophic actions is largely from the endothelial cells, suggesting an autocrine mechanism. ADP released from aggregating platelets may also play a role.

When glomerular capillary or aortic endothelial cells were cultured in polypropylene hollow fibers perfused for 9 days, the endothelial cells formed adherent confluent monolayers with chronic flow, simulating shear stress, but not without flow. Furthermore, the aortic, but not capillary, endothelial cells aligned themselves in the direction of flow. Since (as has been described earlier) ATP is released from endothelial cells by shear stress and because ATP can induce cell migration and proliferation, an involvement of ATP in these trophic changes is indicated. Similarly, mechanical scratching of cell monolayers of bovine pulmonary arterial endothelial cell cultures (which would lead to the release of ATP) induces surviving cells near the wound edge to move and proliferate. Stretch-induced changes in endothelial cell shape and changes produced by hypoxic stress may be mediated by the ATP (and/or adenosine after ectoenzymatic breakdown) released from endothelial cells under both these conditions.

There is evidence at present for P2Y₁, P2Y₃, and P2Y₄ receptor subtypes on endothelial cells mediating the release of NO, endothelium-derived hyperpolarizing factor, and prostanoids; there is also recent evidence for the presence of P2X₂, P2X₃, and P2X₄ subtypes in the endothelium (Figure 1). The functions of the P2X receptors are not yet clear, although they appear to be involved in cell adhesion and gap junction formation. Less is known about which P2 receptor subtypes are involved in the mitogenic actions of nucleotides or, indeed, about the mechanisms underlying their effects.

In a study of the EAhy 926 endothelial cell line, it has been shown that ATP and UTP activate the 42-kDa isoform of MAPK and that this activation is regulated by PKC, using both calcium-dependent and -independent mechanisms, but that G protein is not involved. Regulation of rat brain capillary endothelial cells via P2Y receptors (probably P2Y₂ and/or P2Y₄, since UTP was equipotent with ATP) has been shown to be coupled to Ca²⁺, phospholipase C (PLC), and MAPK. In cultured endothelial cells from guinea pig cardiac vasculature, UTP and VEGF were mitogenic and chemotactic factors. The possibility that UTP was acting indirectly via VEGF was not examined.

Activation of kinases (including the p42/44 MAPK and c-Jun N-terminal kinase [JNK]) may underlie the sustained effects of ATP and UTP on endothelial cells and smooth muscle, such as increased cell proliferation; by use of the EAhy 926 endothelial cell line, UTP and ATP, but not UDP, inhibited tumor necrosis factor-α (TNFα)–stimulated stress-activated protein kinase activity.

**Vascular Cell Death**

There is increasing evidence that cell proliferation and programmed cell death (apoptosis) are linked. For example, VEGF turns on cell proliferation but inhibits apoptosis. Distinct signal transduction cascades, composed of at least 3 protein kinases, mediate cell proliferation and differentiation, growth arrest, and apoptosis. In diseases such as carcinogenesis, degenerative disorders, and ischemia/reperfusion injury, there is an imbalance between cell division and cell death.
Interactions between purinergic signaling for proliferation and cell death also occur. An example is the turnover of keratinocytes in the squamous epithelium of the epidermis, where there is a continuous progression from cell proliferation in cells at the base of the stratum spinosum (labeled with P2Y$_1$ receptors) to differentiating keratinocytes (labeled with P2X$_7$ receptors), which gradually flatten as they reach the stratum corneum, where they become apoptotic (labeled with differentiation (P2X$_5$ receptor surface. A similar relationship between proliferation and cell death (P2X$_7$-labeled cells) has been shown during the inflammatory response associated with necrosis.

Apoptosis eliminates cells without the attendant risks of an acute inflammatory response associated with necrosis. However, only a limited number of studies have been carried out to examine the possible roles of purines in the development of the pathology of vessels.

The growth of new blood vessels takes place in pathological events such as tumor growth, wound healing, psoriasis, and the ischemic retinopathies that occur in diabetes and sickle cell disease. In the adult, the development of new blood vessels, or neovascularization, occurs by budding from existing blood vessels and is referred to as angiogenesis (as distinct from vasculogenesis, which occurs in embryonic development by vessel formation from mesenchyme precursors or angioblasts). Peptide growth factors such as fibroblast growth factor, transforming growth factor-$
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\alpha$, and VEGF are clearly involved in angiogenesis, but as we have seen earlier in the present review, purines and pyrimidines also contribute to this process. In rheumatoid arthritis, new capillary blood vessels invade the joint and destroy the cartilage. In diabetes, new capillaries in the retina invade the vitreous body, bleed, and cause blindness, and tumor growth and metastasis are angiogenesis dependent. Anginal patients treated chronically with dipyridamole to increase adenosine levels showed an increase in coronary angiogenesis, and dipyridamole has also been used for the prevention of stroke. The former action may involve a preferential effect of adenosine on endothelial cells, since smooth muscle proliferation was inhibited in rabbits pretreated with dipyridamole.

Apoptotic cell death is recognized to occur in a number of vascular diseases, including atherosclerosis, restenosis, and hypertension. Vascular endothelial cells are continuously exposed to variations in blood flow, which plays an important role in vessel growth or regression and in the local development of atherosclerosis. The shear stress that occurs during changes in blood flow leads to a substantial release of ATP (and UTP) from endothelial cells, and these purines might mediate alterations in the balance between proliferation and apoptosis. Occupation of P2X$_7$ receptors leads to the production of proinflammatory cytokines, and TNF-$
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\alpha$ markedly increases endothelial cell apoptosis via the activation of caspase 3.

Atherosclerotic damage results in the disappearance of endothelium-dependent responses to ATP, whereas the relaxing action of smooth muscle is unimpaired. The release of ATP from endothelial cells has been claimed to be impaired in atherosclerotic rat caudal arteries. Long-term supplementation with a high cholesterol diet decreases the release of ATP from the caudal artery of aged rats; there was a significant positive correlation between the unsaturation index of arterial fatty acids and the amount of ATP released and an inverse correlation between the amount of ATP released and blood pressure. Although the roles of endothelial cells and smooth muscle in the pathogenesis of atherosclerosis are still not known precisely, it is known that smooth muscle cells migrate from the media to the intima, where they change to the proliferative phenotype, which leads to thickening of the intima.

In restenosis following balloon angioplasty, there is a peak in the proliferation and apoptosis of vascular smooth muscle cells at 14 days. The first balloon inflation during coronary angioplasty is a preconditioning stimulus leading to a decrease in ischemia during later inflations; intracoronary adenosine administration before coronary angioplasty modi-
fies the preconditioning effect of the first inflation. Further studies show that adenosine preconditions human myocardium against ischemia in vivo. The genetic defects underlying hypertension are unknown, but an increase in sympathetic nerve activity is well established, and there is an associated hyperplasia and hypertrophy of arterial walls. An increased release of ATP as a cotransmitter with NA in sympathetic nerves is likely to occur in SHR and may play a role in the trophic changes in the vessel wall. Also, sympathetic neurons innervating the vasculature are dependent on nerve growth factor (NGF) in development, and an increase in NGF gene expression and protein has been described in SHR. An ATP agonist, was shown to increase NGF secretion by vascular smooth muscle cells in SHR. In cultured aortic smooth muscle cells from SHR, responses to UTP and ATP were predominantly via P2Y4 receptors, and Harper et al have presented evidence to suggest that these receptors are coupled to mitogenesis via p42/p44 MAPK.

Pericytes partially envelop endothelial cells in most capillaries and have been implicated in capillary vasculogenesis and wound repair. In addition, pericytes participate in the negative regulation of endothelial cell proliferation. Along with its stimulating effect on bovine retinal capillary endothelial cells, adenosine has been shown to have an inhibitory effect on retinal pericytes, and it has been hypothesized that this dual function plays a role in the pathological neovascularization process that takes place in diabetes. Diabetic microangiopathy has been implicated as a fundamental feature of the pathological complications of diabetes, including retinopathy, neuropathy, and foot ulceration. Ischemia and hypoxia lead to a substantial release of ATP from endothelial cells, and adenosine is released from hypoxic heart and skeletal muscle. Adenosine has several cardiovascular protective effects in addition to vasodilation, including the promotion of endothelial cell proliferation and an increased expression of VEGF mRNA. Adenosine also appears to play an important role in preconditioning.

When venous segments are transplanted into the arterial tree, the vein smooth muscle proliferates, and within ~2 weeks, it resembles an artery and vice versa. It is possible that ATP (and, subsequently, adenosine), which is released from the damaged cells during the operation and released from endothelial cells in response to the distension produced by increased blood pressure, is involved in the plasticity of change in vessel structure. Endothelial cells spread in response to localized injuries, and ongoing localized injury leads to the release of purines, which might be involved in the repair process. High-velocity bolus doses of intracoronary adenosine have been used successfully as a technique to overcome the slow or “no-reflow” problem that complicates ~10% to 15% of cases of catheter-based revascularization of degenerated saphenous vein bypass grafts. However, the mechanism involved seems likely to be largely the vasodilator actions of adenosine rather than trophic actions producing increased proliferation.

ATP is released from endothelial cells during hypoxia and, together with its breakdown product adenosine, produces

![Figure 2. Schematic diagram of long-term (trophic) actions of purines released from nerves, platelets, and endothelial cells (which also release UTP) acting on P2 receptors to stimulate or inhibit cell proliferation. ATP released as a cotransmitter from sympathetic nerves and sensory-motor nerves (during axon reflex activity) stimulates smooth muscle cell proliferation via P2Y2 and/or P2Y4 receptors via a MAPK cascade, whereas adenosine resulting from enzymatic breakdown of ATP acts on P1 (A2) receptors to inhibit cell proliferation (via elevation of cAMP). ATP and UTP released from endothelial cells stimulate endothelial and smooth muscle cell proliferation via P2Y6 and P2Y4 receptors. Adenosine resulting from ATP breakdown acts on P1 (A2) receptors to stimulate endothelial cell proliferation and regulate the release of PDGF from platelets.](image)
Conclusions

A summary of the main trophic actions of purine nucleosides and nucleotides and of vascular cell proliferation is shown in Figure 2. There is compelling evidence that there is regulation of vascular smooth muscle and endothelial cell proliferation by P1 (A₂) and P₂Y₁ and P₂Y₂ receptors that acts through MAPK pathways. However, there is still much to learn about the precise pathways involved; e.g., there is only preliminary evidence for the involvement of ERKs and c-Jun N-terminal kinases, and other pathways may also be involved.143,144 (Figure 3). Furthermore, there has been no exploration to determine whether the more recently cloned P₂Y receptors, P₂Y₁₁, P₂Y₁₂, and P₂Y₁₃,147–149 mediate the MAPK pathways that might be involved in vascular cell proliferation. Direct evidence for the involvement of these purinergic mechanisms in atherosclerosis, hypertension, and restenosis is awaited.

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References


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Trophic Purinergic Signaling in Blood Vessels


