Published in final edited form as:

Curr Opin Nephrol Hypertens. 2012 March ; 21(2): 122–127. doi:10.1097/MNH.0b013e3283503ce9.

Novel tyrosine kinase signaling pathways: Implications in vascular remodeling

Sri N. Batchu and Vyacheslav A. Korshunov*

Department of Medicine, Aab Cardiovascular Research Institute, University of Rochester School of Medicine and Dentistry, Rochester, NY USA

Abstract

The purpose of the review is to summarize recent advances in molecular mechanisms by which five classes of receptor tyrosine kinases (RTKs) contribute to vascular remodeling.

Recent findings have expanded our knowledge regarding RTK regulation. In particular, G-protein coupled receptors, mineralocorticoid receptors, mechanical and oxidative stresses transactivate RTKs. These receptors are highly interactive with many downstream targets (including tyrosine kinases and other RTKs) and function as key regulatory nodes in a dynamic signaling network. Interactions between vascular and non-vascular (immune and neuronal) cells are controlled by RTKs in vascular remodeling. Inhibition of RTKs could be an advantageous therapeutic strategy for vascular disorders.

In summary, RTK-dependent signaling is important for regulation of key functions during vascular remodeling. However, current challenges are related to integration of the data on multiple RTKs in vascular pathology.

Keywords

receptor tyrosine kinase; signal transduction; vascular remodeling

Introduction

Tyrosine kinases are enzymes that catalyze a transfer of a phosphate group from ATP to a distinct set of tyrosine residues on protein substrates. These phosphorylated tyrosines act as docking sites that harbour and activate proteins that are involved in receptor tyrosine kinase (RTK)-mediated signal transduction. RTKs are the second major type of cell surface receptor[1]. The molecular structure of all RTKs contains extracellular (N-terminal) and cytoplasmic (C-terminal) domains that are connected by a single trans-membrane helix. The N-terminal is a ligand-binding region, while the C-terminal has tyrosine kinase function. There are 58 RTKs identified in human, which are divided into 20 different classes based on the domain sequences[2]. RTKs are known to play a critical role during developmental processes such as cell growth, differentiation, adhesion, motility and regulation of cell death[1]. Over-activation of RTKs is responsible for several pathological conditions such as cancer, chronic immune and cardiovascular disorders. RTKs are highly regulated during

*To whom correspondence should be addressed: Vyacheslav "Slava" A. Korshunov, Aab Cardiovascular Research Institute, 601 Elmwood Avenue, Box CVRI, Rochester, NY 14642, USA, Phone: 585-276-9793, Fax: 585-276-9830, Slava_Korshunov@URMC.rochester.edu.

Disclosures:

None

Disclosure of funding: Dr. Korshunov's laboratory is supported by National Institutes of Health grant HL105623.

vascular remodeling, a process that can be described by changes in blood vessel wall mass and size. For example, vascular smooth muscle cells (VSMCs) growth response is mediated by RTK-dependent signals[3]. However, mechanisms of activation of RTKs are complex and unique for each RTK[2]. In addition, reactive oxygen species (ROS) inhibit protein tyrosine phosphatases, enzymes that are responsible for inactivation of RTKs via dephosphorylation. It is also important to note that G-protein coupled receptors (GPCRs) have bidirectional interactions with RTKs that modulate downstream signals and cell functions[4]. These features of RTK regulation are particularly important for understanding mechanisms of vascular remodeling. Inhibition of RTKs lead to development of a new generation of therapeutic agents for cancer treatment[2]. In this review we summarized recent advances in our understanding involvement of five classes of RTKs in mechanisms of vascular remodeling (Fig. 1).

ErbB receptor family

Epidermal growth factor receptor (EGFR or ErbB1) is a member of the ErbB receptor tyrosine kinase subfamily (Fig. 1). Two repeats of L- and cysteine-rich domain are contained in the extracellular region of ErbB receptors, which are activated by various ligands including epidermal growth factor (EGF), transforming growth factor (TGF), amphiregulin, and heparin-binding EGF (HB-EGF)[5]. EGFR activation leads to recruitment of Grb2/Shc/Sos complexes and activation of extracellular-signal-regulated kinase 1/2 (ERK1/2) that increase VSMC proliferation[6]. A targeted deletion of EGFR in cultured VSMCs enhanced cell death, reduced ERK1/2 activation by G-protein-coupled receptors or ROS and disturbed cellular matrix homeostasis[7]. However, a recent study[8]* suggested that 15(S)-hydroxyeicosatetraenoic acid phosphorylates EGFR and activates the Src/Jak2/STAT3 pathway resulting in increased monocyte chemoattractant protein-1 (MCP-1) expression and VSMC migration. This ROS-dependent mechanism of EGFR activation affects neointima formation, a type of vascular remodeling in response to injury. In addition, EGFR activity is also required for aldosterone (Aldo)/salt-induced phenylephrine- or angiotensin II (Ang II)-mediated vasoconstriction and not for vessel wall thickening[9]**. Recently it has been demonstrated that inhibition of metalloprotease 17 (ADAM17) significantly reduced EGFR phosphorylation and VSMC growth[10]**. Interestingly, maintenance of caveolin-1 (Cav-1) at the cell membrane has been shown to inhibit AngII-mediated activation of EGFR and ADAM17 release in vascular cells[11]**. Thus, activation of EGFR is regulated by GPCR and oxidative stress that controls vascular cell functions (proliferation, inflammation and vasoconstriction) via ERK1/2 and STAT3 pathways and contributes to vascular remodeling (Fig. 2).

Insulin-like growth factor receptor family

Insulin-like growth factor receptor 1 (IGF1R) is a transmembrane receptor which mediates a broad spectrum of events from cell growth to cellular metabolism[12]. These effects of IGF1R are mediated by binding of a ligand to the two extracellular α -subunits and two intracellular β -subunits (Fig. 1). Insulin like growth factor (IGF) and insulin are known to interact with IGF1R[13]. It has been demonstrated that IGF1R mediates vascular remodeling by stimulating VSMCs proliferation, migration and survival[13–16]. Mechanical stretch augmented insulin-induced cell proliferation via IGF1R activation and Src/EGFR-mediated activation of ERK and Akt pathways[13]. Importantly, IGF1R was also increased in hypertensive rats, suggesting its pathophysiological role in vascular remodeling in hypertension. Mechanical stretch up-regulates early growth response-1 (Egr-1) transcriptional factor which is responsible for IGF1R activation in VSMCs, explaining 50% of neointima formation in a vein graft mouse model[16]*. Finally, IGF1R trans-activation is necessary for VSMC cytoskeletal reorganization in response to AngII by PKC/Src-mediated cortactin

phosphorylation[17]. However, a PI3K/Akt pathway wasn't involved in IGF1R-mediated cytoskeletal remodeling in VSMCs. Thus, IGF1R is trans-activated by AngII or mechanical stretch via up-regulation of Egr-1 that mediates vascular remodeling (Fig. 2).

Platelet-derived growth factor receptor family

Signaling through platelet-derived growth factor receptor (PDGFR) is one of the well recognized pathway that mediates vascular remodeling. There are two types of PDGFR (α and β) that have Ig like domains on the extracellular region (Fig. 1). PDGFR- α is known to bind to all possible PDGF ligands (PDGF-A, PDGF-B, PDGF-C and PDGF-D in either homodimer or heterodimer forms), while PDGFR- β isoform binds to PDGF-AB and PDGF-BB only[18,19]. Mechanical or shear stress activates both isoforms of PDGFR and initiates vascular remodeling by modulating VSMC growth[6,19,20]. High levels of AngII trans-activate PDGFR- β through AngII receptor type 1 (ATR1) and ROS production in VSMCs[21,22]. Stimulation of PDGF-PDGFR- α/β signaling initiates and progresses vascular remodeling via activation of Akt and ERK1/2 pathways[18]. A monomer of PDGFR- β heterodimerizes with a monomer of fibroblast growth factor receptor 1 (FGFR1) that leads to a change in VSMC phenotype from contractile to a synthetic[23]. In addition, PDGFR- β also mediates vascular remodeling by trans-activation of EGFR via stimulating ADAM17 activity[24]**. A recent study[25] showed that endothelial and smooth muscle cell-derived neuropilin-like protein (ESND) mediates ubiquitination of PDGFR- β in VSMCs and is critical for neointima formation. In summary, activation of PDGFR plays a critical role in the initiation and progression of vascular remodeling by interaction with multiple growth factor receptors (Fig. 2).

Vascular endothelial growth factor receptor family

Vascular endothelial growth factor receptors (VEGFRs) are very important in vascular biology[26]. There are five ligands (VEGF-A, VEGF-B, VEGF-C, VEGF-D and placenta growth factor (PlGF)) that activate three VEGFRs (Fig. 1). VEGFR-dependent signaling stimulates MAPKs, initiates angiogenesis, and regulates multiple vascular functions[26]. A recent study identified PlGF as a novel downstream target of Aldo in regulation of vascular remodeling[27]**. Authors reported a vascular-specific Aldo/mineralocorticoid receptor/PlGF/VEGFR-1 pathway that is involved in response to arterial injury. Studies in mice with low VEGF levels showed dysfunction of contractile smooth muscle cell phenotype and structural remodeling of the neuroeffector junction in resistance arteries[28]. Pang and colleagues[29] found that G-protein-coupled receptor kinase interacting protein-1 (GIT1) is critical for mediating VEGF-dependent pulmonary angiogenesis by modulating the PLC γ /ERK1/2 pathway in endothelial cells. In addition, a recent study[30] suggested that myeloid cell-derived VEGF controls angiogenesis and prevents fibrosis. Similarly, inhibition of VEGF-dependent signaling reduced arterial remodeling but provoked fibrogenesis in a model of pulmonary hypertension[31]. Finally, a functional VEGFR-1 on T cells has augmented the recruitment of lymphocytes to the vessel wall during neointima formation[32]**. In summary, these findings indicate that signal transduction through VEGFR affects several important functions and interactions between vascular, immune and neuronal cells that determine vascular remodeling (Fig. 2). However, VEGFRs are important for preventing tissue fibrosis. Thus, systems biology approaches may provide in depth details of cellular and molecular mechanisms of the VEGFR family[33].

TAM receptor family

TAM (Tyro3, Axl and Mertk) family of RTKs has two Ig and fibronectin III motifs on its N-terminal (Fig. 1). Two ligands activate the TAM receptors, growth arrest-specific protein 6 (Gas6) and Protein S. Gas6 has the highest affinity for Axl, while Protein S binds to Tyro3

and MerTK[34]. In the first report implicating the TAM family in response to vascular injury authors found that AngII and thrombin increased Axl expression in VSMCs *in vitro*[35]. The Gas6/Axl pathway activates PI3K/Akt that protects VSMCs from apoptosis[36]. Cellular microenvironment is important for regulation of VSMC functions by Axl[37]. In particular, high glucose increased ERK1/2-mediated migration via expression of higher molecular weight isoform of Axl (140kDa), while low glucose activates the PI3K/Akt/mTOR via the lower molecular weight isoform of Axl (114kDa) and increased VSMC survival[37]. Our group recently reported a novel ROS-mediated post-translational modification that explains Axl-dependent migration of VSMCs[38]*. Specifically, Axl interacts with glutathiolated non-muscle myosin heavy chain-IIB in response to ROS and increases migration during vascular remodeling. We found that a selective block of Axl signaling with small molecular inhibitors (R428 and R572; Rigel Pharmaceuticals) was effective in preventing induction of oxidative stress in VSMCs[39]*. Two recent reports confirm the effectiveness of R428 in animal models of tumorigenesis and obesity[40,41]*. Our unpublished findings support an important role for Axl-dependent signaling in vascular and immune cells in vascular remodeling (Gerloff and Korshunov, unpublished data). Another member of TAM family, MerTK, appeared to play a significant role in immune cell functions in atherosclerosis[42]. In particular, a clearance of apoptotic cells from advanced atherosclerotic lesions was reduced and resulted in increased necrotic plaques in MerTK/ApoE double knockout mice. However, genetic deletion of Gas6 had no effect on atherosclerotic plaque size and only affected plaque composition on ApoE knockout background[43]. A recent study showed that cleavage of the soluble form of MerTK is mediated by metalloproteinase ADAM17 in macrophages[44]*. The molecular mechanism of MerTK proteolysis requires activation of NADPH oxidase (Nox2) and PKC δ /p38 pathway. In summary, TAM family plays multiple roles in vascular remodeling. Further exploration of the TAM family functions in vascular and immune cells is particularly important for our understanding of vascular pathophysiology (Fig. 2).

Therapeutic potential of RTK inhibitors

Inhibition of RTKs has been a successful therapeutic strategy for cancer treatment[2]. However, specificity of the RTK inhibitors and the off-target effects are the major issues associated with these drugs. For example, inhibitors to VEGFR (vandetanib and telatinib) were effective in controlling tumour growth but lead to increases in blood pressure[45,46]*. The telatinib treatment caused rarefaction (reduction in capillary density) and changes in microvascular density are possible mechanisms for the increase in blood pressure[45]. A recent study[46]* suggested that a decreased constitutive NO production by eNOS and a decrease in conduit artery resting diameter may explain pro-hypertensive effects of vandetanib. Despite these side-effects the RTK inhibitors might be beneficial in cardiovascular treatment. For example, selective inhibition of Axl by R428 was effective in animal tumour models without obvious sideeffects[40]*. We recently found that R428 was effective in ligand-independent activation of Axl and limited ROS production in VSMCs[39]*. Nevertheless, understanding systems biology of RTKs in vascular pathophysiology will help us to develop more specific therapeutic agents.

Conclusions

RTKs are critical players in vascular biology and recent studies showed novel mechanisms of five classes of RTKs in vascular remodeling (Fig. 2). Activation of these receptors stimulates cell growth, migration and survival during vascular remodeling. Importantly, RTKs can be activated by ligand-dependent and ligand-independent mechanisms that include trans-activation by G protein coupled receptors, mineralocorticoid receptor and ROS. This is a particularly important feature of the RTKs' biology in vascular remodeling.

In addition, RTKs interact with many targets, including different classes of RTKs, that direct downstream signal transduction and determine cellular functions in the remodeled artery. It is now well appreciated that signaling pathways are not linear and linked into a very complex and dynamic network[2,33]. In fact, RTKs are proposed as key nodes in the signaling network that determines cellular functions (proliferation vs. migration vs. survival). RTKs also function in non-vascular cell types (immune and neuronal cells) that influence molecular mechanisms of vascular remodeling. Finally, RTK inhibitors are proven therapeutic agents in cancer but have to be carefully explored in cardiovascular disorders. Thus, RTK-dependent signaling is important for regulation of key functions during vascular remodeling. However, current challenges are related to integration of data on multiple RTKs in vascular pathology.

Acknowledgments

We would like to thank Dr. Elaine Smolock for critical reading of the manuscript. Dr. Korshunov is supported by National Institutes of Health grant HL105623.

References and recommended reading

Papers of particular interest, published with the annual period of review, have been highlighted as:

*, Of special interest

**, Of outstanding interest

1. Robinson DR, Wu YM, Lin SF. The protein tyrosine kinase family of the human genome. *Oncogene*. 2000; 19:5548–5557. [PubMed: 11114734]
2. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell*. 2010; 141:1117–1134. [PubMed: 20602996]
3. Berk BC. Vascular smooth muscle growth: autocrine growth mechanisms. *Physiol Rev*. 2001; 81:999–1030. [PubMed: 11427690]
4. Gavi S, Shumay E, Wang HY, Malbon CC. G-protein-coupled receptors and tyrosine kinases: crossroads in cell signaling and regulation. *Trends Endocrinol Metab*. 2006; 17:48–54. [PubMed: 16460957]
5. Jorissen RN, Walker F, Pouliot N, Garrett TP, Ward CW, Burgess AW. Epidermal growth factor receptor: mechanisms of activation and signalling. *Exp Cell Res*. 2003; 284:31–53. [PubMed: 12648464]
6. Birukov KG. Cyclic stretch, reactive oxygen species, and vascular remodeling. *Antioxid Redox Signal*. 2009; 11:1651–1667. [PubMed: 19186986]
7. Schreier B, Dohler M, Rabe S, Schneider B, Schwerdt G, Ruhs S, Sibilica M, Gotthardt M, Gekle M, Grossmann C. Consequences of epidermal growth factor receptor (ErbB1) loss for vascular smooth muscle cells from mice with targeted deletion of ErbB1. *Arterioscler Thromb Vasc Biol*. 2011; 31:1643–1652. [PubMed: 21512163]
- 8*. Singh NK, Wang D, Kundumani-Sridharan V, Van Quyen D, Niu J, Rao GN. 15-Lipoxygenase-1-enhanced Src-Janus kinase 2-signal transducer and activator of transcription 3 stimulation and monocyte chemoattractant protein-1 expression require redox-sensitive activation of epidermal growth factor receptor in vascular wall remodeling. *J Biol Chem*. 2011; 286:22478–22488. This paper shows that ROS-dependent 15(S)-hydroxyeicosatetraenoic acid phosphorylates EGFR and activates inflammation and migration of VSMCs during neointima formation. [PubMed: 21536676]
- 9**. Griol-Charhbil V, Fassot C, Messaoudi S, Perret C, Agrapart V, Jaisser F. Epidermal growth factor receptor mediates the vascular dysfunction but not the remodeling induced by aldosterone/salt. *Hypertension*. 2011; 57:238–244. This study demonstrates that aldosterone increases

vascular contractility and not arterial thickening via activation of EGFR-dependent signaling. [PubMed: 21199998]

- 10**. Takaguri A, Kimura K, Hinoki A, Bourne AM, Autieri MV, Eguchi S. A disintegrin and metalloprotease 17 mediates neointimal hyperplasia in vasculature. *Hypertension*. 2011; 57:841–845. This report shows that ADAM17 stimulates vascular growth by activation of EGFR signals. [PubMed: 21357274]
- 11**. Takaguri A, Shirai H, Kimura K, Hinoki A, Eguchi K, Carlisle-Klusacek M, Yang B, Rizzo V, Eguchi S. Caveolin-1 negatively regulates a metalloprotease-dependent epidermal growth factor receptor transactivation by angiotensin II. *J Mol Cell Cardiol*. 2011; 50:545–551. These findings indicate that Cav-1 is a negative regulator for AngII-mediated ADAM17 release and activated EGFR in vascular cells. [PubMed: 21172357]
12. LeRoith D, Werner H, Beitner-Johnson D, Roberts CT Jr. Molecular and cellular aspects of the insulin-like growth factor I receptor. *Endocr Rev*. 1995; 16:143–163. [PubMed: 7540132]
13. Liu G, Hitomi H, Hosomi N, Lei B, Nakano D, Deguchi K, Mori H, Masaki T, Ma H, Griendling KK, et al. Mechanical stretch augments insulin-induced vascular smooth muscle cell proliferation by insulin-like growth factor-1 receptor. *Exp Cell Res*. 2011; 317:2420–2428. [PubMed: 21854769]
14. Ma Y, Zhang L, Peng T, Cheng J, Taneja S, Zhang J, Delafontaine P, Du J. Angiotensin II stimulates transcription of insulin-like growth factor I receptor in vascular smooth muscle cells: role of nuclear factor-kappaB. *Endocrinology*. 2006; 147:1256–1263. [PubMed: 16322063]
15. Song H, Mowbray AL, Sykes MC, Jo H. Emerging role of IGF-1R in stretch-induced neointimal hyperplasia in venous grafts. *Arterioscler Thromb Vasc Biol*. 2007; 27:1679–1681. [PubMed: 17634521]
- 16*. Wu X, Cheng J, Li P, Yang M, Qiu S, Liu P, Du J. Mechano-sensitive transcriptional factor Egr-1 regulates insulin-like growth factor-1 receptor expression and contributes to neointima formation in vein grafts. *Arterioscler Thromb Vasc Biol*. 2010; 30:471–476. This paper demonstrates that transcriptional factor Egr-1 is responsible for increases in expression of IGF1R in response to mechanical stress. [PubMed: 19965784]
17. Zahradka P, Storie B, Wright B. IGF-1 receptor transactivation mediates Src-dependent cortactin phosphorylation in response to angiotensin II. *Can J Physiol Pharmacol*. 2009; 87:805–812. [PubMed: 19898563]
18. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. *Genes Dev*. 2008; 22:1276–1312. [PubMed: 18483217]
19. Shaw A, Xu Q. Biomechanical stress-induced signaling in smooth muscle cells: an update. *Curr Vasc Pharmacol*. 2003; 1:41–58. [PubMed: 15320852]
20. Ma YH, Ling S, Ives HE. Mechanical strain increases PDGF-B and PDGF beta receptor expression in vascular smooth muscle cells. *Biochem Biophys Res Commun*. 1999; 265:606–610. [PubMed: 10558917]
21. Higuchi S, Ohtsu H, Suzuki H, Shirai H, Frank GD, Eguchi S. Angiotensin II signal transduction through the AT1 receptor: novel insights into mechanisms and pathophysiology. *Clin Sci (Lond)*. 2007; 112:417–428. [PubMed: 17346243]
22. Touyz RM. Intracellular mechanisms involved in vascular remodelling of resistance arteries in hypertension: role of angiotensin II. *Exp Physiol*. 2005; 90:449–455. [PubMed: 15890798]
23. Chen PY, Simons M, Friesel R. FRS2 via fibroblast growth factor receptor 1 is required for platelet-derived growth factor receptor beta-mediated regulation of vascular smooth muscle marker gene expression. *J Biol Chem*. 2009; 284:15980–15992. [PubMed: 19339244]
- 24**. Mendelson K, Swendeman S, Saftig P, Blobel CP. Stimulation of platelet-derived growth factor receptor beta (PDGFRbeta) activates ADAM17 and promotes metalloproteinase-dependent cross-talk between the PDGFRbeta and epidermal growth factor receptor (EGFR) signaling pathways. *J Biol Chem*. 2010; 285:25024–25032. This study demonstrates a cross-talk between PDGFRβ and EGFR via stimulation of ADAM17 activity. [PubMed: 20529858]
25. Guo X, Nie L, Esmailzadeh L, Zhang J, Bender JR, Sadeghi MM. Endothelial and smooth muscle-derived neuropilin-like protein regulates platelet-derived growth factor signaling in human

- vascular smooth muscle cells by modulating receptor ubiquitination. *J Biol Chem.* 2009; 284:29376–29382. [PubMed: 19696027]
26. Koch S, Tugues S, Li X, Gualandi L, Claesson-Welsh L. Signal transduction by vascular endothelial growth factor receptors. *Biochem J.* 2011; 437:169–183. [PubMed: 21711246]
 - 27**. Jaffe IZ, Newfell BG, Aronovitz M, Mohammad NN, McGraw AP, Perreault RE, Carmeliet P, Ehsan A, Mendelsohn ME. Placental growth factor mediates aldosterone-dependent vascular injury in mice. *J Clin Invest.* 2010; 120:3891–3900. Authors reported vascular-specific aldosterone-dependent activation of VEGFR-1 pathway in response to arterial injury. [PubMed: 20921624]
 28. Storkebaum E, Ruiz de Almodovar C, Meens M, Zacchigna S, Mazzone M, Vanhoutte G, Vinckier S, Miskiewicz K, Poesen K, Lambrechts D, et al. Impaired autonomic regulation of resistance arteries in mice with low vascular endothelial growth factor or upon vascular endothelial growth factor trap delivery. *Circulation.* 2010; 122:273–281. [PubMed: 20606119]
 29. Pang J, Hoefen R, Pryhuber GS, Wang J, Yin G, White RJ, Xu X, O'Dell MR, Mohan A, Michaloski H, et al. G-protein-coupled receptor kinase interacting protein-1 is required for pulmonary vascular development. *Circulation.* 2009; 119:1524–1532. [PubMed: 19273721]
 30. Stockmann C, Kerdiles Y, Nomaksteinsky M, Weidemann A, Takeda N, Doedens A, Torres-Collado AX, Iruela-Arispe L, Nizet V, Johnson RS. Loss of myeloid cell-derived vascular endothelial growth factor accelerates fibrosis. *Proc Natl Acad Sci U S A.* 2010; 107:4329–4334. [PubMed: 20142499]
 31. Farkas L, Farkas D, Ask K, Moller A, Gaudie J, Margetts P, Inman M, Kolb M. VEGF ameliorates pulmonary hypertension through inhibition of endothelial apoptosis in experimental lung fibrosis in rats. *J Clin Invest.* 2009; 119:1298–1311. [PubMed: 19381013]
 - 32**. Zhang J, Silva T, Yarovsky T, Manes TD, Tavakoli S, Nie L, Tellides G, Pober JS, Bender JR, Sadeghi MM. VEGF blockade inhibits lymphocyte recruitment and ameliorates immune-mediated vascular remodeling. *Circ Res.* 2010; 107:408–417. This report suggests that VEGFR-1 is expressed on T lymphocytes and augment T cell recruitment to the vessel wall during neointima formation. [PubMed: 20538685]
 33. Mac Gabhann F, Popel AS. Systems biology of vascular endothelial growth factors. *Microcirculation.* 2008; 15:715–738. [PubMed: 18608994]
 34. Nagata K, Ohashi K, Nakano T, Arita H, Zong C, Hanafusa H, Mizuno K. Identification of the product of growth arrest-specific gene 6 as a common ligand for Axl, Sky, and Mer receptor tyrosine kinases. *J Biol Chem.* 1996; 271:30022–30027. [PubMed: 8939948]
 35. Melaragno MG, Wuthrich DA, Poppa V, Gill D, Lindner V, Berk BC, Corson MA. Increased expression of Axl tyrosine kinase after vascular injury and regulation by G protein-coupled receptor agonists in rats. *Circ Res.* 1998; 83:697–704. [PubMed: 9758639]
 36. Melaragno MG, Cavet ME, Yan C, Tai LK, Jin ZG, Haendeler J, Berk BC. Gas6 inhibits apoptosis in vascular smooth muscle: role of Axl kinase and Akt. *J Mol Cell Cardiol.* 2004; 37:881–887. [PubMed: 15380678]
 37. Cavet ME, Smolock EM, Ozturk OH, World C, Pang J, Konishi A, Berk BC. Gas6-axl receptor signaling is regulated by glucose in vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol.* 2008; 28:886–891. [PubMed: 18292389]
 - 38*. Cavet ME, Smolock EM, Menon P, Konishi A, Korshunov VA, Berk BC. Gas6-Axl pathway: the role of redox-dependent association of Axl with nonmuscle myosin IIB. *Hypertension.* 2010; 56:105–111. This report suggests that ROS-dependent post-translational modification of non-muscle myosin heavy chain-IIB lead to Axl binding and migration of VSMCs. [PubMed: 20479336]
 - 39*. Smolock EM, Korshunov VA. Pharmacological inhibition of Axl affects smooth muscle cell functions under oxidative stress. *Vascul Pharmacol.* 2010; 53:185–192. Small molecule inhibitors of Axl are effective in blocking ligand-independent (oxidative stress) activation of VSMCs. [PubMed: 20643227]
 - 40**. Holland SJ, Pan A, Franci C, Hu Y, Chang B, Li W, Duan M, Torneros A, Yu J, Heckrodt TJ, et al. R428, a selective small molecule inhibitor of Axl kinase, blocks tumor spread and prolongs survival in models of metastatic breast cancer. *Cancer Res.* 2010; 70:1544–1554. This is the first

report effectiveness of small molecule inhibitor of Axl (R428) in mouse models of tumorigenesis *in vivo*. [PubMed: 20145120]

41. Lijnen HR, Christiaens V, Scroyen L. Growth arrest-specific protein 6 receptor antagonism impairs adipocyte differentiation and adipose tissue development in mice. *J Pharmacol Exp Ther*. 2011; 337:457–464. [PubMed: 21285281]
42. Thorp E, Cui D, Schrijvers DM, Kuriakose G, Tabas I. MERTK receptor mutation reduces efferocytosis efficiency and promotes apoptotic cell accumulation and plaque necrosis in atherosclerotic lesions of apoE^{−/−} mice. *Arterioscler Thromb Vasc Biol*. 2008; 28:1421–1428. [PubMed: 18451332]
43. Lutgens E, Tjwa M, Garcia de Frutos P, Wijnands E, Beckers L, Dahlback B, Daemen MJ, Carmeliet P, Moons L. Genetic loss of Gas6 induces plaque stability in experimental atherosclerosis. *J Pathol*. 2008; 216:55–63. [PubMed: 18570189]
- 44*. Thorp E, Vaisar T, Subramanian M, Mautner L, Blobel C, Tabas I. Shedding of the Mer Tyrosine Kinase Receptor Is Mediated by ADAM17 Protein through a Pathway Involving Reactive Oxygen Species, Protein Kinase C δ , and p38 Mitogen-activated Protein Kinase (MAPK). *J Biol Chem*. 2011; 286:33335–33344. This study demonstrates ROS-dependent mechanisms by which ADAM17 cleaves MERTK in immune cells. [PubMed: 21828049]
45. Steeghs N, Gelderblom H, Roodt JO, Christensen O, Rajagopalan P, Hovens M, Putter H, Rabelink TJ, de Koning E. Hypertension and rarefaction during treatment with telatinib, a small molecule angiogenesis inhibitor. *Clin Cancer Res*. 2008; 14:3470–3476. [PubMed: 18519779]
- 46*. Mayer EL, Dallabrida SM, Rupnick MA, Redline WM, Hannagan K, Ismail NS, Burstein HJ, Beckman JA. Contrary effects of the receptor tyrosine kinase inhibitor vandetanib on constitutive and flow-stimulated nitric oxide elaboration in humans. *Hypertension*. 2011; 58:85–92. This study provides NO-dependent mechanism of increase in blood pressure after treatment with vandetanib. [PubMed: 21482957]

Key points

- RTKs play a critical role in vascular biology. Over-activation of these receptors is known to stimulate vascular remodeling
- RTKs are not only activated by their ligands but also via trans-activation by G-protein coupled receptors, mineralocorticoid receptors, oxidative and mechanical stresses, which are crucial during vascular remodeling
- RTKs are highly interactive with many proteins (including tyrosine kinases and RTKs) and function as key regulatory nodes in a dynamic signaling network
- Recent experimental studies implicate RTKs in functions of non-vascular (immune and neuronal) cells, which is important for mechanisms of vascular remodeling
- Pharmacological inhibition of RTKs has a great therapeutic potential as was shown in cancer. However, RTK inhibitors should be further evaluated in cardiovascular disorders

Figure 1.

The roles of five families of RTKs in vascular remodeling. Stimuli, structural organization, RTK family members, downstream signalling targets and the regulation of cell functions in vascular remodeling are listed from the top to the bottom. The extracellular region of RTKs (above the cell membrane) represents ligand-binding domain and specified in the reference box. The intracellular region (below the cell membrane) shows kinase domain. Please, see text for details.

Figure 2.

New mechanisms by which five families of RTKs mediate vascular remodeling. Please, see text for details.