Abstract—The vascular wall contains intimal endothelium and medial smooth muscle that act as contiguous tissues with tight spatial and functional coordination in response to tonic and episodic input from the bloodstream and the surrounding parenchyma. Focal adhesions are molecular bridges between the intracellular and extracellular spaces that integrate a variety of environmental stimuli and mediate 2-way crosstalk between the extracellular matrix and the cytoskeleton. Focal adhesion components are targets for biochemical and mechanical stimuli that evoke crucial developmental and injury response mechanisms including cell growth, movement, and differentiation, and tailoring of the extracellular microenvironment. Focal adhesions provide the vascular wall constituents with flexible and specific tools for exchanging cues in a complex system. The molecular mechanisms that underlie these vital communications are detailed in this review with the goal of defining future targets for vascular tissue engineering and for the therapeutic modulation of disordered vascular growth, inflammation, thrombosis, and angiogenesis. (Circ Res. 2006;98:606-616.)

Key Words: cell adhesion ■ extracellular matrix ■ integrin ■ mechanical force ■ cell signaling ■ focal adhesion ■ vascular endothelium ■ vascular smooth muscle

Focal adhesion (FA) biology proffers several features that are paradigmatic for the precise and efficient coordination of signaling events. The initiation event is cell adhesion to specific ligands in the extracellular matrix (ECM) environment via transmembrane integrin receptors. This adhesive interface matures through recruitment of additional integrins and cytoskeletal components. Signal propagation involves the ordered interaction and aggregation of more than 50 diverse proteins and their downstream cascades in patterns that are tailored to specific environmental cues. FAs incorporate robust examples of cellular signaling integration, such as gating through conformational changes in integrin ligand-binding domains and modular localization of intermolecular adapter interactions.¹

Four major factors influence the assembly rate, size, specific constituency, signaling repertoire, and functional impact of FAs. These are (1) the biophysical and biochemical properties of the ECM, (2) integrin activation and avidity, (3) the contraction state of the cytoskeleton, and (4) the specific cellular and tissue milieu in which these events occur.
Excellent recent reviews describe the interactions between FA proteins and the identity and molecular function of many of the more than 24 known integrin heterodimers. In this report, we review FA signaling mechanisms within the context of the vascular wall.

Key Building Blocks and the Birth of the Field

Figure 1A shows the 3 major partners in FA formation and signaling: extracellular fibronectin fibrils in blue, polymerized f-actin in green, and FAs (in this case with labeled vinculin) in red. Seminal work on FA constituents used monoclonal antibodies and affinity chromatography to isolate component proteins from homogenates of chicken embryo or chicken gizzard, followed by antibody labeling of ECM proteins and cytoskeletal elements at the cell-matrix nexus. Concurrently, the first descriptions of the transmembrane integrin family were in progress. These investigations defined specific integrin receptors and biological roles for fibronectin and laminin and identified novel actin- and integrin-interacting proteins including α-actinin, vinculin, talin, and paxillin, thereby advancing our understanding of the integration of transmembrane surface receptors and the cytoskeleton.

Family of Cell-Matrix Adhesions

Early studies of cell adhesion to ECM recognized that these sites begin as small colocatal aggregates of fibronectin and the cytoskeleton-associated protein vinculin. Other investigators described the evolution of early “nodes” of talin forming at the perimeter of spreading lamellipodia into FAs with larger dimensions and broader molecular constituents. These nascent adhesive structures (~1 μm in diameter) were later termed focal complexes and shown to contain focal adhesion kinase (FAK) and paxillin. They are induced by the Rho family members Rac and cdc42, but not by Rho itself. The maturation of focal complexes into FA is dependent on interactions with the actin cytoskeleton and Rhomodulated actomyosin tension, and Rho also mediates FA turnover. FA components can be centripetally segregated into linear arrays at a rate of up to 18 μm per hour and these have been dubbed fibrillar adhesions. Tensin and α5β1 integrin are principal fibrillar adhesion components, and their segregation is dependent on the mobility of ECM ligands and the expression of Src. Figure 1B demonstrates the presence, morphology, and topography of focal complexes, FA, and fibrillar adhesions in human endothelium (HUVEC).

FA Structure and Function

Integrin Subunits and Domains

Integrins are a remarkably conserved family of transmembrane adhesion receptors on metazoan cells. A total of 18 integrin α chains and 8 β chains associate in noncovalently linked parallel arrays to form more than 24 heterodimers. Integrins containing β1, -3, -4, -5, and -8 bind specificity to small peptide sequences on ECM ligands, forming the centriperece of the classical FA structure. Integrins are cellular localization signals with profound consequences for the success of the host organism. They facilitate developmental, immune, hemostatic, and repair functions. Key integrin domains include the extracellular ligand-binding region, the membrane proximal extracellular segment, the transmembrane domain, and the cytoplasmic tail. Specificity in integrin signaling is made possible by the particular α and β chains that form the heterodimeric pair and the distinct binding interactions of the cytoplasmic tails of these pairs with the actin cytoskeleton and with signaling molecules. Integrin signaling occurs via a large array of intracellular second message systems including calcium channels, phosphatidylinositol-4,5-bisphosphate, phospholipase-Cγ, the Na/H antiporter, tyrosine and serine/threonine kinases, phosphatases, Rho family GTP-binding proteins, mitogen-activated protein (MAP) kinases, and cyclin D1.
density of integrin receptor molecules at these sites increases the avidity of adhesion. Concomitant with clustering, integrins must be switched “on” by conformational modification of extracellular ECM-binding domains that increase the specific binding activity of individual integrin molecules.22 The activation and spatial distribution of integrin-mediated cell-matrix adhesion sites on the cell surface can profoundly influence diverse signaling events including the directional control of actin organization by vinculin and Arp2/3, and vascular cell differentiation.29,30

The bidirectional feature of integrin signaling is based on reciprocal, intramolecular, allosteric changes that are initiated in either the cytoplasmic tail or the extracellular domain and then transmitted to the other end of the molecule. This enables ECM ligation to propagate signals in an “outside-in” direction, whereas intracellular changes in cytoskeletal tension can generate “inside-out” signaling.3,22,31

Integrins and Cytoskeletal Dynamics
Reciprocal communication between integrins and proteins that regulate the actin cytoskeleton is an important feature of FA signaling. Thus, Rho activation accentuates FA growth,32 whereas integrin engagement has direct effects on Rho activity and Rho-mediated FA turnover via Src21,33,34 and FAK.17,35 Additionally, integrins regulate the availability and turnover of Rac by directing Rac interactions with caveolae and the plasma membrane.36,37 Meanwhile, the Rho family of GTP-binding proteins and myosin light chain kinase (MLCK) generate dynamic inside-out integrin signals via cytoskeletal remodeling38,39.

Molecular Signal Generators
A recurrent theme in FA biology is that even constituent proteins without recognized enzyme domains are involved in dynamic signal processes: there are no “passengers.”40 This point is underscored by several proteins classically thought to be “structural” FA components: vinculin is selectively activated by changes in head–tail interactions regulated by binding to talin41,42; α-actinin forms a signaling complex with the Abl/Arg kinase adapter ArgBP243; and paxillin integrates diverse inputs including tyrosine kinases and Rho family regulators.44 Additionally, FAs contain a rich diversity of enzymatically active proteins that direct cell fate, shape, and motion (see Figure 2).3,18,44 The nonreceptor tyrosine kinases Src and FAK are distinguished by their wide-ranging impact on vascular biology, with roles in apoptosis, vasculogenesis, and reperfusion injury.45–51 Regulatory mechanisms of these 2 enzymes highlight an important motif in FA signaling: domain-dependent (modular) intermolecular scaffolding. Src and FAK are each activated by autophosphorylation on specific tyrosine residues (Y419 and Y397 respectively). This activation trigger is dependent on localization to FA and precise intermolecular associations.52,53 Auto-activated FAK recruits Src by binding to its Src-homology type 2 (SH2) domain, and the proline-rich sequences in FAK are potential binding sites for the SH3 domain of Src.53,54 The fact that both the activities and the cooperative interaction of Src and FAK are controlled by subcellular localization is vital to their utility as adhesion-modulated signal generators.

FAK exhibits a remarkable proclivity for unique and specific intermolecular interactions that regulate key cellular processes (shown in Figure 2). For example, FAK may control cell fate (purple in Figure 2).45,46,55 The FAK amino terminus binds to the death domain of RIP, and prevents RIP interaction with the Fas-containing death complex,56 and the FAK N-terminus also binds to the transactivation domain of p53 to block activation of the Bax promoter.57 On a transcrip-
tional level, FAK induces the expression of the transcription factor KLF8 and augments its binding and activation of the cyclin D1 promoter. Caspase-8 interactions with FAK have been noted to inhibit Rb-mediated apoptosis, and caspase-3 mediates FAK degradation in the setting of cisplatin therapy.

Membrane extension and cytoskeletal tension (blue in Figure 2) are also modulated by FAK through multiple interactions with regulators and effectors of Rho family proteins including the GTPase-activating proteins p190RhoGAP and GRAF, the guanine nucleotide exchange factors ASAP1, Trio, and PIX and the Rac effector p95PKL. FAK also binds the adapter protein paxillin and tyrosine phosphorylates it at Y31 and Y118, thereby altering paxillin interactions with the integrin and the PKL-PIX-PAK complex at the leading edges of spreading lamellipodia.

FAK may influence cell motility and directional control (the green arm of the pinwheel in Figure 2) by mediating FA interactions with caveolae and microtubules. Tyrosine-phosphorylated caveolin 1 and 2 colocalize with activated (Y397-phosphorylated) FAK at the leading edges of migrating human microvascular endothelial cells. Surprising new work on FA disassembly (a critical process in the directional control of cell migration) implicates FAK as a localization signal for FA destruction. These data indicate that microtubule-targeted FA disassembly is dependent on Y925. FAK interaction with the proline-rich domain of the GTPase dynamin via GRB2. In an interaction mediated by targeting to the FAK N terminus, calpain is incorporated into a complex with p42ERK and provides another mechanism of FA turnover. Further, FAK can also propel motility by activating and assembling signaling complexes driven by MAP kinases including e-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), p130, Grb2, SOS, Crk, and C3G.

Understanding of FAK control over both the assembly and the proteolytic destruction of ECM is evolving rapidly. Matrix assembly (yellow segment in Figure 2) is covered in more detail later in this review (see below, under heading Links out: Shaping the Matrix). FAK regulation of this cellular process appear to involve interactions with Src and phosphatidylinositol 3-kinase (PI3K) and the tyrosine phosphorylation of tensin. Focusing ECM proteolysis to FA sites during tissue invasion (see the red area of Figure 2) also entails specific targeted intermolecular orchestration by FAK. The second proline-rich motif in the FAK C terminus can bind to endophilin A2, a mediator of endocytosis. In an apparent 2-step cooperative venture with Src, FAK tyrosine phosphorylates endophilin A2, rendering it inactive and unable to internalize MT1-MMP. Thus, FAK increases the amount of this membrane-bound protease on the cell surface and abets tissue invasion.

Although cell survival, mobility, and invasion may be mutually complementary programs, the number and variety of cellular processes and binding interactions in which FAK participates suggest that FAK serves as a cellular signaling “switch.” Proposed mechanisms for this molecular switching include alternate folding of the FAK FA targeting domain, leading to graded availability of Y925, and/or distinctive degrees and patterns of tyrosine phosphorylation. Further exploration of the mechanisms that underlie FAK switching between its many signaling and scaffolding roles is needed.

Mechanical Signals and the Vascular Wall
Vascular wall FAs are influenced by many inputs, including shear force, cyclic stretch, angiogenic signals, and proinflammatory stimuli (Figure 3). Each of these inputs alters various aspects of the adhesive relationships between endothelial and smooth muscle cell populations, as well as the relationships between these cells and the ECM. Color coding is used in Figure 3 to reference the regulatory input to each of the individual FA proteins listed, as described in the legend. Mechanical stress responses of FA components and molecular mechanisms of mechanotransduction are the topics of this section and the next.
Endothelial cells and smooth muscle cells in the vascular wall are exposed to hemodynamic forces, and FAs most likely serve as primary mechanosensors for multiple signal cascades with different activation times. Accordingly, ion channels (Na⁺ channel, K⁺ channel, chloride-selective channel) and heterotrimeric G proteins (Gq) are activated within seconds of changes in mechanical stimulation, whereas protein kinase C, MAP kinases, and the nonreceptor protein tyrosine kinase, Src, are activated within minutes. Each of these events leads to specific cytoskeletal protein phosphorylation, actin cytoskeleton remodeling, and gene induction in vascular wall cells.

The character of applied mechanical forces is translated to specific patterns of cellular response. Cyclic stretch causes the activation of FAs containing αvβ3 integrins, resulting in Src-dependent activation of FAK, FAK phosphorylation of paxillin, and the formation of a complex including FAK, paxillin, and GIT1. These effects are tightly linked to stress fiber formation and reorientation of the actin cytoskeleton perpendicular to the vector of the mechanical strain. FA rearrangement under stretch is also mediated via Rho-dependent mechanisms.

In contrast to cyclic stretch, shear stress affects endothelial cell FAs by an indirect avenue, either by affecting transcellular actin meshworks or by stimulating changes within caveolae at the luminal surface. In addition, shear stress triggers Rac activation with redirection of FAs to the cell periphery. This supports the enhancement of a peripheral cortical actin rim that is essential to increasing endothelial monolayer tethering and barrier properties. These effects of shear stress in endothelial cells are mediated by the αvβ3 and αvβ1 integrins.

**Mechanical Coupling in FAs**

Translation of mechanical events to biochemical signals occurs in FA sites in the vascular wall. Four schemata for this translation are presented in Figure 4 and discussed as 4 levels of focus, ranging from intraluminal intercellular events to intra- and intermolecular rearrangements within the FA. This section is based in part on the incisive thinking and groundbreaking efforts of several investigators over the past 14 years.

The first scenario involves intermolecular changes at a site of focal injury within the blood vessel lumen (Figure 4A). Cellular damage leads to the release of soluble factors that affect neighboring intimal endothelial cells by juxtacrine (intercellular) or autocrine (same cell) mechanisms. An example is the release of barrier-enhancing sphingosine 1-phosphate (S1P) from platelet thrombi. S1P induces activation of G protein–coupled endothelial differentiation gene...
family (Edg) receptors on the surface of the contiguous intima. Edg receptor ligation is followed by downstream activation of the nonreceptor tyrosine kinase Src, which leads to Src-mediated phosphorylation of FAK at Y576, with subsequent involution of FA structure and alterations in endothelial cell barrier function.88,89 The second motif (Figure 4B) involves intramolecular coupling of vascular mechanical stimuli to biochemical signaling pathway activation and may pertain to the huge multidomain guanine nucleotide exchange factor obscurin (∼800 kDa).90 The ankyrin-like repeats of obscurin may provide targeting to the cell membrane and physical interaction with mechanosensitive molecules.86,87,96 The formin mDia1, a barbed end capper of actin filaments, has been implicated as a transducer of mechanical force to FA growth.97 One hypothesis is that a pulling force and facilitates actin monomer addition through a “stair-step” action by which the formin moves along the actin filament and nucleates actin polymerization as it goes, a procedure known as “processive” capping.86 This magnitude of force at individual actin filaments is consonant with measurements of the total force at individual FA sites by other investigators (∼5 nN).98,99 Shortly after this model was proposed, the crystal structure of the FH2 domain of a yeast formin in complex with actin was solved, confirming the presence of an actin-bound dimeric ring of 2 formin FH2 domains that transitions between 2 configurations as a Brownian ratchet in response to actin monomer addition, a second wave of subunit rearrangement and addition.41,42,87,100 The mechanosensitivity of FA growth is consistent with a thermodynamic model of protein aggregate self-assembly in which mechanical distortion lowers the chemical potential of the aggregate and favors subunit addition from a soluble pool.57 This model predicts the requirement for progressive addition of subunits without disrupting the underlying aggregate. A possible solution to this molecular intrigue is provided by recent data indicating that the head domain of vinculin undergoes a conformational conversion to a helical bundle on activation by talin,41 and this active conformation of vinculin exhibits punctate colocalization with actively growing FA sites.42 The physical link between force-directed actin filament growth and FA assembly is likely provided by α-actinin.101,102 The trophic effect of integrin clustering on FA growth predicted by this new thermodynamic model of FA self-assembly under tension fits well with observed patterns of FA development51,103 and may be part of a feedback loop that accelerates integrin activation through increasing tension at enlarging FA sites (discussed below).

A fourth type of mechanical force transduction at FA (Figure 4D) is an intramolecular mechanism and involves tension-induced conformational change. A well-studied example is the opening of the ECM ligand-binding sites in β1 and β3 integrins in response to traction forces (elegantly reviewed in Hynes5). This involves straightening and activation of specific ligand-binding domains in the extracellular portions of these integrins, allosteric changes that are transmitted from one end of the molecule to the other.84,104 The bidirectional character of conformational changes in the integrin molecule deserves special emphasis. Just as inside-out signaling is provided by cytoskeletal traction forces that induce integrin activation, outside-in signaling is initiated upon ECM binding and the simultaneous conformational change in the extracellular domain. These extracellular changes lead to altered spatial separation of the cytoplasmic tail components and increases interaction with FA signaling molecules.1 In addition, integrin activation and binding to ECM provides a more efficient extracellular anchor for the transmembrane tethering of the FA structure, enhancing the process of elastic deformation and subunit addition within the FA.

These four separate yet related means for mechanical responsiveness demonstrate that FA are uniquely positioned and engineered to direct environmental sensing and cellular responses in the rapidly changing ambience of the circulation.

**Functional Impact of FAs**

**Cell-Matrix Communication in Vascular Development and Repair** Developmental control of the vascular wall by the ECM proteins and their integrin receptors has been documented at the levels of homing, tissue organization, and differentiation. Targeted gene deletion studies have demonstrated the critical roles that fibronectin and α5β1 integrin serve in stabilization and branching morphogenesis during vascular development in the murine embryo.105 An elegant ovine model of patent ductus arteriosus used fetal transfection of a “decoy” RNA to
sequester the mRNA binding protein for fibronectin and demonstrated that smooth muscle cell migration, intimal cushion development, and ductal closure are all fibronectin-dependent events.

Similarly, the ECM protein tenasin-C is an essential contribution of the homeobox gene Prx-1 to endothelial cell differentiation in the mesoderm.

Additionally, laminin 8 regulates tube formation, early vessel branching, and both pericyte and smooth muscle cell recruitment during vasculogenesis, and the α8- and αβ1 integrins direct smooth muscle cell migration.

Steady-state vascular housekeeping functions and vascular injury responses also rely on the ECM. The α2β1, α3β1, α5β1, and αvβ3 integrins all mediate cell shape and matrix adhesion in human endothelial cells. Homeostatic functions including the regulation of cell shape and permeability are dependent on laminin 10 in mature endothelia, and the antithrombotic quality of the intimal surface is supported by regulation of the αIIbβ3 integrin. Following tissue injury, laminin 1 profoundly alters endothelial cell gene expression and induces angiogenesis, and the laminin receptor αvβ3 integrin is known to direct endothelial cell membrane extension and movement during angiogenesis.

Following hypoxia, FAK regulates smooth muscle cell migration and angiogenesis. Taken together, these data indicate that FA signals provide important adaptive mechanisms to the life of the vascular wall from its formation well into senescence.

Vascular Permeability

Regulation of endothelial permeability is a balance between contractile elements in the actomyosin apparatus of the microfilament cytoskeleton and tethering elements including FA and adherens junctions (reviewed in Ren et al). FA in adherent endothelial cells normally undergo a constant basal rate of turnover that accelerates with activation. Several lines of inquiry suggest that changes in barrier function may result from altered FA turnover kinetics, specific tyrosine phosphorylation events, and reassignment of FA constituents to new subcellular arrays.

In thrombin-induced endothelial permeability, FAs are rearranged to withstand increased mechanical loading from contracting actomyosin stress fibers. Resulting FA signaling includes the Src-dependent association of GIT1 and GIT2 with FAK and paxillin, and prominent FAK phosphorylation at Y397, Y576, and Y925. GIT1 and FAK may facilitate FA disassembly in this setting and set the stage for permeability changes. FAK-driven FA disassembly and redistribution are also required for the increased permeability mediated by C5a-activated neutrophils and vascular endothelial growth factor (VEGF).

Interestingly, the increase in barrier function induced by physiological concentrations of sphingosine-1-phosphate also involves the partial disassembly of preexisting FAs coincident with the transient association of GIT1 with FAK. This is followed by the translocation of FAK and paxillin from the cytosol to peripheral GIT2-containing FAs contiguous to a newly reinforced cortical actin ring. The keys to the differences in vascular permeability following these various stimuli may lie in the interplay between FA mobilization and Rho- or Rac-driven changes in cytoskeletal force distribution that directs FA to new locations.

Vascular Smooth Muscle Hypertrophy

Mechanical force detection is an important adaptive behavior in vascular smooth muscle cells that hinges on multifactorial molecular signaling including FA, growth factors, and the angiotensin system. Experiments using UV-irradiated type III collagen to stimulate exaggerated growth behavior in rat aortic smooth muscle cells indicate that the growth control exerted by β1 integrins may be downregulated by abnormal ECM surfaces. These findings are consistent with studies showing that normal ECM ligands for β1 integrins can downregulate angiotensin II–induced calcium release in smooth muscle cells from spontaneously hypertensive rats. Further investigations into FA regulation of angiotensin II have shown that dominant negative FAK blocks angiotensin II induction of MAP kinase activation. FAs also regulate gene expression in vascular smooth muscle cells following hypertrophic stimuli. Thus, the zinc-finger–containing FA protein zyxin exhibits a specific response to cyclic stretch (but not to cytokine or osmotic stress) by translocation from FA to the nucleus and inducing the expression of a number of genes, including the endothelin B receptor, tenasin-C, and plasminogen activator inhibitor-1.

Links in: Mechanotransduction and Gene Expression

As shown by the example of zyxin above, mechanical stresses trigger alterations in gene expression via FA elements in the vascular wall. These include Src and FAK, which are activated by both shear stress and cyclic stretch. These Src and FAK activation events promote association of the FA adapter proteins paxillin, p130CAS, and CRK with the guanine nuclear exchange factor C3G and the small GTPases Rap1 and Raf. These events then trigger the MEK-ERK-MAP kinase cascade, leading to cell proliferation.

A growing body of evidence suggests that specific interactions between FA adapter proteins and signaling cascades may lead to distinct cell responses to various mechanical stimuli as defined by the nature of mechanical stimuli (ie, shear versus strain), the force magnitude, and the type of underlying matrix. For example, both time- and amplitude-dependent changes in gene expression in human pulmonary endothelial cells have been reported following cyclic stress. Furthermore, a role for FA in the selectivity of these responses is indicated by the strong pattern of different specific integrin-mediated ECM signals during mechanical stress in vascular smooth muscle cells. Thus, laminin, collagens I and IV, and fibronectin modify the patterns of caldesmon expression that are induced by cyclic stretch. A pattern of convergence for integrin signaling is also exhibited by endothelium under shear stress in which the αβ1, αβ1, and αvβ1 integrins each associate with Shc in FA.

Links out: Shaping the Matrix

An exciting implication of bidirectional signaling at FAs is that cells can shape the microarchitecture of the ECM environment through inside-out signaling. This is particularly...
salient to development and remodeling of the vasculature given the critical roles that ECM, and especially fibronectin, play in this arena. Fibronectin is actively secreted by endothelium and forms an inactive dimer in its soluble form. Attachment of this dimer to the cell surface is recognized as the first step in fibril assembly. The binding of fibronectin to the cell surface primarily occurs through the α5β1 integrin. Fibrinogen is then assembled into fibrils, which are anchored to the ECM at the cell periphery and are cell-bound near the center of the cell. Fibrils are bundles of fibronectin filaments, which are each approximately 5 nm in diameter. These elastic fibrils can be stretched to approximately 4 times their resting length. The FNIII domain of fibronectin is highly folded and contains a cryptic binding domain, which becomes exposed when the fibronectin molecule is under tension from cytoskeletal traction forces that are transmitted to the cell-matrix interface. Exposure of this cryptic site is thought to mediate intermolecular association, fibrinogen polymerization, and fibril assembly. Fibrillogenesis is dependent on several FA constituents. Tensin, Src, PI3K, and FAK are critical mediators of integrin translocation, fibronectin assembly, and fibrillogenesis in both cell culture and embryo culture models of vascular development.

Therapeutic Considerations and Future Directions

Regulatory and signaling events in the vascular wall are prime targets for pharmaceutical innovation. Modulating or silencing bidirectional signaling along the cytoskeleton–integrin–matrix axis at FA sites is an attractive treatment strategy for vascular disorders and an important frontier in tissue engineering. Three examples of therapeutic targets and potential solutions are outlined here. FAs provide anchors for the cytoskeletal tension that governs wall tension in vascular smooth muscle cells. The function of the FA-anchored actin cytoskeleton has been targeted biochemically using agents that specifically and competitively inhibit ATP-binding by the Rho effector protein Rho kinase. This strategy is currently undergoing preclinical and clinical trials of inhalation, intravenous, and enteral therapy for pulmonary and systemic hypertension and cerebral and coronary vasospasm.

The balance of Rho and Rac activation determines the route of FA redistribution during inflammation and acute lung injury, and this balance is a target for drug development. SIP may provide an important tool for increasing Edg-1 receptor–mediated Rac activation in vascular endothelial cells. Furthermore, the statin family of HMG-CoA inhibitors may be useful adjunctive agents because they also block the critical geranylgeranylation of Rho-GTP. This prevents Rho from targeting to lipids in the plasma membrane and interacting with its downstream effectors. Statins, therefore, tip the Rho/Rac balance in favor of the latter and have even been shown to increase Rac activity.

Another proposed therapeutic strategy involves dual-targeted nanoparticles for selective gene silencing at sites of acute malaise. This approach targets short interfering RNA (siRNA) to sites of intravascular crisis by combining an outer layer of endothelial-targeted peptide ligand and an siRNA core in a single self-assembled nanoparticle. Because pharmacological inhibition and transgenic gene silencing of the FA protein Src have both been shown to modify postischemic intravascular thrombosis and vasogenic edema, siRNA-mediated Src silencing in ischemia–reperfusion models may provide an excellent forum to test this FA-targeted gene therapy.

It is likely that FA constituents will continue to provide inspiration for therapeutic strategies for vascular disorders.

Summary

FAs mediate communication between the ECM and the cytoskeleton, providing vascular wall components a means to sense biochemical and biophysical cues from the matrix in the extracellular environment. This “outside-in” signaling directs rearrangements in cytoskeletal organization and nuclear gene expression in response to changing conditions in the circulation. The bidirectional feature of communication at FAs also provides an “inside-out” signaling component through which cells change the ECM and the behavior of neighboring cells and tissues. The molecular diversity and plasticity of FA present a rich array of potential therapeutic targets for the management of vascular dysfunction and disease.

We hope that this review will provide insight and impetus to the student of vascular biology in the spirit of the challenge offered by Dr. Carl J. Wiggers: “Nevertheless, it happens that many phenomena of the circulation, normal and abnormal, remain undetected by our unaided senses.”

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