therapeutic outcome, but also shed light on the mechanistic bases for resistance to treatment and even identify novel targets for antiviral drugs.

Conclusions

Although it still remains for these markers to be validated, the early results presented in this study are promising (8). It is interesting to speculate on the relationship between these markers and other markers, particularly those based on host characteristics. The circulating virus is not an independent entity, but is continually shaped by host selective pressures even as it in turn modulates its host environment. Viral sequences observed prior to treatment may very well represent the success or failure of the host in selecting against the most treatment-resistant variants. Covariance networks may serve as an exciting new tool in further studies along this avenue; networks generated from viral sequences obtained during acute viral infection should be particularly informative.

With the sustained and rapid growth of both computational power and sequencing capabilities, we expect covariation analyses to become increasingly common as a tool to study different aspects of HCV biology (14). The high mutation rate of RNA viruses and the intense competition within the quasispecies makes them particularly amenable to this technique. We look forward to seeing further application of covariance networks to questions ranging from protein structure and protein-protein interactions to drug resistance, host selection pressures, and viral evolution.

Acknowledgments

The authors acknowledge Catherine Murray for her assistance in the preparation of this manuscript. Work in the laboratory of C.M. Rice is supported by the Greenberg Medical Research Institute and the Starr Foundation.

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Role for α3 integrin in EMT and pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is characterized by progressive (myo)fibroblast accumulation and collagen deposition. One possible source of (myo)fibroblasts is epithelial cells that undergo epithelial-mesenchymal transition (EMT), a process frequently mediated by TGF-β. In this issue of the *JCI*, Kim et al. report that epithelial cell–specific deletion of α3 integrin prevents EMT in mice, thereby protecting against bleomycin-induced fibrosis (see the related article beginning on page 213). The authors propose a novel mechanism linking TGF-β and β-catenin signaling in EMT through integrin-dependent association of tyrosine-phosphorylated β-catenin and pSmad2 and suggest targeted disruption of this interaction as a potential therapeutic approach.

Conflict of interest: The author has declared that no conflict of interest exists.

Nonstandard abbreviations used: AEC, alveolar epithelial cell; EMT, epithelial-mesenchymal transition; IPF, idiopathic pulmonary fibrosis.

Citation for this article: *J. Clin. Invest.* **119**:7–10 (2009). doi:10.1172/JCI38084.

Idiopathic pulmonary fibrosis (IPF) is a progressive disorder of unknown etiology characterized by fibroblast accumulation, collagen deposition, and ECM remodeling leading to parenchymal destruction (1). Historically, inflammation has been viewed as central to the pathogenesis of IPF. A recent paradigm shift proposes a model in which injury to the epithelium initiates a proinflammatory and profibrotic cascade, resulting in fibroblast expansion and progressive fibrosis reminiscent of abnormal wound healing (2). Myofibroblasts (activated fibroblasts) are key effector cells in pulmonary fibrosis, being responsible for matrix deposition and structural remodeling. The source of myofibroblasts in IPF remains the subject of debate: in addition to arising from circulating progenitors and resident fibroblasts, myofibroblasts have recently been shown to be derived from alveolar epithelial cells (AECs) through epithelial-mesenchymal transition (EMT) (3, 4).

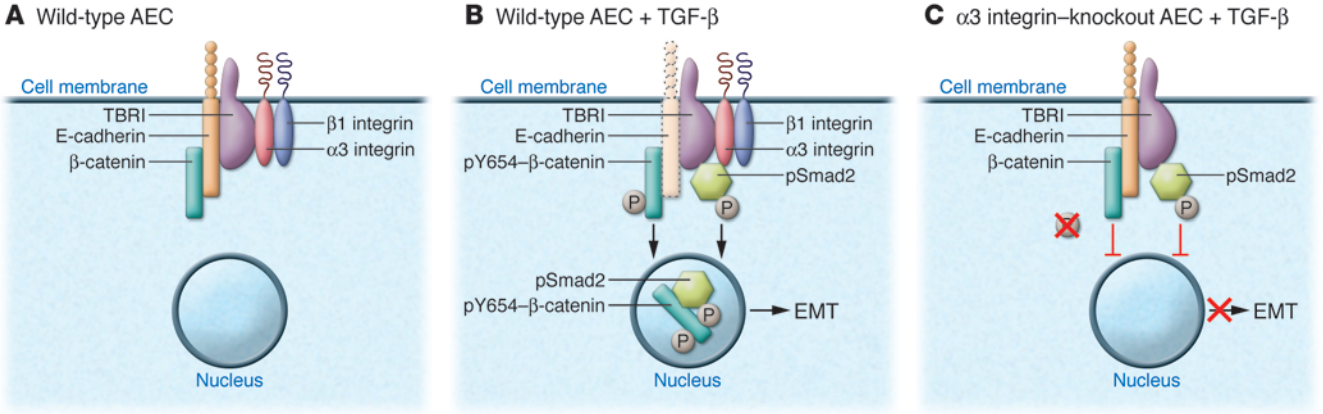

Figure 1
Model depicting role for α3 integrin in transducing extracellular signals to the nucleus in TGF-β–induced EMT. (**A**) In wild-type AECs at baseline, this study demonstrates that α3 integrin forms a tripartite complex with TGF-β receptor I (TBRI) and E-cadherin at the cell surface. β-catenin has previously been reported to interact with the cytoplasmic tail of E-cadherin and to be important for preventing E-cadherin degradation, thereby maintaining intercellular adhesion. (**B**) As shown by Kim et al. in their study in this issue of the journal (20), α3 integrin is required for tyrosine phosphorylation (P) of β-catenin in the presence of TGF-β, which is necessary for complex formation between phosphorylated β-catenin (pY654–β-catenin) and pSmad2. This in turn leads to nuclear translocation of pY654–β-catenin. Nuclear pY654–β-catenin is postulated to induce EMT in a β-catenin–dependent fashion, although the precise mechanisms whereby it acts in conjunction with pSmad2 to induce EMT remain to be determined. Disruption of the interaction between β-catenin and E-cadherin likely also contributes to degradation of E-cadherin and disruption of intercellular adhesion. (**C**) Deletion of α3 integrin in AECs prevents tyrosine phosphorylation of β-catenin following addition of TGF-β, allowing β-catenin to remain complexed to E-cadherin, which is protected from degradation. Non-phosphorylated β-catenin does not form a complex with pSmad2 and does not undergo nuclear translocation, thereby rendering cells resistant to EMT.

EMT

EMT is characterized by loss of polarity, disassembly of cell-cell contacts associated with loss of junctional and intercellular adhesion proteins (e.g., E-cadherin), cytoskeletal reorganization, and transition to a mesenchymal phenotype characterized by acquisition of mesenchymal markers (e.g., α-SMA) and migratory properties (5). EMT is well recognized during development and tumor invasion and recently has been implicated in the pathogenesis of fibrosis in response to epithelial stress/injury in a number of organs, including kidney and lung (3, 4, 6). TGF-β is regarded as the prototype cytokine for induction of EMT in vitro and in vivo (7), frequently in conjunction with other cytokines and signaling pathways (e.g., the Wnt pathway). EMT can also be modulated by proteolytic destruction of basement membrane and interactions with ECM (8).

β-catenin: bifunctional regulator of transcription and cell adhesion

β-catenin is a key protein in the Wnt/β-catenin signaling pathway with dual roles: it regulates Wnt-mediated transcription in conjunction with lymphocyte enhancer factor-1/T cell factor (LEF/TCF) transcription factors while serving as an integral component of cadherin-based junctions that mediate cell-cell adhesion (9). Classical (canonical) signaling is initiated by extracellular ligands known as Wnts. In the absence of ligand, β-catenin is phosphorylated on serine by glycogen synthase kinase-3β (GSK-3β) and targeted for degradation. Following ligand binding, inhibition of GSK-3β stabilizes β-catenin, leading to cytoplasmic accumulation and nuclear translocation of β-catenin, at which point it regulates target gene expression (10). As a component of adherens junctions, β-catenin forms a complex with the cytoplasmic tail of E-cadherin, linking it to the actin cytoskeleton (reviewed in ref. 11). Importantly, β-catenin complexed to E-cadherin exists in equilibrium with cytoplasmic β-catenin, so that when β-catenin is freed from E-cadherin (e.g., following injury, growth factor–mediated reductions in E-cadherin) cytoplasmic β-catenin increases and becomes available for translocation to the nucleus through interactions with other proteins (e.g., Smads and LEF/TCF) (9, 12). This dual role of β-catenin is particularly important in the context of EMT, when changes in E-cadherin levels can dramatically alter the balance between bound and cytoplasmic β-catenin. Conversely, β-catenin is essential for maintaining stable cell-cell adhesion by protecting E-cadherin from degradation (13). Integrity of the E-cadherin/β-catenin complex is regulated by tyrosine phosphorylation at the conserved tyrosine 654 residue (Y654) of β-catenin (14), with phosphorylation dramatically reducing affinity of β-catenin for E-cadherin and disrupting cell-cell adhesion.

Role for Wnt/β-catenin signaling in EMT and pulmonary fibrosis

Activation of Wnt/β-catenin–dependent signaling modulates expression of EMT-related genes in the context of development and tumor progression, often in conjunction with TGF-β, but a role for this pathway in fibrotic EMT has not been defined (15). Activation of Wnt/β-catenin signaling and increased expression of components of this pathway and downstream target genes have been demonstrated in lung and AECs in IPF, suggesting a role for Wnt/β-catenin signaling in fibrosis (and perhaps EMT) (16, 17). However, mechanisms underlying activation of β-catenin (specifically its dependence on Wnt signaling) and its role in disease pathogenesis remain to be elucidated. Cooperation between TGF-β and β-catenin pathways has been well described during development, with more recent studies suggesting interactions in adult epithelial and other cells at multiple levels in the course of differentiation processes, including during EMT (18).

Linking ECM to EMT

The epithelial integrin α3β1 is a laminin receptor that colocalizes with E-cadherin and β-catenin at adherens junctions (19). In their study in this issue of the *JCI*, Kim et al. investigated the role of α3β1 integrin in EMT and pulmonary fibrosis (20). They demonstrate that mice with lung epithelial cell–specific loss of α3 integrin (referred to as *FASC mice*) are protected from bleomycin-induced pulmonary fibrosis. FASC mice have decreased accumulation of myofibroblasts and type I collagen, a blunted increase in hydroxyproline and a decrease in EMT, suggesting that protective effects are related at least in part to prevention of myofibroblast differentiation from epithelial cells. Primary AECs from FASC mice did not undergo EMT on fibronectin, conditions previously reported to promote EMT through activation of endogenous TGF-β (4). Levels of phosphorylated Smad2 (pSmad2) or Smad7 were unchanged, invoking alternate mechanisms besides activation of TGF-β. The authors next determined that in wild-type AECs, α3 integrin interacts physically with E-cadherin and TGF-β receptor I. α3 integrin was required for phosphorylation of β-catenin at Y654 and for complex formation between β-catenin and pSmad2. They further demonstrate that pY654–β-catenin accumulates in the nucleus of wild-type AECs undergoing EMT on fibronectin. Consistent with in vitro findings, the authors demonstrate pY654–β-catenin–pSmad2 complexes and nuclear pY654–β-catenin in lungs of control but not FASC mice following bleomycin-induced injury, indicating a requirement for epithelial α3 integrin for complex formation in vivo and leading them to suggest a pathogenetic role for these complexes in EMT. Finally, pY654–β-catenin–pSmad2 complexes and nuclear staining for pY654–β-catenin were detected in myofibroblasts and AECs in human IPF (but not in normal or emphysematous) lung samples.

These studies demonstrate a key role for α3β1 integrin in pulmonary fibrosis and EMT. By promoting tyrosine phosphorylation of β-catenin, α3 integrin is proposed to facilitate complex formation between β-catenin and pSmad2. In this model, α3-dependent phosphorylation of β-catenin modulates the ability of TGF-β to induce EMT (Figure 1). This in turn may be regulated by the ability of α3β1 to engage a particular type of ECM. Previous studies investigating cross-talk between TGF-β and Wnt/β-catenin pathways have addressed transcriptional and intracellular mechanisms rather than interactions with membrane-bound E-cadherin or β-catenin. This study therefore identifies a novel link between β-catenin and TGF-β signaling independent of Wnt ligand activation and suggests a potential mechanism whereby signals can be transmitted from the α3–E-cadherin complex to the nucleus (20). However, it remains to be determined how pY654–β-catenin–pSmad2 complexes promote EMT. In this regard, while previous studies have demonstrated that tyrosine phosphorylation modulates interactions between β-catenin and E-cadherin (11), the current study further demonstrates that pY654–β-catenin translocates to the nucleus (20). Since it has been suggested that β-catenin must be dephosphorylated at N-terminal residues 37 and 41 for transcriptional activation to occur, it remains to be determined whether nuclear translocated pY654–β-catenin–pSmad2 complexes are transcriptionally active and directly regulate target genes important in EMT.

Future directions

The current study (20) provides evidence for what is believed to be a novel role for integrins in regulating interactions between E-cadherin–bound β-catenin and pSmad2, a downstream mediator in the TGF-β pathway. Furthermore, it suggests a mechanism whereby integrins could contribute to differential induction of EMT on specific matrices depending on their ability to function as integrin ligands. α3 integrin is shown to be required for tyrosine phosphorylation of β-catenin by TGF-β and formation of pSmad2–β-catenin complexes. However, the precise mechanisms whereby α3 integrin facilitates phosphorylation of β-catenin and whether nuclear localized pY654–β-catenin plays a causative role in EMT remain to be determined.

The impressive protection from fibrosis conferred by deletion of α3 integrin is difficult to explain simply by prevention of EMT, making it likely that other mechanisms are involved. Interestingly, FASC mice are physiologically normal despite increases in collagen IV and hydroxyproline and an increase in the number of type II AECs. The possibility should be further explored that beneficial effects may be attributable to these or other baseline phenotypic changes. This also raises the question of whether α3 integrin deletion affects expression of other genes (including other integrins) that may influence cell phenotype and response to injury and whether these baseline changes affect long-term survival.

It would also be interesting to know whether the observed role for α3 integrin in IPF can be extended to other fibrotic diseases, especially nonspecific interstitial pneumonia, in which myofibroblasts have not been emphasized as a prominent histologic feature. Regardless, this study (20) demonstrates a novel role for integrins in regulating EMT and pulmonary fibrosis and suggests the exciting possibility of modulating TGF-β–mediated effects in a highly targeted fashion. However, a word of caution is in order. Bleomycin-induced injury is widely used as a model of pulmonary fibrosis but does not fully recapitulate human IPF. Many agents that have been shown to prevent bleomycin-induced fibrosis are less effective when administered once fibrosis is already established. Thus, despite the demonstration of nuclear pY654–β-catenin in IPF tissue, more work is needed before extrapolating therapeutic benefits seen in this model to human disease.

Acknowledgments

Z. Borok is supported by the Hastings Foundation and NIH research grants HL89445, HL62569, HL64365, HL38621, and HL38578 and holds the Ralph Edgington Chair in Medicine. The author gratefully acknowledges Edward D. Crandall, Roland M. du Bois, Michael Kahn, and Ami Oren for thoughtful reading of the manuscript.

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Revisiting Notch in remyelination of multiple sclerosis lesions

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MS results from destruction of the protective myelin sheath surrounding axons, which prevents the transmission of nerve impulses. Precursors of oligodendrocytes, the cells capable of myelinating axons, are preserved in demyelinating lesions; however, why these precursors do not differentiate into mature oligodendrocytes and remyelinate axons is unknown. Contactin is a noncanonical Notch receptor ligand that mediates oligodendrocyte differentiation. In this issue of the *JCI,* Nakahara et al. show that Contactin is abundantly expressed on demyelinated axons in human chronic MS lesions and that Notch1 is activated in oligodendrocyte precursor cells (see the related article beginning on page 169). However, Notch1 intracellular domain coassociates with the nuclear transporter Importin β but fails to show evidence of nuclear translocation. These cytoplasmic aggregates also contain TAT-interacting protein 30 kDa (TIP30), a proapoptotic factor, which inhibits nuclear transport and, consequently, Notch1-mediated oligodendrocyte differentiation and remyelination. These data target TIP30 as a new pathogenic factor in MS.

MS is an inflammatory, demyelinating disease of the CNS that is thought to be mediated by an immune attack directed against oligodendrocytes and myelin. Clinically, patients usually present in early adulthood with a relapsing/remitting form of the disease that over time develops into a chronic progressive state with increasing disability. Pathological staging of MS lesions remains controversial, but they are usually categorized as active/acute, chronic active, and chronic inactive/silent. Acute and chronic active lesions are characterized by perivascular cuffs of lymphocytes and macrophages associated with areas of primary demyelination, with chronic active lesions often showing a chronic core and an active edge, whereas chronic silent lesions display loss of oligodendrocytes, myelin, and axons, with little to no evidence of ongoing inflammation (1). At the edge of some lesions, substantial numbers of premyelinating oligodendrocytes can be observed, indicating that the potential for repair is not limited by the loss of these cells but rather reflects gain or loss of signals that promote oligodendrocyte migration into lesioned areas of the brain and their differentiation into mature myelinating oligodendrocytes. Remarkably, all three types of lesions may be found within adjacent areas of the same brain, suggesting that it is the microenvironment of the lesion itself that influences lesion outcome.

Notch receptor family members (Notch1–Notch4) are type 1 transmembrane proteins that, following ligand binding, are cleaved by a metalloproteinase and a γ-secretase, generating Notch intracellular domain (NICD), which then translocates to the nucleus where it acts as a second messenger to modulate expression of target genes (2). Depending upon the ligand involved in Notch1 activation, these target genes may either inhibit (via canonical signaling) or promote (via noncanonical signaling) differentiation and maturation of oligodendrocyte precursor cells (OPCs) (Figure 1). Ligands belonging to the canonical pathway, such as Delta, Serate/Jagged, and Lag2 (DSL), transduce signals through the CSL/NICD/Mastermind (where CSL represents CBF1, Su[H], Lag1) signaling pathway, leading to transcriptional activation of the inhibitory genes hairy and enhancer of split 1 (*HES1*), *HES5,* and *HES7* as well as hairy and enhancer of split related with YRPW

Conflict of interest: The authors have declared that no conflict of interest exists.

Nonstandard abbreviations used: DSL, Delta, Serrate/Jagged, Lag2; HES1, hairy and enhancer of split 1; NICD, Notch intracellular domain; OPC, oligodendrocyte precursor cell; PLP, myelin proteolipid protein; TIP30, TAT-interacting protein 30 kDa.

Citation for this article: *J. Clin. Invest.* **119**:10–13 (2009). doi:10.1172/JCI37786.