The ATS Journals' Policy on Image Manipulation

Images of gels, radiographs, immunohistochemistry, confocal microscopy, and other representative data sources are frequently shown in articles appearing in the ATS journals. A number of studies have shown that manipulation of images is disturbingly frequent, with as many as 20% of all published scientific manuscripts containing figures in which the presentation has been enhanced in some manner (1–3). Fraudulent manipulations are rare, occurring in an estimated 1% of articles, but can result in major misdirection of scientific investigation and effort. Our own recent survey of a random set of figures obtained from accepted articles to the *AJRCMB* found that approximately 23% of images had undergone some alteration, including erasure or filling in of parts of the background, splicing of bands from one gel into another, and “cloning,” in which pixels are transferred from one area to another in a photo.

Our instructions to authors for the *AJRCCM* and *AJRCMB* were changed in 2007 to note that while it is acceptable to adjust the brightness, contrast, or color balance of an image, this can only be done if such changes are applied to the whole image and as long as there is no misrepresentation of any information in the image (4). This language and approach is consistent with that of many other scientific journals, and permits authors to generate optimal quality figures demonstrating their primary data (2, 5). However, a major concern for us remains fraudulent manipulation of images that misrepresents the results of experiments.

New software has become available that permits detection of image manipulation and is now being routinely and uniformly used in the evaluation of all figures from articles nearing acceptance at ATS journals, including *AJRCCM*, *AJRCMB*, and *PATS* (4, 6). The Editors are informed of all instances of image manipulation and will contact authors for explanation before publication if we have concerns that their data are not being impartially presented. We remind our authors that they should always keep and have access to their original unprocessed images to provide to the Editor upon request (cf. the image manipulation section of the Instructions for Contributors [<http://www.thoracic.org/go/journals>]).

We understand that authors want to present high-quality figures that optimally show their data, and we have no issues with

this approach. At the same time, we need to ensure that the information presented in the ATS journals is unbiased and appropriately represents the original experimental results. Our policy to analyze all images in accepted articles provides a high level of confidence that what the readership sees fairly and accurately presents the data generated in the authors' investigative setting.

Conflict of Interest Statement: E.A. has no financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.B.A. has served on an advisory board for Sepracor, Inc., for which he received \$5,000 in 2007 and \$5,000 in 2006; he has served on the Scientific Advisory Board of the Hamner Institute for Health Sciences, for which he received \$4,000 in 2007 and \$2,000 in 2008; he received a research grant from Sepracor, Inc. for approximately \$100,000 in 2008–2009. S.D.S. has served on advisory boards for GlaxoSmithKline, Boehringer, Wyeth, and Novartis; he also serves as Editor of *AJRCMB*, which is compensated by ATS. A.R.L. is the head of GlaxoSmithKline Center of Excellence, a grant award through him to the University of Chicago; this is for investigator-initiated basic research and is in the amount of approximately \$500,000 direct costs/year since 2000; he has a grant unrelated to this subject for \$75,000 from Merck and Co. to investigate the cell biology of neutrophils; this work is in progress; he had a similar grant from Merck to perform studies in eosinophils 2 years previously for the same amount; he has received an honorarium on occasion in which he chaired or spoke at the Lund Conference for AstraZeneca (approximately \$2,500); none of his papers or talks related to currently marketed products by any company.

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What the Lung Has Taught Us about Latent TGF- β Activation

In the December 2007 issue of the *Journal*, Koth and colleagues show that the multifunctional cytokine transforming growth factor (TGF)- β can claim influence over yet one more process: surfactant

homeostasis (1). The key to this discovery was the observation that mice lacking an important lung epithelium integrin, $\alpha\beta 6$, which activates the latent form of TGF- β , have foamy-appearing alveolar macrophages. This result adds to a growing list of TGF- β functions in the lung that are downstream of $\alpha\beta 6$ -mediated TGF- β activation.

LATENT TGF- β ACTIVATION: IRREDUCIBLE COMPLEXITY?

TGF- β was first isolated as a factor that stimulates the growth of fibroblasts in soft agar (2). It soon became apparent that TGF- β

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* Unless appended by -1, -2, or -3, the term “TGF- β ” here refers generically to all three TGF- β isoforms.

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in fact causes growth arrest of most cell types (including epithelial cells, endothelial cells, and stimulated lymphocytes); that it occurs in three isoforms encoded by separate genes*; and that it is released from cells in a latent form. All three TGF- β isoform genes have been knocked out in mice, and this and other work indicated that TGF- β s play crucial roles in diverse processes (heart and vascular development, control of inflammation, fibrosis in many tissues including lung, fusion of the secondary palate, apoptosis, and carcinogenesis).

Activation of latent TGF- β is increasingly recognized as a critical step in TGF- β actions (3). TGF- β latency (that is, inability of the cytokine to bind TGF- β receptors) occurs because TGF- β is secreted noncovalently connected to its propeptide, which is called latency-associated peptide (LAP). TGF- β activation means altering or completely eliminating the TGF- β :LAP interaction so that TGF- β can engage its receptors. Extensive work on this process, some of it related to TGF- β 's role in lung fibrosis models, and most of it done *in vitro*, led to two classes of putative TGF- β activators. First, various proteases (e.g., plasmin) were proposed to activate TGF- β by degrading LAP (4, 5). Second, other molecules nonproteolytically alter LAP's conformation sufficiently to allow TGF- β activation. Thrombospondin-1 (TSP1) is the best-characterized activator in this class; oxidation reactions also alter LAP's affinity for TGF- β 1 (6–8).

Despite this biochemical progress, the mechanisms involved in specific TGF- β functions *in vivo*, like lung fibrosis, remained obscure for many years. Knockouts of putative TGF- β activators mimicked TGF- β -null animals either loosely, in the case of TSP1 (9), or not at all (e.g., plasminogen and other proteases). Most putative TGF- β activators alluded to above have multiple functions, so the effects of genetically or pharmacologically silencing these activators are hard to interpret. It appeared that TGF- β might have numerous, ill-defined, and overlapping modes of activation that would be impossible to unravel.

α v β 6: A NONREDUNDANT TGF- β ACTIVATOR IN THE LUNG

However, recent work related to integrins shows that genetic models can pin down TGF- β activation *in vivo*. Both TGF- β 1 and TGF- β 3 LAPs have an RGD sequence, a binding motif in ligands for a subset of integrins. Integrins are transmembrane heterodimers of α and β subunits that typically bind matrix molecules or cellular counter-receptors. The integrins α v β 1, α v β 3, α v β 5, α v β 6, α v β 8, α 5 β 1, α 8 β 1, and α IIb β 3 are RGD-binding integrins. Two of them (α v β 6 and α v β 8) bind and activate latent TGF- β 1 and TGF- β 3 (10–13). α v β 6 accomplishes this via a cytoskeleton-mediated traction process acting on latent TGF- β 1 immobilized in the extracellular environment (14); immobilization occurs

because LAP forms disulfide bonds with the matrix-bound molecule LTBP1. In contrast, α v β 8 activates latent TGF- β 1/3 in association with MT1-MMP-mediated proteolysis of LAP.

More than other organs, the lung has provided a clear picture of how specific TGF- β effects are mediated by a single TGF- β activator, in this case α v β 6, whose expression appears to be restricted to epithelium. Lungs of mice with a null mutation in the β 6 gene (*Itgb6*^{-/-}) develop clusters of activated lymphocytes around airways and vessels, strikingly similar to the lungs of *Tgfb1*^{-/-} mice (15, 16). However, the inflammatory lesions in *Itgb6*^{-/-} mice are limited to the lung, and to some extent the skin, rather than appearing in multiple organs as in *Tgfb1*^{-/-} mice. The lung inflammation in *Itgb6*^{-/-} mice is “rescued” by the simultaneous transgenic expression of a constitutively active form of TGF- β 1 (17). Therefore, it is highly likely that the *Itgb6*^{-/-} lung inflammation phenotype is due to lack of TGF- β (although it is possible that TGF- β lung overexpression acts nonspecifically to block inflammation).

Other TGF- β -mediated processes in the lung are now known to be downstream of α v β 6-mediated TGF- β activation (see Table 1). Lung fibrosis after bleomycin and radiation are TGF- β mediated; *Itgb6*^{-/-} mice are completely protected in these models (10, 30), and microarray analysis revealed that a group of TGF- β -inducible genes is not up-regulated in bleomycin-treated *Itgb6*^{-/-} mice compared with bleomycin-treated controls (18). This analysis also revealed that one alveolar macrophage gene, that for MMP12 (an elastase whose expression is suppressed by TGF- β signaling) was strongly up-regulated in *Itgb6*^{-/-} mice. Subsequent work by Morris and colleagues showed that *Itgb6*^{-/-} mice develop MMP12-dependent emphysema due to lack of TGF- β (17). Sheppard and colleagues showed that acute lung injury (in this case, capillary leak after bleomycin injury) is also α v β 6- and TGF- β dependent (19). Recently, Kim and colleagues showed that epithelial-mesenchymal transition (EMT), a TGF- β -mediated process that may be relevant to cancer and fibrosis, is dependent upon α v β 6-mediated TGF- β activation in alveolar epithelial type 2 cells under specific culture conditions (20). Also, Takabayshi and coworkers have shown that the default mode in the lung is for α v β 6-activated TGF- β to suppress alveolar macrophage functions, presumably to prevent lung damage; this block can be transiently reversed by the action of microbial products on Toll-like receptors (21).

Considered as an ensemble, these studies provide very strong evidence that α v β 6 is a nonredundant supplier of active TGF- β in the lung. Moreover, one can make the case that functionally α v β 6 does nothing but activate TGF- β , because the best-studied phenotypes of *Itgb6*^{-/-} mice all appear attributable to TGF- β deficits. However, other functions of α v β 6 have been proposed, such as cell migration on substrates like fibronectin and control

TABLE 1. LUNG ABNORMALITIES IN *Itgb6*^{-/-} MICE DUE TO LACK OF TGF- β

Process	Description	Reference
Inflammation	Activated lymphocytes around airways and vessels; similar to lesions in <i>Tgfb1</i> ^{-/-} mice	(14)
Fibrosis	Protection from bleomycin-induced lung fibrosis	(9)
Acute lung injury	Reduced capillary leak after bleomycin-induced lung injury	(18)
Emphysema	Late onset emphysema due to excess MMP12 production by alveolar macrophages	(16)
EMT	Alveolar epithelial type 2 cells cultured on fibronectin undergo EMT due to α v β 6-mediated TGF- β activation	(19)
Alveolar macrophage function	α v β 6-mediated TGF- β activation inhibits alveolar macrophage functionality; inhibition can be overridden by Toll-like receptor signaling	(20)
Surfactant homeostasis	α v β 6-mediated TGF- β activation is required for normal surfactant homeostasis, probably via effects on alveolar macrophage-mediated surfactant catabolism	(23)

Definition of abbreviations: EMT, epithelial-mesenchymal transition; TGF- β , transforming growth factor- β .

of cell proliferation by a unique cytoplasmic sequence in the $\beta 6$ integrin subunit (22, 23).

A NEW FUNCTION FOR $\alpha \nu \beta 6$ AND TGF- β : SURFACTANT HOMEOSTASIS

Koth and colleagues, in their work on MMP12-dependent emphysema, noted that alveolar macrophages in *Itgb6*^{-/-} mice have an enlarged, vacuolated morphology, which is reversed by transgenic expression of active TGF- β 1. Pursuing this observation, and noting that similar-appearing macrophages occur in pulmonary alveolar proteinosis (PAP), Koth and coworkers elegantly show that high levels of surfactant material accumulate in lungs of *Itgb6*^{-/-} and *Tgfb1*^{-/-} mice, that the abnormality is rescued by expression of active TGF- β 1 in *Itgb6*^{-/-} lung, and that the defect appears to be in the clearance of surfactant by alveolar macrophages (1). It is interesting that this phenotype represents a third example in which alveolar macrophage function is critically dependent upon $\alpha \nu \beta 6$ -mediated TGF- β activation by the lung epithelium (see Table 1). Although alveolar macrophages, which do not express $\alpha \nu \beta 6$, can activate TGF- β *in vitro* under certain conditions (4), evidently this mechanism is not sufficient *in vivo* to compensate for loss of epithelial $\alpha \nu \beta 6$.

Mice lacking GM-CSF signaling develop a PAP-like lung disease, and patients with PAP often have antibodies against GM-CSF, which by blocking GM-CSF signaling cause a human phenocopy of the genetic murine disorders (24). The cause of PAP-like pathology due to reduced GM-CSF signaling is failure of alveolar macrophage differentiation, but this is not the case in the *Itgb6*^{-/-} mice. *Tgfb1*^{-/-} mice develop autoantibodies, but anti-GM-CSF antibodies were not found in the current study. The findings of Koth and colleagues should spur investigators to determine how (or whether) the TGF- β and GM-CSF signaling pathways interact to control surfactant homeostasis, which in general is poorly understood.

THE BIGGER PICTURE

TGF- β 1- and TGF- β 3-null mice have abnormalities in many tissues, but the problems in *Itgb6*^{-/-} mice are mostly limited to the lung—so what are the other TGF β 1/3 activators *in vivo* that rescue the *Itgb6*^{-/-} mice? By invoking only a second integrin, $\alpha \nu \beta 8$, it may be possible to account for TGF- β 1 and TGF- β 3 activity in a wider range of tissues. Mice with a knockin mutation of *Tgfb1* that specifically prevents TGF- β 1 activation by RGD-binding integrins have the same multiorgan pathologies that occur in *Tgfb1*^{-/-} mice (25). Therefore, $\alpha \nu \beta 6$ and $\alpha \nu \beta 8$ (and perhaps other RGD-binding integrins) must play key roles in TGF- β 1 activation *in vivo*. Supporting this notion, the phenotypes of $\alpha \nu$ -null and $\beta 8$ -null mice partially overlap those of TGF- β 1-null and TGF- β 3-null mice (25). Indeed, work by Nishimura's lab strongly suggests that $\alpha \nu \beta 6$ and $\alpha \nu \beta 8$ are the major TGF- β 1 and TGF- β 3 activators in the lung airway (13, 26, 27). Most *Itgb8*^{-/-} mice die at birth from cerebral hemorrhage (28); however, on an outbred background *Itgb8*^{-/-} mice can reach maturity, and we have not observed any histologic lung abnormalities in these mice (our unpublished observations). Most of the lung abnormalities in *Itgb6*^{-/-} mice are alveolar processes, so it may be that $\alpha \nu \beta 6$ is a unique TGF- β 1/3 activator in the alveolar space, while both integrins are active in the proximal airways. Also, TGF- β 2 may be the predominant TGF- β isoform expressed in airway epithelium (26, 29), and little is known about its activation.

Koth and coworkers have shown that careful examination of TGF- β activation-impaired mice can identify new TGF- β

functions. Their study and others prove that a single TGF- β activator, $\alpha \nu \beta 6$, accounts for a range of TGF- β effects in the lung. This work should encourage investigators to identify TGF- β activation mechanisms in other lung disorders that might be influenced by TGF- β , such as bronchopulmonary dysplasia, certain infections (e.g., tuberculosis), subepithelial fibrosis in asthma, and cancer.

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