ANIMAL MODELS OF HUMAN LUNG DISEASE

Murine models of pulmonary fibrosis

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Moore BB, Hogaboam CM. Murine models of pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol 294: L152–L160, 2008. First published November 9, 2007; doi:10.1152/ajplung.00313.2007.—Human pulmonary fibrosis is characterized by alveolar epithelial cell injury, areas of type II cell hyperplasia, accumulation of fibroblasts and myofibroblasts, and the deposition of extracellular matrix proteins. The result is a progressive loss of normal lung architecture and impairment in gas exchange. Pertinent features of the human disease include temporal heterogeneity of the fibrotic lesions, progressive nature of the disease, development of fibrotic foci, and in some patients, a rapid worsening of symptoms known as an acute exacerbation. No current animal model recapitulates all of these cardinal manifestations of the human disease. However, investigations using murine models have led to the identification of many pathological cells and mediators that are believed to be important in human disease as well. In this review, we will summarize the characteristics, advantages, and disadvantages of many of the currently utilized murine models of pulmonary fibrosis.

THE INCIDENCE OF IDIOPATHIC PULMONARY FIBROSIS (IPF) may be as high as 30/100,000 in the U.S. population (3). IPF is a disease process characterized by alveolar epithelial cell injury and hyperplasia, inflammatory cell accumulation, fibroblast hyperplasia, deposition of extracellular matrix, and scar formation (44). The end result of this process is the loss of lung elasticity and loss of alveolar surface area leading to impairment of gas exchange and pulmonary function. The pathological process is patchy and temporally heterogeneous, suggesting sequential (multiple) injuries. Interactions between resident or recruited inflammatory cells and structural cells likely result in chronic inflammatory infiltrates, myofibroblast hyperplasia, and disordered collagen deposition (2, 13, 45, 80). The study of the disease in humans is complicated by the fact that the natural history is unknown. By the time patients seek medical treatment for symptoms, the disease process is generally advanced, and the evolution of the process is unclear. Animal models have been developed to study the evolution of fibrotic responses, and these models have identified a number of key cells, mediators, and processes that are likely involved in human fibrosis. The characteristics, advantages, and disadvantages of many of these model systems will be discussed. Table 1 summarizes the advantages and disadvantages of these model systems.

Bleomycin

The bleomycin model of pulmonary fibrosis is the best-characterized murine model in use today. The drug was originally isolated from Streptomyces verticillatus (91). This antibiotic was subsequently found to be effective against squamous cell carcinomas and skin tumors (90); however, its usefulness as an anti-neoplastic agent was limited by dose-dependent pulmonary toxicity resulting in fibrosis (60). Bleomycin has been shown to induce lung injury and fibrosis in a wide variety of experimental animals including mice, rats, hamsters, rabbits, guinea pigs, dogs, and primates over a range of doses induced via intraperitoneal (ip), intravenous (iv), subcutaneous (sc), or intratracheal (it) delivery (summarized in Ref. 60). One advantage of iv administration is that it more closely mimics the way humans are exposed to the drug regimen. Following iv administration of the drug (20 mg/kg, twice weekly for 4–8 wk), the initial lesion appears to be the pulmonary endothelium. It is believed that initial damage of these cells allows the drug access to the lung interstitium where epithelial damage occurs subsequently (1). The pathological response to this injury has been well characterized (reviewed in Ref. 60) and includes signs of acute lung injury (damage to the alveolar epithelium, leakage of fluid and plasma proteins into the alveolar space, alveolar consolidation, and the formation of hyaline membranes). In response to this injury, there is focal necrosis of type I epithelial cells and the induction of metaplasia in type II epithelial cells. Inflammatory infiltrates are noted, and fibrosis develops in subpleural regions. The resultant accumulation of collagen in the lung is measured both by histological and biochemical techniques, most notably via accumulation of hydroxyproline, which is almost totally derived from collagen in the lung and thus serves as a surrogate for whole lung collagen content (14). A disadvantage of this model system, however, is that fibrosis does not develop in all animals, and the time frame for the development of fibrosis is relatively long. In mice treated for 8 wk, fibrosis is first observed at week 4, with septal and interstitial fibrosis becoming more severe up to 12 wk (1).
The delivery of bleomycin via the intratracheal route (generally 1.25–4 U/kg, depending on the source) has the advantage that a single injection of the drug produces lung injury and resultant fibrosis in rodents (69, 85, 89). Intratracheal delivery of the drug to rodents results in direct damage initially to alveolar epithelial cells. This event is followed by the development of neutrophilic and lymphocytic pan-alveolitis within the first week (35). Subsequently, alveolar inflammatory cells are cleared, fibroblast proliferation is noted, and extracellular matrix is synthesized (75). The development of fibrosis in this model can be seen biochemically and histologically by day 14 (Fig. 1) with maximal responses generally noted around days 21–28 (34, 35, 68, 75). Beyond 28 days, however, the response to bleomycin is more variable. Original reports suggest that bleomycin delivered intratracheally may induce fibrosis that progresses or persists for 60–90 days (27, 86, 89); however, other reports demonstrate a self-limiting response that begins to resolve after this period (26, 49, 68). While the resolving nature of this model does not mimic human disease, this aspect of the model system offers an opportunity for studies of fibrotic resolution at these later time points that to date has not been studied.

The fibrotic response to bleomycin in mice is strain-dependent. C57Bl/6 mice are more susceptible to bleomycin-induced fibrosis than are Balb/c mice (28, 75). This likely reflects strain-dependent differences in the expression of the inactivating enzyme, bleomycin hydrolase (76). Additionally, the fact that lungs are particularly sensitive to bleomycin toxicity is a reflection of the low levels of this enzyme in lung tissue compared with other body tissues (66). Bleomycin is thought to induce lung injury via its ability to cause DNA strand breakage (51) and oxidant injury (74). The multitude of studies looking at inflammation, cytokines, chemokines, and growth factors in bleomycin-induced fibrosis are too numerous to detail here, but a few common themes do bear mention. While the development of fibrosis in response to bleomycin is T cell-independent (30, 87), the development of fibrotic lesions is dependent on the release of chemokines, most notably CCL2 or CCL12 from the injured lung, and the recruitment of inflammatory cells such as monocytes, lymphocytes, and fibrocytes (4, 33, 56, 58, 84, 94). The profibrotic cytokine, transforming growth factor (TGF)-β, is also critically involved in the development of bleomycin-induced pulmonary fibrosis (reviewed in Refs. 18 and 78). Disordered coagulation cascades (32, 65, 82) and eicosanoid imbalances, which favor the overproduction of profibrotic leukotrienes and the underproduction of antifibrotic prostaglandins, are also noted (reviewed in Ref. 9). The proinflammatory cytokine, TNF-α, has a dual role in bleomycin-induced fibrosis and has been reported to both promote (67, 83) and repress disease development (25, 46). Additional mechanisms such as al-
tered epithelial-mesenchymal interactions, circulating mesenchymal precursors and epithelial-mesenchymal transition, and their regulation by inflammatory mediators have recently been reviewed (39).

The advantages of the bleomycin model are that it is well characterized, that it has clinical relevance, and the fact that multiple delivery routes are possible for the induction of fibrosis. The disadvantage is that the disease may be self-limiting in mice.

FITC

The FITC-induced model for pulmonary fibrosis was originally described in 1995 by Roberts et al. (72) and involved the intratracheal administration of FITC (0.007 mg per g body wt dissolved in PBS) delivered to Balb/c mice. Instillation of FITC resulted in a marked infiltration of mononuclear cells and neutrophils within the lung interstitium centered primarily around respiratory bronchioles with focal evidence of edema and alveolar epithelial cell hyperplasia. Protein leak was also noted in the bronchoalveolar lavage fluid within the first week indicating acute lung injury. By 5 mo post-FITC, patchy, focal destruction of the normal lung architecture with interstitial fibrosis was noted. Anti-FITC-specific antibodies were detected in treated mice by day 7 post-FITC and persisted for at least 6 wk, suggesting that the immune response to this hapten may be crucial to the development of the disease (72).

The model was further characterized by Christensen et al. (11) who demonstrated that both C57Bl/6 and Balb/c mice were susceptible to FITC-induced fibrosis, with Balb/c mice showing a greater degree of fibrosis to a given dose of FITC. In addition, the protocol was modified slightly. Fourteen milligrams of FITC was dissolved in 10 ml of PBS, and the solution was vortexed and sonicated for 30 s at 50% power before the instillation of 50 µl per mouse. More extensive sonication resulting in a finer particulate being dispersed to the lung results in significantly more acute lung injury and increased mortality (11). However, the effective dose of FITC can vary up to threefold depending on the lot (Moore, unpublished observation). Similar to findings in the bleomycin model, FITC was demonstrated to induce fibrosis by day 21 in CD4-depleted mice, severe combined immunodeficient (SCID) mice, and recombinase activating gene knockout mice despite the abolition of the anti-FITC immunoglobulin response (11) demonstrating that specific T cell immunity is not required for the development of FITC-induced fibrosis. More recent investigations utilizing the FITC model of fibrosis have demonstrated that like bleomycin, the fibrotic response to FITC is dependent on CCR2 signaling (56). Release of CCL12, and to a lesser extent CCL2 (58), in the injured lung results in the recruitment of CCR2-expressing circulating fibrocytes (57) to the lung and the augmentation of fibrosis. FITC also induces the

Fig. 2. Fibrosis develops in areas of FITC deposition. FITC was instilled intratracheally into C57Bl/6 mice on day 0. On day 21, lungs were harvested for histology. A: H&E stain at ×4 magnification showing areas of consolidation, inflammation, and fibrosis. B: serial section of A at ×4 magnification and viewed under UV light to show areas of FITC deposition. Note that areas of fibrosis in A correspond to areas of FITC fibrosis in B. The red arrows represent areas of the lung with normal architecture, which correspond to areas where FITC did not deposit. Patterns of both central and subpleural fibrosis are noted.

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production of IL-13 in the lung, which is essential for the fibrotic response as well (43).

One distinct advantage of the FITC model is the ability to visualize the areas of the lung where deposition occurs via immunofluorescence imaging for the characteristic green color of the FITC (see Fig. 2). Fibrotic changes have only been noted in areas of FITC deposition (11, 72) suggesting that focal injury to the alveolar epithelial cells, and perhaps persistent conjugation of the FITC to stable proteins such as elastin, may perpetuate the remodeling response (72). A second advantage to the FITC model is that the response is persistent (for at least 6 mo) and does not appear to be self-limiting in the way that bleomycin has been reported to be (23). This persistence makes the FITC model ideal for long-term studies. This may be particularly relevant in situations where one wishes to test a therapeutic strategy in a model of established fibrosis. Alternatively, the model lends itself well to studies of viral-induced exacerbations of fibrosis as will be discussed later.

Irradiation-Induced Fibrosis

Irradiation-induced pulmonary fibrosis can be accomplished by exposure to a single dose of 12–15 Gy of total body irradiation, which results in lung fibrosis as early as 20 wk postexposure (53). More commonly, however, thorax-limited radiation protocols (accomplished by shielding all other parts of the mouse via lead-shielding) are employed to induce lung fibrosis evident by 24 wk postexposure (29, 37, 73). The fibrotic response to thoracic irradiation is regulated by both dose and genetic background. C3H/HeJ and CBA/J mice are classified as fibrosis resistant (24, 77). These resistant strains develop a subacute radiation-induced pneumonitis in response to thoracic radiation, whereas C57Bl/6 mice are fibrosis-prone, developing a late fibrotic response (24, 77). A 16 Gy whole thorax exposure of C57Bl/6 mice results in subpleural foci of collapsed alveolar walls with superimposed collagen at 33 wk postirradiation (29). Additionally, inflammatory cells are noted in the air spaces surrounding the fibrotic lesions. In contrast, C3H mice develop thickened alveolar walls and inflammatory cell accumulation in air spaces but no frank fibrosis (29); alveolar apoptosis is more prevalent in C57Bl/6 mice than in C3H mice in response to irradiation (62). Additionally, C57Bl/6 females also appear to be more sensitive to the development of fibrosis than are males (29). The fibrotic response of C57Bl/6 mice in response to 12.5 Gy of thoracic radiation was shown to be associated with elevations in the levels of monocyte- and lymphocyte-derived lymphotactin, RANTES (CCL5), CXCL-10 (IP-10), CCL2 (MCP-1), CCL7 (MCP-3), and MIP-1γ (Scya9) at 26 wk postirradiation that were not evident in fibrosis-resistant C3H mice (36, 37). Additionally, the chemokine receptors CCR1, 2, 5, and 6 were elevated in fibrosis-sensitive mice at 26 wk postirradiation (36, 37). These results have led to the hypothesis that chronic mononuclear cell recruitment and activation may be key features of irradiation-induced fibrosis (36). TGF-β has been implicated as an important early signal in the development of irradiation-induced fibrosis (73). Similarly, differential expression of TNF-α has been implicated as a regulatory factor (10). C3H and C57Bl/6 mice both produce TNF-α early postirradiation. The TNF-α response is strongly upregulated in C3H mice at 3–4 mo postexposure, and this response is downregulated thereafter. In contrast, the fibrosis-prone C57Bl/6 mice do not upregulate the expression of TNF-α at later time points (10). Thus, this cytokine may regulate the pneumonitis vs. fibrosis response. Finally, investigations into the pathogenesis of irradiation-induced fibrosis have indicated that bone marrow-derived cells (in particular, macrophages and fibroblasts) accumulate and proliferate in the areas of lung fibrosis (21). Figure 3 demonstrates the characteristic pathology of irradiation-induced fibrosis seen at week 32. Interestingly, the delivery of manganese superoxide dismutase-plasmid/liposomes via intratracheal injection 24 h before total lung irradiation caused
a reduction in the accumulation of bone marrow-derived cells and a corresponding protection from fibrosis (21). In summary, the advantages of irradiation-induced fibrosis models are the well-characterized differences in susceptibility among inbred mouse strains, which facilitate studies of genetic determinants of fibrosis and the clinical relevance of this model. The disadvantage, however, is the length of time necessary for the fibrotic response to develop necessitating the housing of mice for long periods of time and the associated per diem costs.

Silica

The instillation of mineral fibers into the rodent lung results in the development of fibrotic nodules that resemble lesions which develop in humans following some occupational exposures to mineral dust and particulate aerosols (63). Silica can be delivered to mice via aerosolization (15, 16), intratracheal administration (5, 65), or via oropharyngeal aspiration (47). As noted in other models, the fibrotic response to silica instillation is strain-dependent. C3H/HeN mice exposed to aerosolized cristobalite silica (70 mg/m³, 5 h/day for 12 days) demonstrate fibrotic nodules, increased pulmonary lymphoid tissue, and increased numbers of macrophages, neutrophils, and lymphocytes in the bronchoalveolar lavage fluid 12–16 wk postexposure (16). Prominent fibrotic responses are also noted in MRL/MpJ and NZB mice, whereas Balb/c mice show little response

In the aerosolized model, disease is associated with persistent expression of IL-1 and TNF-α in C3H/HeN mice (17). C57Bl/6 mice have been shown to be more susceptible to the development of fibrosis than CBA/J mice following intratracheal instillation of silica (64). Additionally, NMRI mice are susceptible to the development of silica-induced fibrotic nodules 1 mo after the instillation of 5 mg per mouse of DQ12 crystalline silica intratracheally (48). Silica is retained in the lung, and the response is characterized by a persistent, toxic, and inflammatory response including increased lactate dehydrogenase activity in the bronchoalveolar lavage fluid and alveolar accumulation of proteins and neutrophilia (48). Interestingly, silica can induce a fibrotic response in both rats and mice, but one study suggests that the pathological processes appear to be different in the two rodents (5). In rats, silica induces a chronic and progressive inflammation that is accompanied by the overproduction of TNF-α. Anti-inflammatory therapies are effective in blocking silica-induced fibrosis in rats (5). In mice, the fibrotic response is associated with limited and transient inflammation and overexpression of the anti-inflam-
matory cytokine, IL-10. In this murine model, anti-inflammato
tory therapies have no effect (5). Despite the fact that silica
instillation induces a strong Th2 response in mice (6), these
cytokines are not instrumental to the development of the
disease (54). The classic fibrotic nodules that develop in
response to silica can be seen in Fig. 4.

The silica model of fibrosis has the advantage that silica is
not readily cleared from the lung, thus the fibrotic stimulus is
persistent. Additionally, the fibrosis is easily identified as
fibrotic nodules that develop in areas of silica deposition.
While aerosolization is the method of exposure for humans,
experimental aerosolization requires specialized equipment
that is not readily available in all institutions. Whereas some
studies report the development of fibrosis within the first month
postexposure (47, 48), other studies claim a 60-day period is
necessary for the development of fibrosis (5), which results in
higher per diem costs per experiment.

Transgenic Models of Pulmonary Fibrosis: Pulmonary-
Specific Transgenes

The advent of technologies, which facilitate the permanent
introduction of genomic material into laboratory animals, have
revolutionized our understanding of the fibrotic response in the
lung. From the beginning, transgenic models were recognized
as particularly attractive research tools because they provide an
in vivo system in which to explore molecular mechanisms that
account for the temporal, spatial, and stimulus-responsive reg-
ulation of an individual transgene (15, 31). Accordingly, trans-
genic models have revealed the pathophysiological fibrictic
consequences of increased human or mouse transgenes. Exam-
les are numerous at this point, but some highly cited examples
include human collagenase under the directed expression by
the haptoglobin promoter (15), human TGF-α directed by the
surfactant protein C (SP-C) promoter (43), PDGF-B directed
by the SP-C promoter (43), IL-11 directed by the Clara cell
10-kDa (CC10) protein promoter (88), and IL-13, also directed
by the CC10 promoter (95). Each one of these transgenic
strains showed major features of interstitial pulmonary remod-
eling and fibrosis, which in the case of IL-13 led to severe
mouse morbidity and mortality (95). A major criticism regard-
ing the use of transgenic mice is that early versions of these
models involved the constitutive expression of the transgene
over the lifespan of the mouse, a condition that does not mimic
the clinical fact that pulmonary fibrosis is mainly observed in
late adulthood. More recently, molecular techniques have ad-
vanced to the point whereby it is now possible to induce the
expression of a given inserted transgene in appropriately aged
mice with an initiating signal provided by doxycycline (38).
The attraction of these newer, regulated transgenic models is
that the duration of expression of a given transgene is con-
trolled, and once the transgene is silenced upon the removal of
the initiating signal, processes that naturally lead to the regres-
sion of pulmonary fibrosis can be subsequently examined. The
major drawback of transgenic mouse models of pulmonary
fibrosis is that the vast majority of these models involve the
generation of pharmacological quantities of a single gene
product, thereby potentially creating an “artificial” pulmonary
environment that might have little to do with the multi-genetic
nature of pulmonary fibrosis.

Transgenic Models of Pulmonary Fibrosis: Virus-Targeted
Transgene Delivery

The advent of replication-deficient recombinant adenovi-
ruses created tremendous optimism that gene therapy would be
a reality for several lung diseases, particularly cystic fibrosis
(19). This enthusiasm was dampened with the clear demon-
stration that these vectors are not benign carriers and actually
pose serious health risks during clinical application. However,
adeno viral vectors have proven useful in studying the effects of
increased recombinant gene expression in airway epithelial
cells when administered directly to the rodent pulmonary
system. When delivered into the lung, adenovirus-delivered
transgenes persist for less than 21 days (19). Adenovirus-
mediated gene transfer techniques have been employed to
transiently overexpress cytokines and chemokines including
GM-CSF (92, 93), TNF-α (55), TGF-β (7, 81), and IL-1β (41),
and each of these transgenes has been shown to cause signific-
ant fibrotic lung injury in rodents. These adenoviral vector-
directed transgenic models have provided valuable animal
models for understanding the pathogenesis of pulmonary

Table 2. Fidelity of animal models of fibrosis to human usual interstitial pneumonia (UIP)

<table>
<thead>
<tr>
<th>Features of Fibrosis</th>
<th>Present in UIP?</th>
<th>Present in Animal Models?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute deterioration</td>
<td>Can be due to infection or idiopathic in nature</td>
<td>Infectious exacerbation can be modeled</td>
</tr>
<tr>
<td>Acute inflammation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Altered lung mechanics</td>
<td>Yes</td>
<td>Yes, but more difficult to measure</td>
</tr>
<tr>
<td>Alveolar collapse</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>Variable</td>
<td>Yes</td>
</tr>
<tr>
<td>Epithelial cell injury</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Extracellular matrix deposition</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fibrotic foci</td>
<td>Yes</td>
<td>Rarely noted in bleomycin or FITC models, may be present in adoptive transfer of human UIP fibroblasts</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>Hyperplastic epithelial cells</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>Intersitial thickening</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Myofibroblast accumilation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Progressive disease course</td>
<td>Yes</td>
<td>The FITC and silica models are persistent, but no animal model is progressive</td>
</tr>
<tr>
<td>Subpleural fibrosis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Temporal heterogeneity</td>
<td>Yes</td>
<td>No</td>
</tr>
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fibrosis. Adenoviruses have also been shown to prove effective in the delivery of antifibrotic transgenes, as shown by the delivery of a transgene for human manganese superoxide dismutase or human copper/zinc superoxide dismutase before irradiation, and these transgenes were found to protect against irradiation-induced lung damage in mice (20). Similar antifibrotic therapies have also been applied to the bleomycin model. For example, the intratracheal injection of a recombinant adenovirus carrying murine Smad7 (an endogenous inhibitor of TGF-β signaling) cDNA prevented bleomycin-induced lung fibrosis (61). While adenovirus-mediated gene delivery has proven effective in manipulating the lung environment to either promote or inhibit fibrosis, these vectors are limited in that they evoke a vigorous immune response, which prevents repeated dosing. Consequently, other vectors have been examined, and vectors such as the recombinant adenovirus associated and helper-dependent viruses have been identified, which also target the pulmonary epithelium without the major inflammatory and immune responses evoked by first-generation adenovirus vectors (22, 40). Another drawback to employing adenoviral vectors to deliver transgenes to the lung is that these viruses are highly trophic for epithelial cells and poorly infect other cell types present in the lung. In response to this limitation of adenoviral vectors, lentivirus has gained popularity as a retroviral vector for experimental gene delivery. Lentiviral vectors permanently insert transgenes into various cells in the lung allowing for analysis of long-term gene overexpression (79). Thus, the use of viral vectors provides for the analysis of the in vivo effect of transgene overexpression on the adult lung, and as such these models have proven useful in the exploration of individual gene products on the initiation and maintenance of experimental pulmonary fibrosis.

Adoptive Cell Transfer Models

Recognizing that we know very little about the initiating soluble factors responsible for the unremitting tissue remodeling response during pulmonary fibrosis, research attention has been directed toward using the cellular players to recapitulate this disease in immunodeficient mice. Fibroproliferation is a major feature that is presumably mediated by dysregulated collagen production by a number of fibroblast subtypes. These subtypes include fibrocytes, epithelial-derived mesenchymal cells, tissue resident progenitor cells, and resident fibroblasts. There is a recognized circulating pool of collagen-producing cells termed fibrocytes that respond to chemotactic stimuli in response to tissue injury and contribute to the wound healing process (8). Phillips and colleagues (70) showed that intravenously introduced human fibrocytes migrate into the mouse lung following bleomycin challenge, and these recruited cells appeared to contribute to the injury (70). Similarly, adoptive transfer of lung fibrocytes to FITC-challenged mice exacerbates the fibrotic response (58). Our group has recently studied the direct impact of cultured human fibroblasts on the pulmonary fibrotic response in C.B-17 SCID/beige (bg) mice. In this model, pulmonary fibrosis was initiated by the intravenous introduction of primary human fibroblast lines into immunodeficient mice (71). Figure 5 shows the distribution of labeled human cells 7 days posttransfer in immunodeficient mice and the resulting pathology noted on day 21. Future studies are directed toward understanding the manner in which diseased human fibroblasts initiate and maintain fibrosis in the mouse lung.

MURINE FIBROSIS MODELS

Mice Models For Infectious Exacerbations of Fibrosis

Pulmonary fibrosis in humans can be associated with at least two disease patterns. In the first, patients experience a slow progressive disease course over months to years. In the second, patients may experience a rapid worsening of symptoms over a period of 4 wk or less. When the rapid deteriorations are idiopathic in nature, they are termed acute exacerbations (reviewed in Ref. 12). Infections can also cause a rapid deterioration of symptoms with enhanced morbidity and mortality in fibrosis patients (52). There is no animal model for the development of idiopathic acute exacerbations, but several studies have suggested that viral infections, particularly infections with herpesviruses, may augment fibrotic responses. Infection with murine gamma herpesvirus-68 (γHV-68) 1 wk before the instillation of bleomycin results in augmented fibrotic responses (50). Thus, γHV-68 can augment fibrotic responses when given before the fibrotic challenge. γHV-68 infection alone can cause multi-organ fibrosis when delivered to an IFNγ receptor-deficient, Th2-biased mouse (59). This is intriguing in light of the fact that murine models of fibrosis are often strongly associated with Th2 cytokine bias (6, 42, 54).

We have recently explored the use of γHV-68 as an agent to exacerbate established FITC-induced fibrosis. Infection of C57Bl/6 mice with 4 × 10^5 pfu γHV-68 on day 14 post-FITC strongly exacerbates the deposition of collagen within the lungs as measured by histology and hydroxyproline content on day 21 (unpublished observations). The persistent nature of the FITC model will allow us to explore the effects of infection at late time points postfibrotic challenge (days 30, 60, and 90 post-FITC) as well. We believe this model will show promise for the dissection of pathways involved in the exacerbation of fibrosis by infection. This is an important problem in the natural history of fibrosis patients and an area where new animal models are needed.

Summary

While none of the animal models reviewed above recapitulate all of the cardinal manifestations of human pulmonary fibrosis (see Table 2), these models do offer valuable research tools for the elucidation of cells, mediators, and signaling pathways that can contribute to fibrotic changes. Additionally, they provide important preclinical models for the testing of hypotheses as well as potential therapeutics.

REFERENCES


