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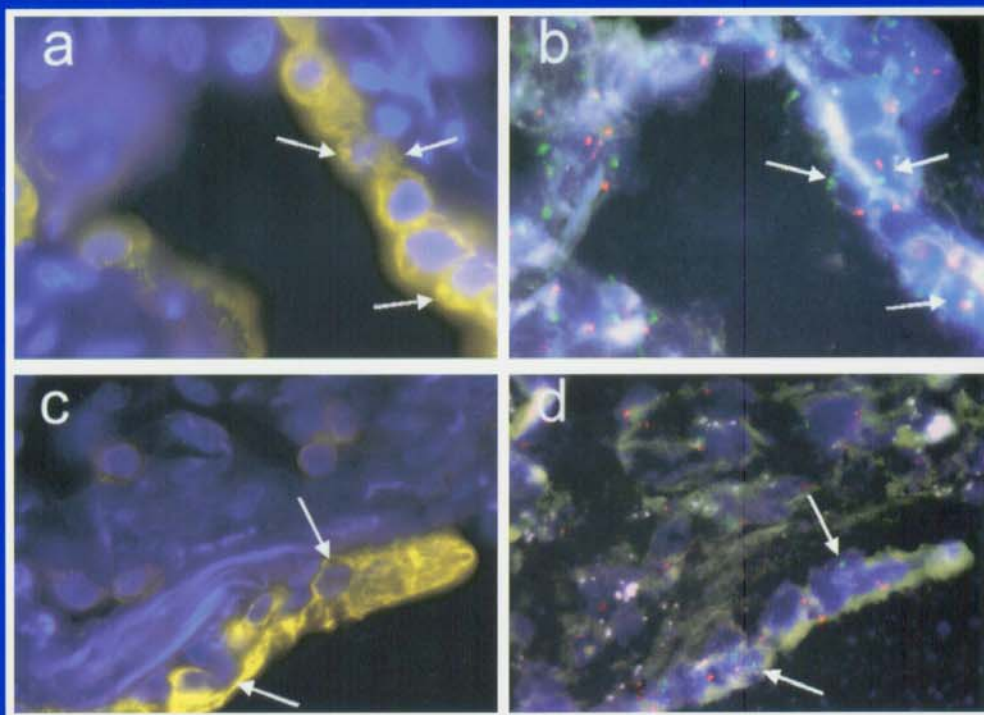
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Human Pulmonary Chimerism after Hematopoietic Stem Cell Transplantation

Benjamin T. Suratt, Carlyne D. Cool, Amanda E. Serls, Lin Chen, Marileila Varella-Garcia, Elizabeth J. Shpall, Kevin K. Brown, and G. Scott Worthen

Department of Medicine, University of Vermont College of Medicine, Burlington, Vermont; Departments of Pathology and Medicine, University of Colorado School of Medicine; and National Jewish Medical and Research Center, Denver, Colorado

Many of the body's tissues once thought to be only locally regenerative may, in fact, be actively replaced by circulating stem cells after hematopoietic stem cell transplantation. Localization of donor-derived cells ("chimerism") has recently been shown to occur in the lungs of mice after either hematopoietic stem cell transplantation or infusion of cultured marrow. To determine whether tissues of the human lung might be similarly derived from extrapulmonary sources, we examined lung specimens from a retrospective cohort of female allogeneic hematopoietic stem cell transplant recipients who received stem cells from male donors. Tissue samples from three such patients who had undergone diagnostic lung biopsy or autopsy were examined. Slides were stained by immunohistochemistry for cytokeratin (epithelium) and platelet endothelial cell adhesion molecule, CD31 (PECAM) (endothelium) and were imaged and then examined by fluorescent *in situ* hybridization analysis to identify male cells. The resulting overlapping *in situ* hybridization and immunohistochemistry images were examined for the presence and, if present, cell type of donor cells in the lung. We found significant rates of epithelial (2.5–8.0%) and endothelial (37.5–42.3%) chimerism. These results suggest that significant chimerism of the human lung may follow hematopoietic stem cell transplantation and that adult human stem cells could potentially play a therapeutic role in treatment of the damaged lung.

Keywords: bone marrow transplantation; stem cells; cell lineage; endothelium, vascular/cytology; epithelial cells/cytology

Although the lung has typically been thought of as a complex organ with limited regenerative capacity, there is substantial evidence that reparative and compensatory growth can nonetheless occur (1). Such growth has traditionally been attributed to *in situ* proliferation and phenotypic conversion of resident cells such as Clara cells or type II pneumocytes within the lung to replace its various tissue compartments after injury (2). Recently, developments in the field of stem cell biology have suggested that many of the body's tissues previously believed to be only locally regenerative (or altogether nonregenerative) may, in fact, be actively replaced under a variety of circumstances through processes involving circulating stem cells (3). Animal models have demonstrated the derivation of endothelium (4–7), skeletal and cardiac muscle (7–11), and neural (12–16) and hepatic (17–19) tissues

from putative stem cells. Human studies after allogeneic hematopoietic stem cell and solid-organ transplantation have demonstrated the subsequent appearance of endothelium (20, 21), hepatocytes (22, 23), skin epithelium (23), and renal mesenchymal cells (24) of donor origin (in the case of hematopoietic stem cell transplantation [HSCT]) or recipient origin (in the case of solid-organ transplantation), suggesting derivation of these cells from circulating stem cells. Such "chimerism" has recently been shown to occur experimentally in the lungs of mice after either stem cell transplantation with radioablation (type II pneumocytes) (25, 26) or cultured bone marrow infusion after bleomycin lung injury (type I pneumocytes) (27).

We examined a cohort of sex-mismatched allogeneic HSCT patients to determine whether the tissues of the lung might be derived from extrapulmonary sources in the human, as well.

METHODS

Selection of Tissue Specimens for Review

A retrospective review of all allogeneic hematopoietic stem cell transplants performed under institutional review board–approved protocols at the University of Colorado Health Sciences Center from January 1995 to June 2001 was performed. Of the 161 transplants (including bone marrow, $n = 51$; cord blood, $n = 37$; and peripheral blood stem cells, $n = 73$), 76 were sex mismatched. Transplants of male donor cells to female recipients occurred in 46 cases (bone marrow, $n = 16$; cord blood, $n = 10$; and peripheral blood stem cells, $n = 20$). Twenty six of these 46 patients had undergone diagnostic lung biopsy or autopsy. Tissue specimens showing infection ($n = 13$) or extensive tumor metastasis ($n = 3$) or with insufficient tissue for analysis ($n = 5$) were excluded. Tissue specimens (one surgical lung biopsy and two autopsies) from three successfully engrafted patients were analyzed. Additional tissue specimens (one surgical lung biopsy and one autopsy) from a patient who underwent two transplants without long-term engraftment and two tissue specimens (both surgical) from untransplanted patients (one male and one female) who had undergone diagnostic biopsies were used as control subjects.

Of the four transplanted patients selected, one received both related allogeneic bone marrow and peripheral blood stem cells from the same donor, whereas three received unrelated allogeneic cord blood transplants (28) (see the online supplement). All specimens were stripped of identifying data, except for sex and transplant status before analysis.

Tissue Preparation

Five consecutive 5- μ m sections were cut from each formalin-fixed paraffin-embedded specimen. The first and fifth sections were examined by hematoxylin and eosin staining and fluorescent *in situ* hybridization (FISH) for the sex chromosomes, respectively, whereas two center sections were used for fluorescent immunohistochemistry for either cytokeratin (epithelial cells) or PECAM (endothelial cells), followed by FISH of the same section, as detailed later here. The remaining section was dual stained for PECAM and CD45 to distinguish between endothelium and leukocytes and followed by FISH.

Immunohistochemistry

Tissue sections were stained with antibodies to cytokeratin (CAM 5.2; B-D Biosciences, San Jose, CA), PECAM (JC/70A; DAKO, Carpint-

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Correspondence and requests for reprints should be addressed to Benjamin T. Suratt, M.D., Division of Pulmonary Sciences and Critical Care Medicine, University of Vermont Health Sciences Research Facility, Room 230, 149 Beaumont Avenue, Burlington, VT 05405. E-mail: benjamin.suratt@uvm.edu

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eria, CA), or both CD45 (PD7/26 and 2B11; DAKO) and PECAM (SC-8306; Santa Cruz, Santa Cruz, CA) (*see* online supplement). Imaging was performed by identifying areas of interest using the hematoxylin and eosin-stained slide of each tissue specimen. These areas were then located on the corresponding immunohistochemistry-stained slides from the same tissue specimen (*see* online supplement for details).

FISH and Analysis

A modified protocol for dual-color FISH assays of formalin-fixed tissue sections was used to identify the sex chromosomes (29) using CEP X SpectrumOrange and CEP Y SpectrumGreen probes (Vysis, Inc., Downers Grove, IL) (*see* the online supplement). Because of sectioning of the nuclei in some cells, some nuclei displayed signal for only one sex chromosome, and these were scored as male (Y only) or indeterminate (X only). Less than 100% of cells in the specimens were identifiable as male or female because of truncation of nuclei by sectioning or incomplete hybridization. Endothelial and epithelial cells of donor (male) origin were identified by analysis of the mapped overlapping immunohistochemistry and FISH images. Epithelial cells were identified on the basis of morphology and strong staining for cytokeratin. Endothelial cells were identified by appropriate endothelial morphology with bright, granular PECAM staining, as well as an absence of CD45 staining in dual-stained slides.

RESULTS

Patient Characteristics

Clinical characteristics of the six patients, including conditioning regimen, source, and dose of CD34+ cells, are shown in Table 1. Tissue specimens were obtained from these patients at 50–463 days after transplantation (Table 2). Analysis of hematopoietic chimerism, as determined by FISH of uncultured marrow or sorted peripheral blood cells, is shown in Table 2. These assays were performed within 2 weeks of obtaining lung tissue, except in patient 3, whose last assay preceded lung biopsy by 8 months and who had no evidence of subsequent graft failure. All patients showed complete hematopoietic chimerism at the time of tissue sampling (Table 2), except patient 4, who had received two transplants from the same donor without successful long-term hematopoietic engraftment (data for both transplants are presented in Table 1). Biopsy-proven chronic graft versus host disease was present in patients 3 and 4 at the time of tissue sampling and was manifested in patients as a skin rash and obliterative bronchiolitis (Table 2). In patient 4, this occurred despite failure of engraftment and appeared related to repeated donor lymphocyte infusions that were employed to treat recurrent leukemia. Histopathologic diagnoses of the lung tissue specimens included diffuse alveolar damage, bronchiolitis obliterans and organizing pneumonia, and obliterative bronchiolitis (Table 2).

Identification of Donor-derived Cells in Lung

FISH analysis of control tissues demonstrated excellent sensitivity (84.8% positive for Y in male control) and specificity (0% positive in female control) (Table 2). A large overall percentage (27.7–55.2%) of cells from the three successfully engrafted patients (Table 2; patients 1–3) was found by FISH to be of donor origin. Review of corresponding tissue sections stained by hematoxylin and eosin suggested that the majority of these cells were leukocytes based on morphology. Only a small fraction (0.9–1.0%) of donor-derived cells was found in the two tissue specimens from patient 4, who lacked long-term engraftment (Table 2), and these cells appeared to be lymphocytes by morphology. In patients 1–3, further analysis was performed to establish the cell type of the donor-derived nonleukocyte cell populations.

Donor-derived Pulmonary Epithelial and Endothelial Cells

Immunohistochemical staining for endothelial cells (PECAM) and epithelial cells (cytokeratin) was performed on tissue specimens from patients 1–3 and both sex control subjects (patients 5 and 6). The overall percentages of endothelial and epithelial cells present in the analyzed fields were 25–34% and 39–50% of nucleated cells, respectively. Representative fields for PECAM (Figures 1a and 1c) and cytokeratin (Figures 2a and 2c) are shown. The same slides were subsequently examined by FISH for donor (male) cells (Figures 1b, 1d, 2b, and 2d). As shown in Table 2, tissue specimens from patients 1 and 3 demonstrated that 35.7–42.3% of the endothelial and 2.5–8.0% of the epithelial cells were of donor origin. In contrast, none of the endothelial or epithelial cells examined in patient 2 were of donor origin. Specimens stained for both PECAM and CD45 (leukocyte common antigen) demonstrated an absence of cells staining for both antigens and confirmed the high incidence of donor-derived endothelial cells (Figures 3a and 3b).

Donor-derived epithelial and endothelial cells were predominantly found in the alveoli, although donor-derived epithelial cells were occasionally found in the bronchiolar lining (Figures 2c and 2d). Although endothelial chimerism was extensive in the alveolar capillaries, no endothelial chimerism was identified in arterioles or arteries. Unfortunately, because of the absence of areas of normal lung in specimens from patients 1 and 2, no correlation between degree of tissue injury and chimerism was possible. Interestingly, donor-derived epithelial and endothelial cells were largely absent from areas of graft versus host disease-related obliterative bronchiolitis (patient 3). None of the morphologically identified fibroblastic tissue present in the specimens (primarily in areas of obliterative bronchiolitis and organizing acute and organizing diffuse alveolar damage) appeared to be of donor origin.

TABLE 1. PATIENT CHARACTERISTICS

Patient Number	Sex	Diagnosis	Age at Transplant (Years)	Conditioning Regimen	Transplant Source	HLA Match	CD34 Cell Dose (kg)
1	F	HD	24	TBI/MEL/ATG	Cord blood	5/6 B	4.3 × 10 (4)
2	F	Breast cancer	32	BU/MEL/ATG	Cord blood	6/6	1.9 × 10 (4)
3	F	NHL	40	TBI/MEL/ATG	Cord blood	5/6 B	1.4 × 10 (5)
4	F	CML	34	BU/MEL/ATG	Related BM	6/6	5.1 × 10 (6)
			36	TBI/FLU/ATG	Related PBSCs	6/6	24.0 × 10 (6)
5	F	Control	(51)				
6	M	Control	(74)				

Definition of abbreviations: ATG = antithymocyte globulin; B = HLA mismatched at the "B" locus; BM = bone marrow; BU = busulfan; CML = chronic myelogenous leukemia; FLU = fludarabine; HD = Hodgkin's disease; HLA = human lymphocyte antigen; MEL = melphalan; NHL = non-Hodgkin's lymphoma; PBSCs = peripheral blood stem cells; TBI = total body irradiation. Numbers in parentheses represent age at biopsy.

TABLE 2. PATIENT HEMATOPOIETIC CHIMERISM AND BIOPSY RESULTS

Patient No.	Hematopoietic Chimerism at Time of Biopsy	GVHD	Days Post-transplant to Biopsy	Histopathologic Pattern	Percentage of Y+ Cells		
					Overall	Epithelium	Endothelium
1	PB 99.2% MNC 99.8% CD3+ 100%	None	200	DAD	46.1	2.5	35.7
2	BM 99.3%	None	50	DAD	27.7	0.0	0.0
3	BM 100%	Lung, skin	462	OB	55.2	8.0	42.3
4	PB ND; MNC ND; CD3+ 9%	Lung, skin	225	OB	0.9	ND	ND
4	PB ND; MNC ND; CD3+ 9%	Lung, skin	241	BOOP	1.0	ND	ND
5				DAD	0.0	0.0	0.0
6				BOOP	84.8	84.0	80.8

Definition of abbreviations: BM = bone marrow; BOOP = bronchiolitis obliterans and organizing pneumonia; DAD = acute and organizing diffuse alveolar damage; GVHD = graft versus host disease; MNC = mononuclear cell; ND = not determined; OB = obliterative bronchiolitis; PB = peripheral blood.

DISCUSSION

We report finding phenotypically differentiated donor cells incorporated into the recipients' lungs after therapeutic HSCT. Although this is the first report of such pulmonary chimerism in humans after HSCT, the existence of such phenomena has previously been demonstrated in murine lungs (25–27), as well as in a variety of other animal and human tissues after both hematopoietic and solid-organ transplantation (3).

In both our study and the animal studies of Krause and colleagues and Kotton and colleagues (25–27), there appears to be an overall alveolar predominance to this phenomenon, consistent with the belief that the most regenerative compartments of the lung appear to be the most distal (1). Yet incorporation was also found in the bronchiole of one subject (Figures 2c and 2d). This finding is of interest, as a recent publication suggests that upper airway chimerism (as manifest in nasal epithelium) does not occur after marrow transplantation (30). Although it was not possible to examine the potential relationship of tissue injury to tissue chimerism (because of the limited num-

ber of patients examined and the scarcity of normal tissue within the specimens), we did not observe any correlation between degree of epithelial or endothelial chimerism and presence of active graft versus host disease (as evidenced by bronchiolitis obliterans). A similar lack of correlation was found by Korbly and colleagues, in their examination of skin and liver chimerism after HSCT (23). The apparent absence of fibroblastic tissue of donor origin in the lung specimens contrasts with previous demonstrations of host-derived fibrotic tissue in chronic rejection after allogeneic kidney transplantation (24). This discrepancy raises the interesting possibility that fibroblastic cells, although derived from circulating stem cells in the case of intimal fibrosis after renal allograft, may not be derived from the constituents of cord blood after engraftment (at least within the time frame of up to 462 days we examined).

The high rates of endothelial chimerism found in two specimens (35.7–42.3%) are similar to those reported in kidney and liver after transplant (20, 21). This incidence also appears to correlate with the rate of incorporation of circulating endothelial

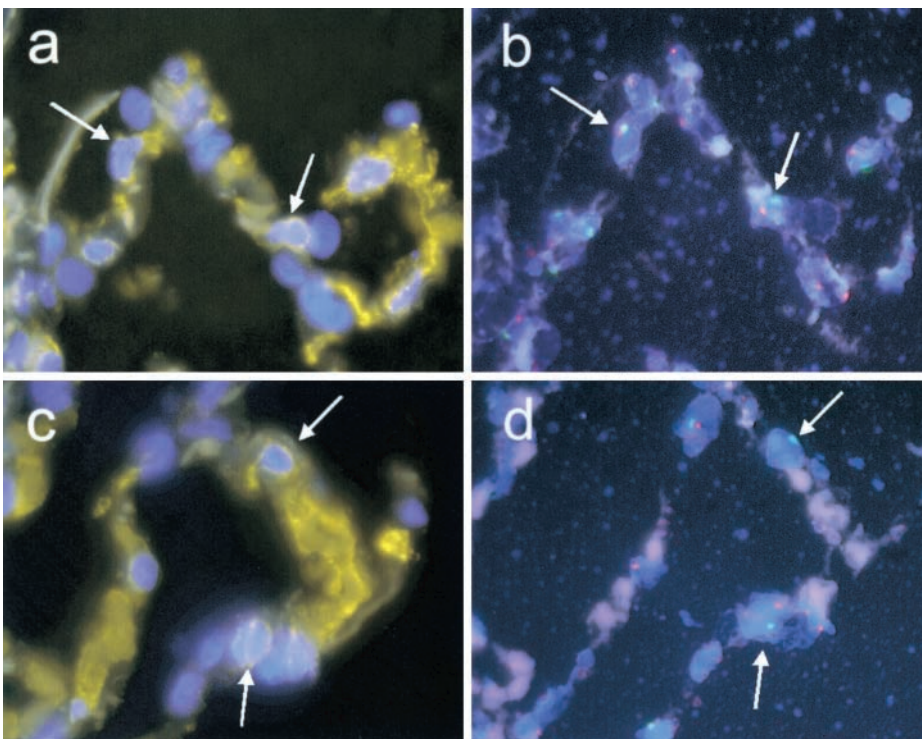


Figure 1. Lung specimens from patients after sex-mismatched HSCT and stained with endothelial cell-specific antibody (PECAM), followed by FISH for the sex chromosomes. (a and c) Staining of specimens with endothelial-cell specific antibody (PECAM, yellow) and nuclear dye (4',6'-diamidino-2-phenylindole hydrochloride, blue) showing distribution of endothelium in the alveolar capillaries. Arrows indicate same cells in paired images (a and c, c and d). (b and d) Same specimens labeled by *in situ* hybridization of X (red) and Y (green) chromosomes, showing presence of donor-derived (male, green) endothelial cells (arrows) in alveolar capillaries of female HSCT recipients.

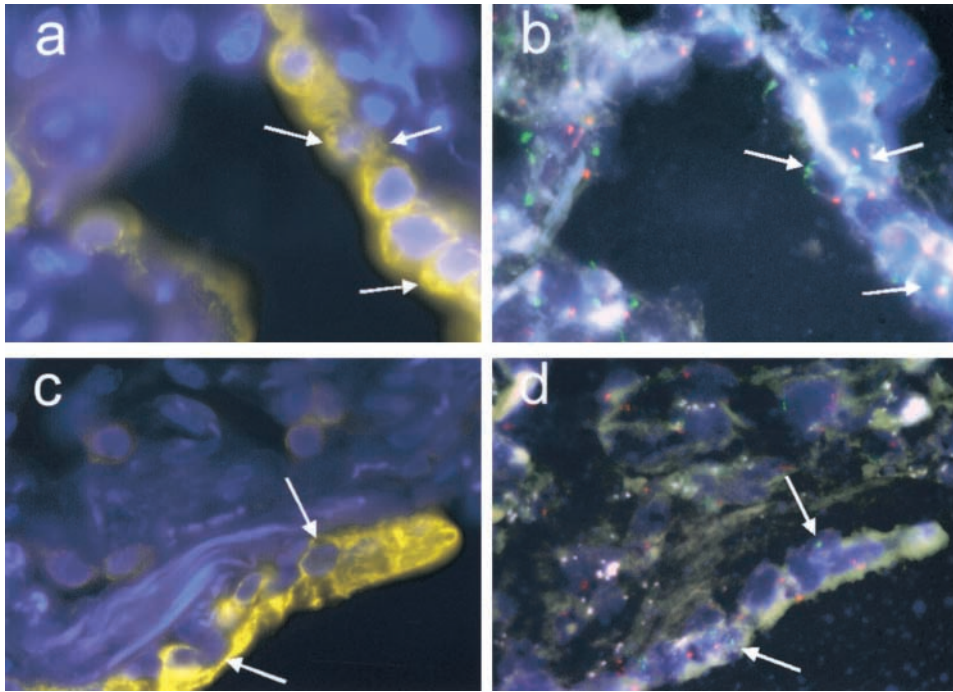


Figure 2. Lung specimens stained with epithelial cell-specific antibody (cytokeratin), followed by FISH for the sex chromosomes. (a and c) Staining of specimens with epithelial cell-specific antibody (cytokeratin, yellow) and nuclear dye (DAPI, blue) showing distribution of epithelium in the alveolar wall (a) and terminal bronchiole (b). Arrows indicate same cells in paired images (a and b, c and d). (b and d) Same specimens labeled by *in situ* hybridization of X (red) and Y (green) chromosomes, showing presence of donor-derived (male, green) epithelial cells (arrows) in the alveolar walls and distal airways of female HSCT recipients.

progenitors into blood vessels during experimental models of neoangiogenesis (31). Pulmonary epithelial chimerism appears to occur at a much lower incidence (2.5–8.0%), and although comparable to the reported incidence of skin epithelial chimerism (23) after HSCT, the incidence is significantly less than that reported (20%) in Krause’s mouse model of pulmonary chimerism after transplant (25).

Although the small sample size of this study limits definitive conclusions, the lack of chimerism in patient 2 is of interest. Given the patient’s relatively brief engraftment period at the time of biopsy (50 days) compared with patients 1 and 3 (200 and 462 days, respectively), this might reflect a requirement for long-term engraftment before circulating stem cell incorporation (or differentiation) in the lung. Alternatively, the differences in conditioning regimens between patient 2 and patients 1 and 3 (melphalan versus irradiation) could suggest that regimen-specific lung injury may modulate the recruitment or retention of stem cells.

Although our findings suggest that pulmonary chimerism may derive from circulating stem cells after HSCT, the possibility exists that such cells were directly incorporated into the recipi-

ents’ lungs after infusion, perhaps by cell “fusion” (32). We attempted to control for this by examining a patient who underwent two hematopoietic infusions (although not cord blood) without long-term engraftment (patient 4) and who in fact was found not to have donor cells present in her lung. Similarly, no chimerism was seen in one patient within 50 days of cord blood infusion (patient 2), suggesting that simple cell trapping is less likely to account for our findings in the other patients.

Our findings, although demonstrating the occurrence of pulmonary chimerism after HSCT, must be considered preliminary in nature, given the limited number of patients analyzed. Technical limitations of our approach also may limit our conclusions, as we may slightly underestimate the incidence of tissue chimerism (because of the requirement of serial staining) or overestimate it (because of small numbers of leukocytes contaminating, in particular, the CD31[+] cell population). Given these limitations, detailed analysis of the true incidence and degree of pulmonary chimerism after transplant, as well as factors that may influence its appearance, must await the development of better techniques and the examination of large numbers of HSCT recipients.

We provide the first evidence of chimerism in the human

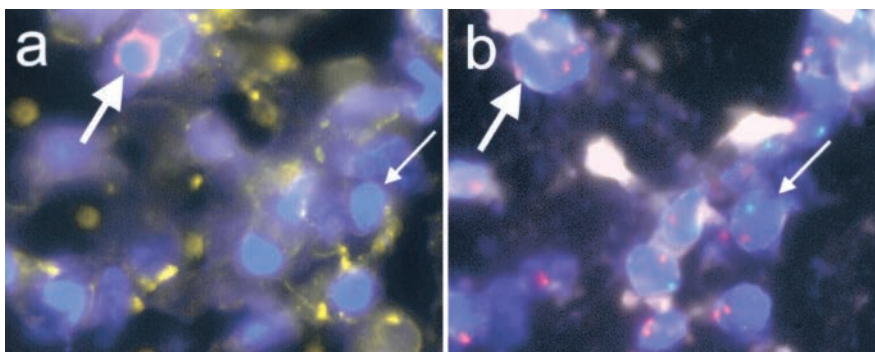


Figure 3. Dual-stained lung specimen with leukocyte-specific antibody (CD45) and endothelial cell-specific antibody (PECAM), followed by FISH for the sex chromosomes. (a) Staining of specimen with endothelial cell-specific antibody (PECAM, yellow), leukocyte-specific antibody (CD45, red), and nuclear dye (DAPI, blue) showing that capillary endothelium and leukocytes do not contain. Arrows indicate same cells in paired images (a/b). (b) Same specimen labeled by *in situ* hybridization of X (red) and Y (green) chromosomes, showing presence of donor-derived (male; green) endothelial cell (small arrow) and leukocyte (large arrow) in the alveoli of a female HSCT recipient.

lung after HSCT. Although the role of circulating stem cells in tissue regeneration and repair in the lung is as yet poorly delineated, these findings are potentially of considerable therapeutic interest and warrant further investigation.

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