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Transmission of donor lymphocytes in clinical lung transplantation

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Abstract Passenger mononuclear cells in organ grafts are known to influence the alloimmune response to the graft. To assess their relevance in clinical lung transplantation, we studied the amount, distribution, cell types, and surface marker expression of mononuclear cells in human donor lungs. Two major compartments of mononuclear cells could be differentiated: lymph nodes containing resting T and B lymphocytes, and the lung tissue itself, containing mainly activated lymphocytes as well as monocytes/macrophages. Tissue-associated mononuclear cells make up $20–40 \times 10^9$ cells per lung, about 30–50 % of which are lymphocytes. Tissue-associated lymphocytes are predominantly T and NK cells; most of the T cells are $CD8^+$ $CD45R0^+$ and express HLA-DR. Strong expression of the adhesion molecules LFA-1 and ICAM-1 is present on infiltrating cells as well as on resident cells of the organ. Moreover, the lymphocytes inside the lung tissue are functionally highly active, with a strong stimulatory as well as alloreactive potency. Thus, large numbers of allogeneic mononuclear cells and particularly large numbers of functionally active lymphocytes are obviously transmitted by human lung allografts. The immunological in vivo relevance of these cells after lung transplantation may include allostimulation and graft-versus-host activity, but also beneficial immunomodulatory effects.

Key words Lung transplantation, donor lymphocytes · Lymphocytes, donor, lung transplantation
Transmission, donor lymphocytes, lung transplantation

Introduction

The lung represents an organ that is in the first line of contact with foreign, i.e., environmental and microbiological, antigens. Because of this barrier function, the organ is endowed with a potent local immune system consisting of mononuclear cells distributed all over the lung tissue [6, 14], as well as with a large number of regional lymph nodes. In organ transplantation these lung-associated mononuclear cells may become of particular relevance when they are transferred into an allogeneic environment. The relevance of passenger lymphocytes and monocytes is highlighted by individual cases of graft-versus-host-disease [7] after lung transplantation, and also by experimental data on the sensitizing function of donor-derived antigen-presenting cells [9]. Previously, we were able to show that considerable numbers of passenger mononuclear cells are transferred by human liver grafts [19] and that these cells can be found in the circulation of patients after transplantation [18]. In this study we have analyzed the amount, localization, and types of passenger mononuclear cells in human donor lungs in order to assess the potential immunological relevance these cells might have after transplantation.

Materials and methods

Donors and the organ harvesting procedure

This study includes five lungs that were harvested from brain-dead organ donors as part of a multiorgan retrieval operation performed using standard techniques. In brief, following preparation of the organs, the lungs were perfused with 10 l of Euro-Collins (EC) solution via the pulmonary artery and were then stored at + 4 °C until transplantation. For analysis of passenger mononuclear cells, specimens of the unused contralateral lung as well as lymph node material from the graft were obtained.

Cell separation techniques

For quantitation of passenger mononuclear cells, these cells were obtained from a lung tissue specimen and from lymph node tissue of defined weight by mechanical disruption and collagenase digestion as described previously for liver allografts [19]. For quantification of donor type mononuclear cells in the lung tissue, core biopsies were taken from different parts of the lung using 14-gauge Tru-Cut biopsy needles (Travenol, Deerfield, Ill., USA). Biopsy cylinders of a defined weight between 50 and 100 mg were then incubated in cell culture medium (RPM 1640, Flow Lab, Meckenheim, Germany) containing 1.5 mg/ml collagenase type IV (Sigma, Deisenhofen, Germany) at 37 °C for 3–4 h with intermittent vortexing. After that time a cell suspension was obtained that consisted predominantly of single cells. Numbers of mononuclear cells in the sample were determined by cell counting in a Fuchs-Rosenthal chamber after dilution with Türk's solution for erythrocyte lysis and with trypan blue dye for exclusion of nonvital cells. The numbers of cells per gram of lung tissue and for the whole lung were then calculated from the number of mononuclear cells present in the defined biopsy specimens of five donor lungs. To exclude localized accumulation of mononuclear cells at certain sites, biopsies from different parts of the same organ were studied. For flow cytometric analysis, mononuclear cells from the livers were additionally obtained by fine needle aspiration biopsies after initial studies had shown that the populations of mononuclear cells obtained by collagenase digestion and by aspiration biopsies were very similar. Additional core biopsies of the lungs were obtained and immediately frozen in liquid nitrogen for immunohistological analysis.

Lymph nodes adjacent to the hilar structures of the lung were separated from the graft. This preparation mostly yielded five to eight smaller lymph nodes for analysis; these lymph nodes usually remain on the graft in clinical transplantation. Mononuclear cells from these lymph nodes were obtained by cutting the tissue into small fragments, suspending them in medium containing collagenase, and passing the fragments through a steel mesh. This led to single cell suspensions in which the number of cells was determined as described above. In addition, these cell suspensions were analyzed by flow cytometry, as described below. Due to the variability in the amount of lymphoid tissue present on the donor lungs analyzed, the cell numbers varied over a wide range.

Antibodies used

For immunocytology and flow cytometry, a variety of commercially available monoclonal antibodies was used, including antibodies from Dianova (Hamburg, Germany) against CD54 (ICAM-1; IOL54), monocytes/macrophages (27E10), CD45R0 (IOL3), and CD11a (LFA-1; IOT6); and from Becton-Dickinson (Heidelberg, Germany) against CD3 (Leu-4), CD20 (Leu-16), CD56 (Leu-19), HLA-DR, CD4 (Leu-3), CD8 (Leu-4), and CD45RA. Most of the antibodies used for flow cytometry were directly labelled with either fluoresceinisothiocynate (FITC) or phycoerythin (PE). For indirect staining, an FITC-labelled goat-anti-mouse antibody (Dianova) was used.

Immunohistology and flow cytometry

To analyze the distribution of passenger cells in the tissue as well as the expression of adhesion molecules and cellular activation markers, biopsy specimens of the donor organ were snap-frozen in liquid nitrogen and cryostat sections were obtained. After fixation of the sections in acetone, Fc receptors were blocked by incubation with human immunoglobulin. Then the slides were incubated with 50 µl of the appropriate antibody dilutions at room temperature for 60 min and subsequently washed with phosphate-buffered saline. Then the slides were incubated with a secondary antibody coupled either with alkaline phosphatase or with peroxidase. After 30 min of incubation, binding of alkaline phosphatase-coupled antibodies was detected by incubation with Fast-Red TR salt, 1 mg/ml, or Fast-Blue, 0.5 mg/ml (Sigma, Deisenhofen, Germany), containing naphtol AS-MX phosphate, dimethylformamide, and levamisol in TRIS buffer solution (pH 8.2) for 20 min; binding of peroxidase-coupled antibodies was detected by incubation with 3-amino-9-ethyl-carbazole (Sigma, Deisenhofen, Germany) in acetate buffer (pH 5.2) containing hydrogen peroxide.

In addition, cells obtained from the lung tissue and from the lymph nodes were subjected to two-color flow cytometric analysis using a FACStar cytometer (Becton-Dickinson, Heidelberg, Germany). After incubation with a human immunoglobulin preparation for Fc-receptor blocking, cell suspensions were incubated with the respective antibodies at 4 °C for 30 min. For double staining, incubation with the respective antibody was followed by incubation with FITC-coupled goat-anti-mouse antibody in cases of indirect staining (as performed for adhesion molecules). For flow cytometric analysis, a life gate was set to include all viable leukocytes, and parameters of 20000–50000 events were accumulated into a list mode file. For analysis of lymphocytes an additional gate was set, based on the forward and side scatter characteristics of these cells. The evaluations were based on an average of about 10000–20000 signals within the lymphocyte gate.

Functional studies

Passenger cells for functional analyses were obtained as described above and were separated by centrifugation over a Ficoll-Hypaque gradient with a density of 1077 g/l; peripheral blood mononuclear cells were obtained by Ficoll separation of heparinized blood. Cells were washed and resuspended in cell culture medium consisting of RPMI 1640 (Flow Lab, Meckenheim, Germany), 10 % heat-inactivated fetal calf serum (FCS; Biochrom, Berlin, Germany), 15 mM HEPES buffer, 4 mM glutamine, 100 IE/ml penicillin/streptomycin. Some 10^5 cells per well were cultured in U-shaped microtiter plates (Nunc, Roskilde, Denmark) in 200 µl of culture medium. Stimulation was performed by 1 µl/ml phytohemagglutinin (PHA-P), 10 ng/ml of the anti-CD3 mouse IgG2a monoclonal antibody OKT3 (Muromonab-CD3, Cilag, Sulzbach, Germany), 20 U/ml interleukin 2 (IL-2, Biotest, Dreieich, Germany), or 10^5 irradiated (40 Gy) allogeneic peripheral blood mononuclear cells obtained from blood donors; alternatively, passenger mononuclear cells were irradiated and used as stimulator cells for allogeneic blood donor cells. After cultivation for 3 or 5 days at 37 °C and 5 % CO_2 in a humidified atmosphere, 1 µCi ^{3}H-thymidine was added for

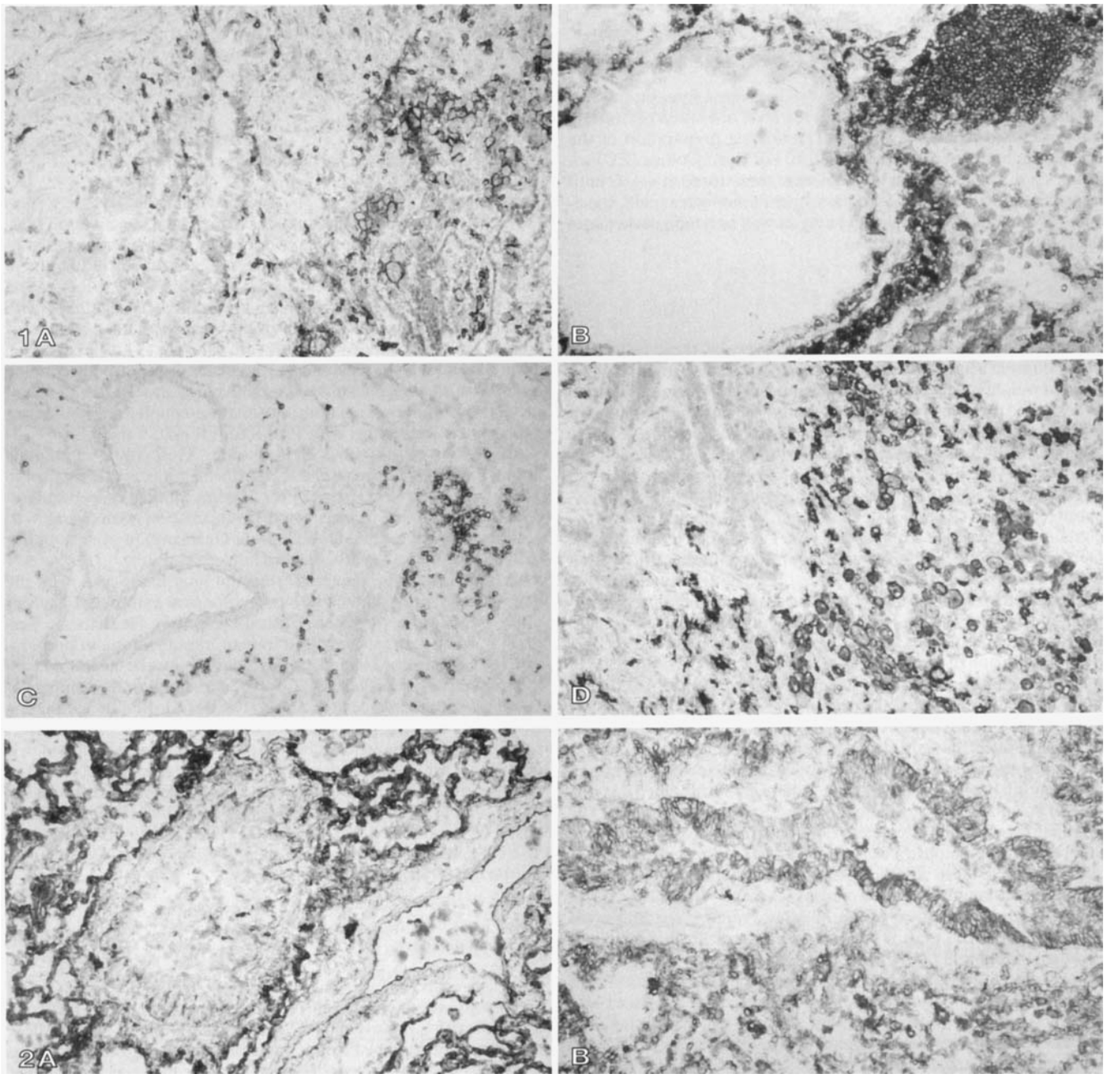

Fig. 1 A–D Populations and distribution of passenger cells in human donor lungs. **A** Immunohistological staining of tissue-associated passenger leukocytes by an antibody against the leukocyte common antigen CD45 reveals: cellular accumulations as well as individual cells mainly in the interstitial spaces; **B** bronchus-associated lymphoid tissue *(BALT)*, as demonstrated by staining for CD45; **C** T-cell distribution, as detected by a monoclonal antibody against CD3; **D** large numbers of monocytes/macrophages stained by the monoclonal antibody 27E10. Staining was performed on cryostat sections of snap-frozen tissue specimens by indirect staining using a peroxidase-coupled secondary antibody (× 125)

Fig. 2 A, B Intensive expression of: **A** adhesion molecule ICAM-1 (CD54) and **B** HLA class II antigens (HLA-DR) on bronchial, vascular, and alveolar epithelium in a human donor lung. Staining was performed on cryostat sections of snap-frozen tissue specimens by indirect staining using a peroxidase-coupled secondary antibody (× 160)

Table 1 Subpopulations and surface marker expression of passenger lymphocytes in human donor lungs

	Parenchyma	Lymph nodes
$CD3^+$	55 %	52 %
$CD20^+$	19 %	45 %
$CD56^+$	15 %	1 %
$DR^+/CD2^+$	60 %	4 %
$CD4^+$	16 %	35 %
$CD8^+$	36 %	16 %
$CD45RA^+/CD3^+$	21 %	76 %
$CD45R0^+/CD3^+$	81 %	22 %
$LFA\text{-}1^{+++}$	95 %	2 %

another 8 h. Subsequently, cells were harvested onto glass fiber filters, scintillation fluid was added after air drying, and ^3H-thymidine incorporation was determined using a beta counter (Betaplate, LKB, Freiburg, Germany). Results are given as mean counts per minute (cpm) of triplicate cultures; the standard deviation was around 10 %–15 %.

Results

Numbers and distribution of passenger mononuclear cells in donor lungs

Perfused human donor lungs contain mononuclear cells in two different compartments: (1) in the lymph nodes, mainly located in the hilum of the lung, and along the major airways; and (2) distributed throughout the tissue of the lung itself. The total number of lymph node cells associated with a graft is highly variable, depending on interindividual differences and on the preparation technique of the organ. Thus, the number of passenger lymph node cells lies between 0.1 and 2×10^9 for a lung graft, and these cells are almost exclusively lymphocytes. The majority of passenger mononuclear cells that we observed, however, was present in the tissue of the lung itself (Fig. 1 A); rarely was bronchus-associated lymphoid tissue (BALT) found (Fig. 1 B). The number of mononuclear cells in a perfused lung is at least $20–30 \times 10^9$, about 50 % of which belong to the monocytic lineage. Most of the passenger lymphocytes we observed were found in the interstitial spaces of the lung and in the perivascular and peribronchial areas, while some cells were also found inside the vessels or in the alveoli. In contrast to the lymph nodes, the lung tissue contained both lymphocytes (Fig. 1 C) and monocytes/macrophages (Fig. 1 D); most of the granulocytes are generally removed by the perfusion of the organ with preservation solution. Passenger monocytes and macrophages were distributed throughout the interstitial spaces and lined the alveolar walls, but could also be found inside vessels and bronchi (Fig. 1 D).

Subpopulations and surface marker expression of passenger lymphocytes

The two compartments, lung tissue and lymph nodes, contained markedly different populations of lymphocytes and differed with regard to their surface marker expression and their state of activation as well (Table 1). Lymph node cells consisted almost exclusively of resting T and B cells, with the majority of T cells being $CD4^+$ and $CD45RA^+$ $CD45R0^-$. In contrast, T and NK cells predominated in the tissue, with fewer B cells in this compartment. A considerable number of the T and NK cells were activated ($HLA\text{-}DR^+$) and most of the T cells were $CD8^+$ and $CD45R0^+$ $CD45RA^-$. Moreover, these cells showed a strong expression of the adhesion molecules LFA-1, VLA-4, VLA-5, and ICAM-1. Cells in the rare BALT were mainly $CD45RA^+$ B cells.

Expression of adhesion molecules and activation markers in donor lung tissue

In the tissue of the donor lungs, a general expression of the adhesion molecules VLA-1, VLA-3, VLA-5, VLA-6, CD51, ICAM-1, ICAM-2, and LFA-3 was observed on vascular endothelial cells. In addition, VLA-2, VLA-3, VLA-6, CD51, and ICAM-1 were, in part, also expressed on bronchial epithelial cells and on alveolar septi (Fig. 2 A). HLA-DR expression was not restricted to many of the passenger mononuclear cells but was also found on bronchial epithelium and on some vascular endothelial cells (Fig. 2 B).

Functional characteristics of tissue-associated passenger mononuclear cells

Passenger mononuclear cells inside the tissue represent functionally active cells. Upon nonspecific stimulation, the cells proliferate vigorously and demonstrate a functional pattern slightly different from that of peripheral blood mononuclear cells. Stimulation by the mitogen PHA is similarly effective in peripheral blood and tissue-associated cells. In contrast, the response to the anti-CD3 antibody is much stronger in the tissue-associated cells, but this difference can be eliminated by the addition of exogenous interleukin-2 (Table 2); the response to IL-2 alone was also stronger in the tissue-associated cells.

The passenger cells also demonstrated a strong proliferative response following stimulation by different allogeneic cells (Table 3). Moreover, as stimulators, irradiated passenger cells were also able to elicit a marked response of allogeneic mononuclear cells that was even slightly stronger than the response induced against peripheral blood mononuclear cells of the same donor (Table 3).

Table 2 Functional profile of passenger mononuclear cells (PC) from human donor lung in comparison to peripheral blood mononuclear cells (PBMC)

Responder cells	Stimulus	Duration (days)	^{3}H-thymidine incorporation (cpm)
PC-A[a]	Medium	3	1130
PC-A	PHA	3	35455
PC-A	OKT3	3	32957
PC-A	OKT3+IL-2	3	92168
PC-A	IL-2	3	15756
PBMC-A[b]	Medium	3	618
PBMC-A	PHA	3	57663
PBMC-A	OKT3	3	1255
PBMC-A	OKT3+IL-2	3	84320
PBMC-A	IL-2	3	9325

[a] Passenger mononuclear cells from donor (A)
[b] Peripheral blood mononuclear cells from donor (A)

Table 3 Functional profile of passenger mononuclear cells (PC) from human donor lung in culture with allogeneic mononuclear cells

Responder cells	Stimulus	Duration (days)	^{3}H-thymidine incorporation (cpm)
PC-A[a]	Medium	5	1139
PC-A	PBMC-B[b]	5	9706
PC-A	PBMC-C[b]	5	35020
PC-A	PBMC-D[b]	5	22096
PBMC-B	Medium	5	4355
PBMC-B	PC-A	5	72871
PBMC-B	PBMC-A[c]	5	56806

[a] Passenger mononuclear cells from donor (A)
[b] Peripheral blood mononuclear cells from allogeneic control B, C, D, respectively
[c] Peripheral blood mononuclear cells from donor (A)

Discussion

Passenger mononuclear cells in human lung grafts can be divided into two compartments that contain markedly different cell types, i.e., the lymph nodes and the pulmonary tissue. While the number of lymph nodes present on human lung grafts is very variable, due to a high donor-related variability as well as to differences in the surgical preparation technique, large numbers of mononuclear cells are generally transmitted by the organ tissue itself. In contrast to the lymph nodes, which contain almost exclusively resting T and B cells, the tissue-associated lymphocytes are mainly T and NK cells. Most of the lymphocytes in the tissue are preactivated, as indicated by their HLA class II expression, and T cells are predominantly $CD8^+$ and $CD45R0^+$. These lymphocyte subsets in the lung are similar to those found in donor livers, although we have observed more B and fewer NK cells, as well as a markedly higher overall rate of activated cells, in the lung tissue [19].

In fact, considerable numbers of lymphocytes have previously been described as being present in human lungs, mainly due to cells adhering to the vascular endothelium [13], but also due to cells in the interstitial spaces [6]. In spite of in situ perfusion of the organ's vascular system during the harvesting procedure, most of the tissue-associated lymphocytes and monocytes/macrophages apparently remain inside the donor organs. This may be due, in part, to the extravascular location of these cells, but also to the strong expression of the adhesion molecule LFA-1, which enables the passenger cells to withstand the mechanical perfusion effect by firmly sticking to the ICAM-1-expressing organ tissue. In comparison to published data about normal, healthy lungs [5, 6], the donor lungs seem to contain increased numbers of lymphocytes, particularly in the interstitial spaces. This may be due to the history and to the condition of organ donors, who have usually been on intensive care treatment and on mechanical ventilation for several days. Such therapy, in combination with an underlying trauma or previous operations, is known to be an adequate trigger for the release of inflammatory mediators such as TNFα [10, 11]. Such mediators can lead to a redistribution of lymphocytes from the blood into the lung tissue within a few hours [17]. An activated state of the donor lungs is also indicated by the strong expression of adhesion molecules and of class II major histocompatibility antigens in the tissue. Thus, donor lungs cannot be regarded as normal, healthy organs; in fact, they contain an increased load of activated mononuclear cells. The majority of those cells remain in the lung during harvesting of the organ and are, therefore, transferred to the recipient during transplantation of the organ.

As for the immunological relevance of passenger mononuclear cells, the marked heterogeneity of the mononuclear cell populations must be considered. In principal, the functional properties of passenger mononuclear cells can be grouped into three categories. First, sensitization of the recipient against the donor antigens may occur, and this may happen either in the periphery or centrally after migration of passenger cells to lymphoid compartments of the recipient [1]. A strong stimulatory activity of the passenger cells has been demonstrated in cell culture studies. Most likely, this is due to the dendritic cells from the graft [20]; however, this might also involve HLA DR-expressing B and T cells [2, 8]. Second, the functional ability of the passenger T lymphocytes in the allogeneic environment may lead to either subclinical or clinical graft-versus-host reactions, as suggested by the alloreactive properties of these cells in vitro. Apart from causing clinically relevant graft-versus-host reactions [7], the reactivity of these cells may also have immunosuppressive properties, enabling graft acceptance, as has been suggested for bone marrow transplantation [12]. Finally, the donor lymphocytes might exert more specific immunomodulatory activites, e.g., by

non-professional alloantigen presentation by the activated HLA DR-expressing T cells or by veto cell mechanisms exerted by the considerable population of $CD8^+$ passenger cells [4, 21]. Analyses in lung transplant patients have demonstrated that donor lymphocytes migrate out of the graft and recirculate in the blood for a few weeks [16]. Thus, there is ample opportunity for the passenger mononuclear cells to interact with the recipient's immune system and to influence the alloresponse in either direction. In contrast, monocyte lineage cells of donor origin seem to be more sessile in the transplanted organ, where they can obviously persist for several months [3, 15].

In conclusion, human donor lungs represent immunologically activated organs containing large numbers of mononuclear cells and may thereby cause considerable numbers of passenger cells to be transferred during transplantation. These cells have the potential to exert a number of immunologically negative as well as positive functions. The overall biological relevance of these cells in vivo may depend on the net effect of their functional properties under the given circumstances. This net effect, however, depends on a large number of variables, including the relative proportion of the individual cell components, their subpopulations, and their activation state, but also on the immunocompetence of the recipient, the immunosuppressive medication, and several other factors. In order to avoid deleterious effects of passenger lymphocytes and to increase beneficial ones, the relevant cell populations, their activation state, and the functional profile of individual subsets have to be defined in more detail. From these results, therapeutic strategies may be developed in order to achieve specific immunomodulation of the recipient by the defined application of donor-derived mononuclear cell populations.

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