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IL-5 Mediates Eosinophilic Rejection of MHC Class II-Disparate Skin Allografts in Mice

Alain Le Moine,*† Murielle Surquin,*† François Xavier Demoor,* Jean Christophe Noël,‡ Marie-Anne Nahori,§ Marina Pretolani,¶ Véronique Flamand,* Michel Y. Braun,* Michel Goldman,* and Daniel Abramowicz†‡

CD4 T cells play a crucial role in the acute rejection of MHC class II-disparate skin allografts, mainly by Fas/Fas ligand-mediated cytotoxicity. Because recent observations indicate that eosinophils may be found within allografts rejected by CD4 T cells, we evaluated the role played by IL-5, the main eosinophil growth factor, and by eosinophils in the rejection of MHC class II-disparate skin grafts. C57BL/6 mice rapidly rejected MHC class II-disparate bm12 skin grafts. Rejected skins contained a dense, aggressive eosinophil infiltrate. Lymphocytes isolated from lymph nodes draining rejected bm12 skin were primed for IL-5 secretion, and IL-5 mRNA was present within rejected grafts. The IL-5/eosinophil pathway played an effector role in allograft destruction, because the rejection of bm12 skin was significantly delayed in IL-5-deficient mice as compared with wild-type animals. The role of the IL-5/eosinophil pathway was further investigated in MHC class II-disparate donor-recipient strains unable to establish Fas/Fas ligand interactions. Fas ligand-deficient gld/gld mice rejected bm12 skins, and bm12 mice rejected Fas-deficient lpr/lpr C57BL/6 skins. Neutralization of IL-5 prevented acute rejection in both combinations. We conclude that MHC class II-disparate skin allografts trigger an IL-5-dependent infiltration of eosinophils that is sufficient to result in acute graft destruction. The Journal of Immunology, 1999, 163: 3778–3784.

A major role is played by CD4-positive T cells in the distinct effector pathways that lead to organ allograft rejection. First, CD4 T cells themselves may display direct cytotoxicity toward cells expressing MHC class II alloantigens (1). This pathway of cytotoxicity involves interactions between Fas ligand (FasL)3 on CD4 lymphocytes and its counterreceptor Fas on allogeneic targets (2, 3). Second, CD4 T cells are the main producers of IL-2 and other cytokines critical for the clonal expansion of alloreactive CD8 cytotoxic cells (4). Third, they provide help to B cells to produce alloantibodies (5, 6). Fourth, CD4 T cells are able to recruit and activate macrophages within the allograft, leading to a delayed type hypersensitivity (DTH) allograft reaction (7–9). Activated macrophages release toxic molecules, including oxygen radicals, TNF-α, and enzymes that contribute to graft damage (10–15). Recent observations suggest that there might be yet another effector mechanism of CD4-dependent allograft destruction involving eosinophils (16–18). Indeed, acutely rejected cardiac allografts from CD8-depleted recipient mice were infiltrated by numerous eosinophils (17). Along the same line, eosinophils were prominent within murine skin allografts rejected by alloreactive CD4 lines secreting IL-5, the major eosinophil growth factor (19–21). Activated eosinophils produce several toxic molecules such as major basic protein and eosinophil cationic protein (22) that, like macrophage products, may damage the allograft. However, whether eosinophils are just innocent bystanders or whether they play an effector role in allograft rejection has not been elucidated yet.

Here, we first show that MHC class II-disparate bm12 skin allografts rejected by C57BL/6 mice display a massive eosinophil infiltrate. The causal role of IL-5 was investigated by performing grafts on IL-5-deficient mice and by injection of neutralizing anti-IL-5 Abs in donor-recipient strains unable to establish Fas/FasL interactions.

Materials and Methods

Mice

C57BL/6 and BALB/c mice were obtained from IFFA CREDO (Brussels, Belgium). C57BL/6-gld/gld FasL-deficient mice, C57BL/6-lpr/lpr Fas-deficient mice, and C57BL/6.CH-2m12 (bm12) mice were obtained from The Jackson Laboratory (Bar Harbor, ME). C57BL/6 IL-5-deficient mice (20) were kindly provided by Dr. M. Kopf, Basel Institute for Immunology, Basel, Switzerland.

Skin grafting

Skin grafts ~1 cm in diameter were prepared from tails of female mice and grafted onto the flanks of the recipients according to an adaptation of the method of Billingham and Medawar (23). Petroleum gauze was placed over the graft, and sticking plaster was applied around the trunk. The bandages were removed after 10 days, and the grafts were monitored daily until day 30. Skins were considered rejected when complete epithelial breakdown had occurred. C57BL/6-gld/gld FasL-deficient mice were always grafted before 6 wk of age.
Ab preparation and in vivo treatments
Anti-CD4 (clone GK1.5), anti-CD8 (clone H35), anti-IL-5 (clone TRFK-5), and isotype control mAbs were produced as ascites in nude mice as previously described (24, 25). The mAb concentrations of ascites were determined by ELISA using anti-rat IgG1 mAb from LO-IMEX, University of Louvain, Louvain, Belgium. CD4- and CD8-positive cells were depleted with the IgG2b rat anti-murine CD4 mAb GK1.5 or the IgG2b rat anti-murine CD8 mAb H35, respectively. Animals received i.p. injections of 1 mg of either mAb 4 days before grafting; on the day of grafting, and then every 10 days until the end of the experiment. Flow cytometry analysis (FACScalibur, Becton Dickinson, Mountain View, CA) performed on the day of sacrifice with the use of PE-conjugated anti-CD4 (PharMingen, San Diego, CA), clone RM4-4) or anti-CD8 mAb (PharMingen, clone 53-6.7) showed <1% of corresponding T cell populations in lymph nodes.

IL-5 was blocked in vivo by repeated i.p. injections of 1 mg of the IgG1 rat anti-mouse IL-5 mAb, TRFK-5 (25) according to the following schedule: 1 day before grafting; 6 days after transplantation; then every 10 days until day 30. Control mice received the isotype-matched anti-DNP rat IgG1 mAb (LO-DNP-2, kindly provided by Dr. H. Bazin, Experimental Immunology Unit, Universit ´ e Catholique de Louvain, Louvain, Belgium), according to the same schedule.

Histological studies
Skin graft histology was performed on tissue sections stained with hematoxylin and eosin, after paraffin embedding. The number of eosinophils infiltrating the graft was quantified by a pathologist unaware of the treatment groups. This was done by averaging the number of eosinophils present in at least three distinct high power fields (0.0025 mm2 across the graft).

Production of cytokines in MLC
Cells from lymph nodes draining the skin allografts were used as responder cells (5 × 10^5/well) and seeded with 5 × 10^5 irradiated (2000 rad) bm12 spleen cells (stimulators) in 48-well flat-bottom plates (150687, Nunc, Roskilde, Denmark). Culture medium consisted of RPMI 1640 supplemented with 20 mM HEPES, 2 mM glutamine, 1 mM nonessential amino acids, 5% heat-inactivated FCS, sodium pyruvate, and 2-ME. Supernatants were harvested after 48–72 h of culture for determination of IFN-γ levels, using ELISA DuoSet (Genzyme, Cambridge, MA). IL-5 was quantified by an enzyme immunoassayic assay, as previously described (26). The lower limits of detection of these assays were 30 pg/ml for IFN-γ and 5 pg/ml for IL-5.

CTL
Responder cells obtained from paraaortic and mesenteric lymph nodes were depleted in vitro of CD8+ cells by incubation with the rat anti-mouse CD8 mAb (H35) followed by addition of rabbit complement. Depletion was confirmed by flow cytometry analysis (FACScalibur, Becton Dickinson, Mountain View, CA) with the use of PE-conjugated anti-CD8 mAb (PharMingen, clone 53-6.7). Of the remaining cells 5 × 10^5 were cultured with 5 × 10^5 irradiated (2000 rad) stimulator spleen cells in 24-well flat-bottom plates. Cultures were incubated at 37°C in 5% CO2 in humidified air for 5 days. Target cells were prepared by incubation of 1 × 10^6 bm12 spleen cells with 30 µg/ml LPS (serotype 0111:B4, Sigma, Bornem, Belgium) in 2 ml medium for 2 to 3 days and pulsed overnight with [3H]thymidine. Effector cells were harvested, washed, and plated at various E:T ratios in 96-well round-bottom plates containing 5 × 10^5 irradiated target cells. Each E:T ratio was performed in triplicate. After 3 h of incubation at 37°C, cultures were harvested on Unifilter plate, and residual radioactivity was measured with a Top Count microplate scintillation counter (Packard, Meriden, CT). The percentage of specific lysis was calculated according to the formula % specific lysis = ([spontaneous (cpm) − experimental (cpm)]/spontaneous (cpm)) × 100, where "experimental" is labeled DNA retained in the presence of effector cells and “spontaneous” is labeled DNA retained in the absence of effector cells.

Cytokine mRNA analysis by reverse transcription PCR
Skin grafts from mice bearing either a syngeneic C57BL/6 transplant (n = 4) or an allogeneic bm12 graft undergoing acute rejection 15 days after transplantation (n = 4) were analyzed for cytokine mRNA. Syngeneic and allogeneic skin grafts were pooled, and total RNA was extracted using the guanidium thiocyanate method (Tripure, Boehringer Mannheim, Mannheim, Germany). Preparations of cDNA and PCR for IFN-γ, IL-5, and β-actin were done. The IL-5 and β-actin gene were performed by standard procedures (24). Briefly, PCR were performed in a total volume of 25 µl as follows: 1) denaturation: 4 min at 94°C; 2) amplification: 38 cycles for IL-5 and 35 cycles for IFN-γ and β-actin, respectively. Cycles were: 20 s at 94°C, 20 s at 55°C, and 30 s at 72°C; and 3) extension: performed for 10 min at 72°C. Twelve microliters of each sample were run on a 2% agarose gel, stained with ethidium bromide, and visualized under UV light. PCR primers used consisted of the following: IFN-γ: sense primer 5′-GCTCTGAGACAAT GAAGCTG-3′ and antisense 5′-AAAGAGATAATCTGGCTCTGC-3′; IL-5: sense primer 5′-TCACCGAGCTCTGTTGACAA-3′ and antisense 5′-CCACATTCTCTTTTGCCGG-3′; and β-actin: sense primer 5′-TG GAACGCTGATCATCAGAAC-3′ and antisense 5′-TAAACG CAGGTCAGTAACACG-3′.

Statistical analysis
Results are shown as a median with the range of values in parentheses. Graft survival curves and cytokine levels were compared by the log-rank test and by the Mann-Whitney nonparametric test, respectively. All comparisons were made two-tailed. In case mice did not reject their graft, they were given an arbitrary survival time of 30 days.

Results
MHC class II-disparate bm12 skin grafts rejected by wild-type C57BL/6 mice display a massive eosinophil infiltrate
Wild-type C57BL/6 mice rapidly reject MHC class II-disparate bm12 skin grafts (Fig. 1). Graft rejection occurred between day 12 and day 20 (median survival time, 15.0 days). Histological examination of rejected skin allografts revealed necrosis and sloughing of the epidermal layer (Fig. 2B). Although only rare eosinophils were present within syngeneic grafts, numerous eosinophils infiltrated the allogeneic skins (Table I). Eosinophils were particularly abundant along the epidermis and hair follicles, both structures that were present within syngeneic grafts, numerous eosinophils infiltrating the allogeneic skins (Fig. 2A). This suggested that eosinophils contributed to tissue damage and rejection of the allogeneic skin.

Cytokine production by lymph nodes and intragraft detection of cytokine mRNAs
Because IL-5 is the main cytokine involved in the proliferation and differentiation of eosinophils, we searched for IL-5 production by lymphocytes from lymph nodes draining rejected bm12 skins, and we examined the intragraft expression of IL-5 mRNA. The presence of IFN-γ was also investigated, as this cytokine is known to be required for the rejection of bm12 transplants by C57BL/6 mice (27, 28). Lymph node cells from naive C57BL/6 mice produced increased amounts of both IL-5 and IFN-γ after stimulation with
bm12 alloantigens in MLR (*p < 0.001 vs syngeneic cultures) (Table II). As compared with these naive animals, lymphocytes from mice that have rejected a bm12 skin secreted about 5 times more IL-5 after stimulation with donor alloantigens. A modest priming for IFN-γ secretion was also seen (2-fold). This pattern of cytokine production was specific for the priming bm12 alloantigens, because no increased cytokine secretion was observed after stimulation with third-party BALB/c alloantigens (Table II). The

Table I. 

<table>
<thead>
<tr>
<th>Donor-Type Skin Graft</th>
<th>Type of C57BL/6 recipient mAb treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wild-type No</td>
</tr>
<tr>
<td>No. of mice</td>
<td>5</td>
</tr>
<tr>
<td>No. of eosinophils/0.025 mm²</td>
<td>1 (0–4)</td>
</tr>
</tbody>
</table>

*+, p < 0.0001 compared with syngeneic skin grafts; †, p < 0.0001 compared with bm12 skins transplanted on wild-type animals; ‡, p < 0.0001 compared with skins grafted onto FasL-deficient mice treated with the control mAb.
presence of IL-5 and IFN-γ mRNA was analyzed for in allogeneic bm12 skin transplants at the time of rejection. Increased amounts of both cytokines mRNA were present within acutely rejected grafts as compared with syngeneic transplants (Fig. 3).

**An IL-5/eosinophil pathway contributes to acute rejection of MHC class II-disparate grafts in wild-type C57BL/6 mice**

To study the possible contribution of IL-5 to the rejection of MHC class II-disparate bm12 skins, grafts were performed on IL-5-deficient mice (Fig. 1). The rejection of bm12 grafts by IL-5-deficient mice was significantly delayed as compared with wild-type animals \( (p < 0.001, \text{Fig. 1}) \). Moreover, 3 of 13 IL-5-deficient mice were unable to reject the bm12 grafts, a finding not observed in wild-type animals \( (n = 37) \), which always experienced rapid rejection \( (p = 0.018) \). Histology of bm12 skin grafts rejected by IL-5-deficient mice revealed only very rare eosinophils (Table I).

**IL-5 neutralization prevents acute rejection of MHC class II-disparate grafts in the absence of Fas/FasL interactions**

The experiments described above indicate that an IL-5/eosinophil pathway contributes to the rejection of MHC class II-incompatible skin grafts. The rejection that still occurs in the majority of IL-5-deficient mice is likely to be mediated by CD4 cytotoxic cells. To investigate the possible role played by the IL-5/eosinophil pathway in the rejection of bm12 allografts when CD4 cytotoxicity is absent, we first performed bm12 skin grafts in C57BL/6 FasL-deficient mice. As shown in Fig. 4, the large majority of FasL-deficient mice acutely rejected bm12 grafts, with a kinetics comparable with that of wild-type mice. In vitro experiments confirmed that CD4 T cells from FasL-deficient mice were unable to mount an anti-bm12 cytotoxic activity (Fig. 5). CD4 T cells from FasL-deficient mice were, however, still required for the rejection process as shown by T cell depletion experiments (Fig. 4). The rejection of bm12 skins by C57BL/6 FasL-deficient mice was associated with the presence of IL-5 and eosinophils similar to those observed in wild-type C57BL/6 mice. Indeed, bm12 skin grafts rejected by FasL-deficient mice displayed a massive eosinophil infiltration (Fig. 2 and Table I); and T cells from rejecting mice were primed for IL-5 production in MLR (Table II). The two bm12 skin allografts that

### Table II. Cytokine production in MLR\(^a\)

<table>
<thead>
<tr>
<th>Responder C57BL/6 Mice</th>
<th>Priming with bm12 Skin Graft</th>
<th>Stimulator Cells</th>
<th>IL-5 (pg/ml)</th>
<th>IFN-γ (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>No bm12</td>
<td>C57BL/6</td>
<td>115 (53–304)</td>
<td>55 (50–219)</td>
</tr>
<tr>
<td></td>
<td>No BALB/c</td>
<td></td>
<td>674 (359–3,200)</td>
<td>1,152 (402–2,716)</td>
</tr>
<tr>
<td></td>
<td>Yes bm12</td>
<td>C57BL/6</td>
<td>253 (83–465)</td>
<td>50 (50–125)</td>
</tr>
<tr>
<td></td>
<td>Yes BALB/c</td>
<td></td>
<td>3,469 (1,835–8,628)</td>
<td>2,178 (1,444–2,434)</td>
</tr>
<tr>
<td>FasL-deficient mice</td>
<td>No C57BL/6</td>
<td></td>
<td>158 (95–414)</td>
<td>50 (50–170)</td>
</tr>
<tr>
<td></td>
<td>No BALB/c</td>
<td></td>
<td>492 (253–1,245)</td>
<td>849 (265–1,018)</td>
</tr>
<tr>
<td></td>
<td>Yes C57BL/6</td>
<td></td>
<td>449 (315–831)</td>
<td>1,686 (150–1,986)</td>
</tr>
<tr>
<td></td>
<td>Yes BALB/c</td>
<td></td>
<td>476 (1,090–10,000)†</td>
<td>718 (126–1,140)</td>
</tr>
<tr>
<td></td>
<td>Yes C57BL/6</td>
<td></td>
<td>206 (271–1,285)</td>
<td>1,148 (176–2,807)</td>
</tr>
</tbody>
</table>

\(^a\) IL-5 and IFN-γ production (pg/ml) in MLR with syngeneic C57BL/6, donor-type allogeneic bm12, or third-party BALB/c stimulator spleen cells. Five mice were tested in each experimental condition. Results are representative of at least three separate experiments. \( \ast, p < 0.05 \) and †, \( p < 0.001 \) compared with unprimed mice of the same responder type.

**FIGURE 3.** Cytokine gene expression within rejected allografts. IL-5 and IFN-γ mRNAs expression was compared within pooled syngeneic C57BL/6 grafts \( (n = 4) \) or bm12 allografts \( (n = 4) \) harvested at the time of rejection. The mRNA of the housekeeping gene β-actin is also shown. Similar results were obtained in two other separate experiments performed on pooled skin grafts \( (n = 3 \text{ to } 4 \text{ per pool}) \).

**FIGURE 4.** bm12 skin graft rejection by FasL-deficient mice. MHC class II-disparate bm12 skin tails were grafted on FasL-deficient mice left untreated \( (\bullet; n = 12) \); injected with isotype-matched control rat IgG1 mAb \( (\blacktriangle; n = 12) \); injected with rat IgG1 anti-IL-5 mAb \( (\triangle; n = 12) \); injected with rat anti-CD8 mAb \( (\bigcirc; n = 11) \); and injected with rat mAb anti-CD4 \( (\bigcirc; n = 10) \).
were not rejected appeared normal, with no eosinophil infiltrate. The functional role played by IL-5 and eosinophils in the rejection of bm12 skin by FasL-deficient mice was tested by the administration of neutralizing anti-IL-5 Abs. As shown in Fig. 4, the majority of anti-IL-5-injected mice were unable to reject their transplants. At day 30 (day of the sacrifice), the tolerated grafts displayed an appearance comparable with that of syngeneic grafts and were devoid of eosinophils (Fig. 2 and Table I). FasL-deficient mice injected with the control mAb experienced rejection with a tempo equivalent to that of untreated FasL-deficient animals, and the rejected grafts were heavily infiltrated by eosinophils (Table I). To further confirm the ability of the IL-5/eosinophil pathway to trigger acute allograft rejection in the absence of FasL/FasL interactions, we performed MHC class II-disparate skin grafts from Fas-deficient C57BL/6-lpr/lpr mice on wild-type bm12 animals. bm12 mice, either untreated or after injections of the control rat IgG1 mAb, promptly rejected the Fas-deficient skins (Fig. 6), which histologically displayed a dense eosinophil infiltrate (not shown). Administration of the anti-IL-5 mAb prevented acute rejection in 80% of mice (p < 0.01) (Fig. 6).

**Discussion**

The main finding from these experiments is that IL-5 and eosinophils represent an effector pathway of the rejection of MHC class II-disparate skin grafts. Eosinophils are a prominent feature of bm12 skins acutely rejected by B6 animals. They are mainly concentrated along the dermoepidermal junction and hair follicles. Eosinophil degranulation was evident, as indicated by the presence of their red granules within graft interstitial tissue. These granules contain several molecules involved in eosinophil toxicity, such as neurotoxin, eosinophil cationic protein, and major basic protein (29, 30). These and other molecules are responsible for the ability of eosinophils to induce cytolysis and acute tissue damage after exposure to allergens or parasites (29, 30). As a matter of fact, activated eosinophils have recently been shown to play a critical role in the rejection of solid tumors in mice (31, 32).

Although the presence of eosinophils within acutely rejected allografts has been observed in other experimental settings (16, 17), their causal role in acute allograft rejection has not been established yet. The infiltration of tissues by eosinophils is critically dependent on the availability of IL-5. Indeed, experiments with IL-5-deficient mice or using neutralizing anti-IL-5 mAbs revealed the essential role of this cytokine in the proliferation and differentiation of eosinophils (19–21, 33, 34), as well as in their recruitment and activation within tissues (35). Therefore, our observations that lymph node cells draining rejected bm12 skins produced large amounts of IL-5 together with the presence of abundant amounts of IL-5 mRNA within rejected grafts readily explain the infiltration of the allograft by eosinophils. To address the possible causal role played by IL-5 in acute rejection, we grafted MHC class II-disparate bm12 skins onto IL-5-deficient C57BL/6 mice. Importantly for these experiments, the classical effector mechanisms that may also contribute to graft rejection such as Ab response and the generation of cytolytic T cells are normal in IL-5-deficient mice (20). Of course, one cannot exclude that blocking IL-5 might also inhibit the alloreactive response by other, as yet undefined mechanisms in addition to preventing eosinophil infiltration. Several IL-5-deficient mice did not experience rejection and maintained the donor bm12 graft in perfect condition for at least 30 days. The rejection that occurred in the other IL-5-deficient animals was significantly delayed as compared with wild-type mice. Taken together, these data indicate that eosinophils represent one effector pathway that contributes to the rejection of MHC class II-disparate skin. It is important to stress that the present observations were made in the bm12→BL/6 strain combination, which differs for only 3 amino acids within the Ia MHC class II Ags. Although IL-5 and eosinophils have also been found within rejected allografts in strains differing at other MHC class II Ags (16, 17), the functional role played by the IL-5/eosinophil pathway in these combinations remains to be defined.

The rejection that still occurs in many IL-5-deficient mice may probably involve cytotoxic anti-MHC class II alloreactive CD4+ T cells. Indeed, transfer experiments have shown that such cells are able to reject a bm12 skin transplanted on nude mice (1). The cytotoxic activity developed by CD4 T cells results from the interactions between FasL and its counterreceptor Fas on allogeneic targets (2, 3). In the skin, keratinocytes are known to express Fas in the basal state and may therefore become sensitive to FasL-mediated apoptosis induced by alloreactive CD4 cytotoxic T cells (36–38). To address the ability of the IL-5/eosinophil pathway to
induce rejection of MHC class II-incompatible grafts when CD4 cytotoxicity is deficient, we grafted MHC class II-disparate skin in two strain combinations unable to establish productive Fas/FasL interactions. In this context, the esoinophilic rejection could be prevented by IL-5 neutralization. As in wild-type mice, T cells from FasL-deficient animals specific for bm12 MHC class II alloantigens were indeed primed for IL-5 production. Because CD8 T cells were shown in different settings to down-regulate tissue esoinophilia and IL-5 synthesis by CD4 T cells (17, 39–41), the priming for IL-5 production in the present model might be related to the lack of disparity for MHC class I Ags. Indeed, in vivo cell depletion experiments confirmed that CD8 T cells were not involved in the rejection process. Interestingly, the anti-bm12 response was not of the Th2 type in that lymphocytes from mice grafted with bm12 skin also produced significant amounts of IFN-γ in MLR. A priming for IFN-γ was observed after bm12 skin grafting in wild-type recipients but not in FasL-deficient mice. The reason for this difference is not known, but it might be because IL-4, a cytokine that may inhibit IFN-γ production (42), was detected in increased amounts with lymphocytes from FasL-deficient mice as compared with wild-type mice after MLR with bm12 alloantigens (A. Le Moine, unpublished results). As recently demonstrated in a model of tumor rejection, IFN-γ and IL-5 may synergize in the induction of tissue damage involving esoinophils (31). If the role of IFN-γ in the rejection of MHC class II-disparate skin allografts has been well established (27, 28), our observations provide the first evidence that IL-5 is a key mediator of rejection in the absence of antitumor cytotoxicity. Because esoinophil infiltrates are often found in biopsies of liver or kidney allografts during rejection episodes (43–46), we suggest that a similar IL-5/esoinophil pathway might contribute to forms of rejection in clinical transplantation.

Acknowledgments

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References


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