Virchows Arch (1996) 429:205–211

ORIGINAL ARTICLE

Wen-gao Lu · Daniël G. Pipeleers · Günter Klöppel
Luc Bouwens

Comparative immunocytochemical study of MHC class II expression in human donor pancreas and isolated islets

Received: 10 May 1996 / Accepted: 30 July 1996

Abstract Expression of major histocompatibility complex (MHC) molecules by pancreatic islets may influence the survival of pancreas or islet grafts in allogeneic recipients. This study compares the presence of MHC class II (HLA-DP, DQ, DX and DR)-positive cells in 27 pancreases and in 10 isolated islet preparations from human donors. Cells expressing MHC class II were present in all tissues examined as histiocytes located in interstitial areas in both the endocrine and nonendocrine components and as endothelial cells in the nonendocrine part. Endocrine, acinar and duct cells were MHC class II negative. In pancreases from donors under the age of 7 years the frequency of MHC class II-positive histiocytes was only one third of that in adults, and they rarely contained MHC class II-positive endothelial cells. The MHC class II-positive histiocytes were further phenotyped as macrophages positive for LCA and acid phosphatase, or dendritic cells negative for the latter markers. Dendritic cells were frequent in adult organs but rare in organs from donors under 7 years of age. In freshly isolated islet preparations from adult donors, less than 1% of the cells were MHC class II positive. These were identified as resident macrophages and dendritic cells. No MHC class II positive cells were encountered in the islet capillaries. The putative role of MHC class II-positive donor cells in allograft rejection suggests that these differences in MHC class II expression influence the immunogenicity of pancreatic and islet grafts in an age-dependent manner.

Key words Major histocompatibility complex class II · Islet transplantation · Dendritic cells · Macrophage · Human pancreas

Introduction

Islet transplantation is considered a potential treatment for insulin-dependent diabetes [5, 11, 20]. In rodents, survival of islet allografts has been prolonged by removing major histocompatibility complex (MHC) class II-positive cells from the donor tissue [14, 18]. These cells, which were characterized as macrophages or dendritic cells, represented only a minor fraction of the total islet cell population [9, 23]. Macrophages and dendritic cells play an important part in the regulation of the immune system and in the onset of rejection. Although the two cell types may share a common origin in the bone marrow, they have been shown to differ functionally. Macrophages are phagocytic cells, whereas dendritic cells are nonphagocytic, and dendritic cells are known to be much more efficient antigen-presenting cells than macrophages [8, 16, 19]. The presence, type and number of MHC class II-positive cells in human islet grafts have not been investigated [3, 22, 29]. We examined these cells in isolated human islet preparations and correlated the findings with an in situ analysis of the same donor pancreas. In addition, we analysed the type and frequency of cells expressing MHC class II in the pancreas in different donor age groups.

W. Lu · L. Bouwens (✉)
Department of Experimental Pathology,
Free University of Brussels, Laarbeeklaan 103,
B-1090 Brussels, Belgium
Tel.: (32) 247 74457, Fax: (32) 247 74545

G. Klöppel
Department of Pathology, University of Kiel, Kiel, Germany

D.G. Pipeleers
Department of Metabolism and Endocrinology,
Free University of Brussels, Brussels, Belgium

Materials and methods

Twenty-seven human pancreases were excised from cadaveric organ donors at European hospitals affiliated with Beta Cell Transplant (European Concerted Action for the Treatment of Diabetes, Brussels, Belgium). Among the donors, 6 were children between 2 and 7 years old (mean = 3.8 years, 3 boys); 12 donors were between 20 and 50 years of age (mean = 42.8 years, 7 men), and 9 were between 60 and 76 years old (mean = 63.6 years, 5 men). All tissue fragments were obtained from the Central Unit of Beta Cell Transplant (Brussels), fixed in 4% formaldehyde overnight and

Table 1 Antibodies used in this study (*MHC* major histocompatibility complex)

Antibodies	Clone	Reactive with	Source
Mouse anti-human HLA-DR,CR3/43 (MHC class II)	CR3/43 (monoclonal)	HLA-DP, -DQ, -DX and -DR (dendritic cells, macrophages and lymphocytes)	DAKO, (Glostrup, Denmark)
Mouse anti-human leucocyte common antigen (LCA)	2B11 and PD7/26 (monoclonal)	Human leucocyte common antigen (leucocytes, macrophages, lymphocytes)	DAKO
Mouse anti-human myeloid /histiocyte antigen (MAC-387)	MAC-387 (Monoclonal)	Human leucocyte antigen L1 (macrophages, lymphocytes)	DAKO
Anti-macrophage (Ham-56)	Ham-56 (monoclonal)	Human macrophage antigen (macrophages)	Åke Lernmark, University of Washington (Seattle, Wash.)
Mouse anti-human macrophage, (CD68)	KP1 (monoclonal)	CD68 antigen (MW 110 kDa) (macrophages, dendritic cells)	DAKO
Rabbit anti-Factor VIII	(Polyclonal)	Factor VIII-related antigen (endothelial cells)	BioGenex (San Ramon, Calif.)
Rabbit anti-synaptophysin	(Polyclonal)	Synaptophysin (endocrine cells)	DAKO

embedded in paraffin according to routine procedures. From 21 pancreases, both frozen and paraffin-embedded tissues were available. In addition, small pieces of 4% formaldehyde-fixed tissue from 2 pancreases were embedded in Spurr plastic.

The islet isolation procedure has been described previously [34]. Aliquots of the islet-enriched fraction were routinely examined by electron microscopy. They consisted of approximately 50–60% endocrine cells. Samples were fixed in 4% formaldehyde overnight, and embedded in 2% agarose and later in paraffin with the same procedure as used for tissue. Some samples were dissociated into single cell preparations by trypsinization [26].

For immunocytochemistry, serial paraffin sections 3–5 μm thick were cut and consecutive pairs of sections were arranged as mirror images on slides. After deparaffinization, endogenous peroxidase activity was blocked in 3% (v/v) hydrogen peroxide-methanol for 30 min. The slides were incubated in 10% normal goat serum for 30 min to block nonspecific background staining. They were then incubated with primary antibody (Table 1) overnight at 4°C, washed, and incubated in biotinylated secondary antibody for 30 min at room temperature. The reaction product was visualized with the streptavidin–biotin horseradish peroxidase complex (ABC: DAKO, Glostrup, Denmark) technique. For double immunocytochemical staining, we used ABC/alkaline phosphatase complex (DAKO, Glostrup, Denmark) and naphthol AS-BI phosphate/new fuchsin (red colour).

Consecutive semi-thin Spurr sections (1 μm) were cut and mounted on glass. These plastic sections were etched with 10% (w/v) NaOH in ethanol (7 min) and then immunostained as above. Frozen sections were fixed in 4% formaldehyde 30 min and then stained as above.

Acid phosphatase activity was detected on frozen sections with a standard cytochemical method using naphthol AS-BI phosphate as substrate and hexazotized pararosaniline as diazonium salt [35].

Negative controls were run by omitting the primary antibody or applying isotype-matched control antibody (monoclonal) or appropriate normal serum (polyclonal). To provide a negative control for double staining, the primary antibody of the second sequence reaction was omitted.

To carry out morphometry sections were double immunostained for synaptophysin to delineate islets of Langerhans and to detect MHC class II or other markers (ABC method). The area of the first 30 islets that were seen was measured by manually tracing the outline on a computer screen connected to a Zeiss Axiophot light microscope by a colour video camera (NIH Image 1.41 software). Within these islets, the number of cells expressing MHC class II (or other markers) was counted, and their frequency per square millimetre of islet tissue was calculated. The total area of islet tissue that was measured equalled about 1 mm^2 per section. In the same section, a similar area of exocrine tissue was analysed for the presence of extra-islet MHC class II-positive cells. Large interlobular ducts, blood vessels and connective tissue were excluded from the exocrine tissue.

The statistical significance of differences between experimental groups was calculated with the Wilcoxon rank sum test and Student's *t*-test.

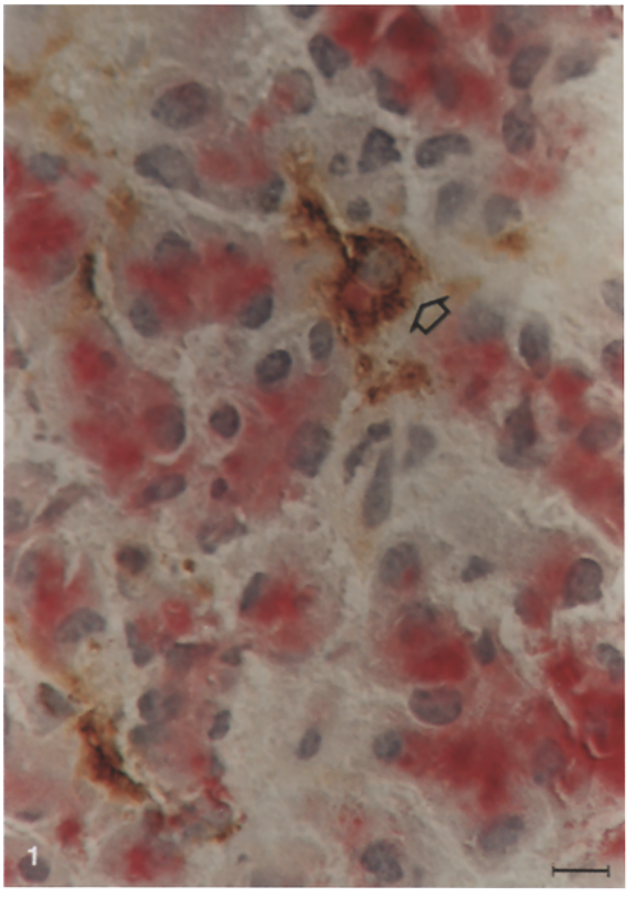
Results

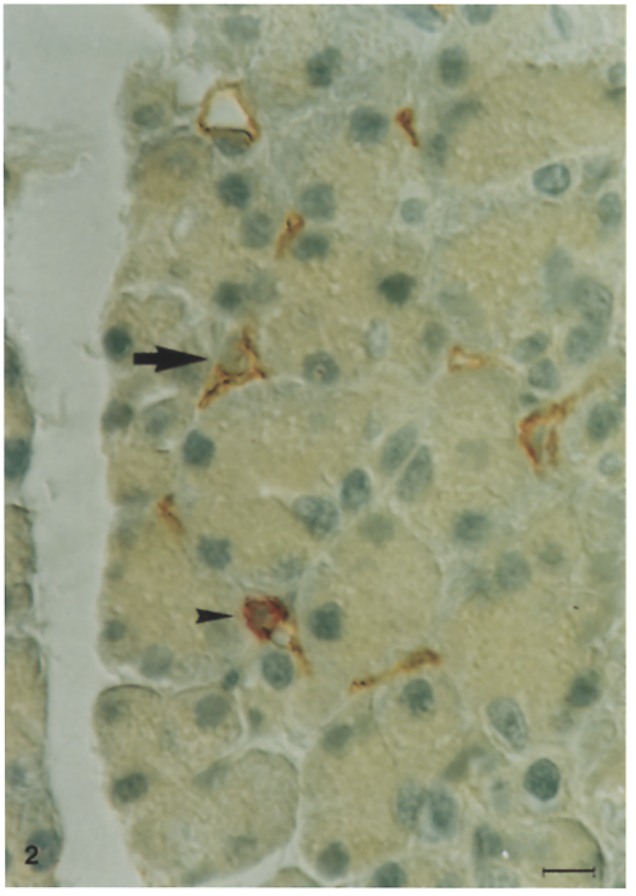
In pancreatic frozen sections (Fig. 1), paraffin sections (Figs. 2, 3) and plastic semi-thin sections, expression of HLA-DR, CR3/43 (MHC class II) was detected on interstitial cells and exocrine endothelial cells (Figs. 2, 3a).

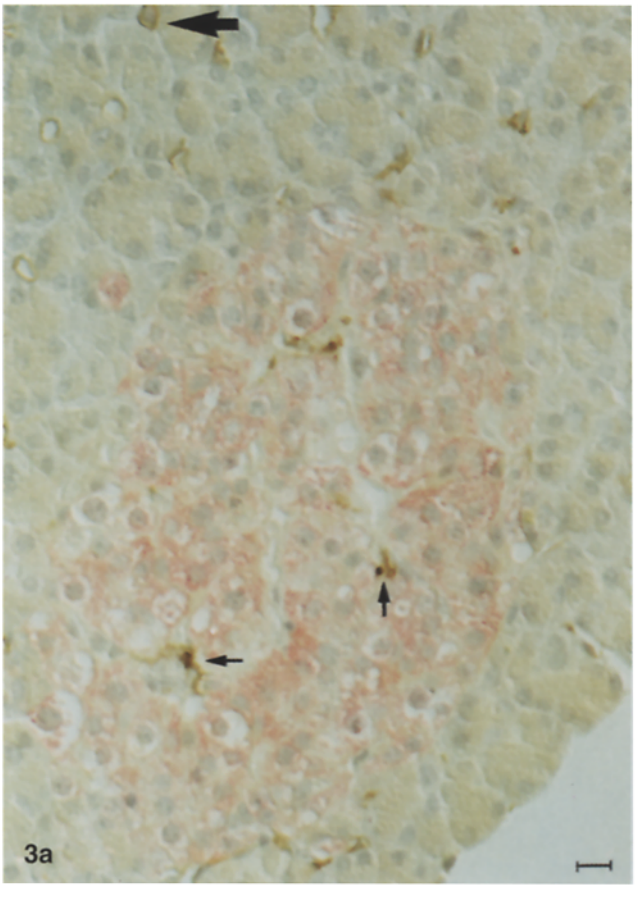
Fig. 1 Immunocytochemical and enzyme cytochemical double staining on a frozen section for the identification of major histocompatibility complex (MHC) class II and acid phosphatase-positive cells. *Large open arrow* a macrophage stained for MHC class II (*brown*) displays cytoplasmic acid phosphatase activity (*red*). *Bar* 10 μm

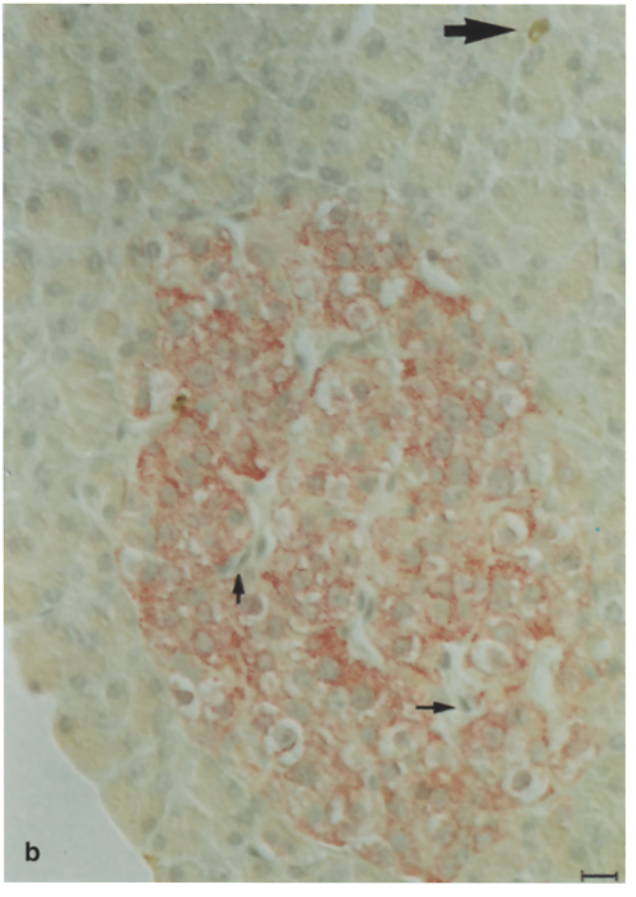
Fig. 2 Immunocytochemical double staining on a paraffin section for MHC class II (*brown*) and leucocyte common antigen (LCA) (*red*). *Arrowhead* a double-positive macrophage. *Arrow* a dendritic cell does not express LCA. *Bar* 10 μm

Fig. 3a, b Immunocytochemical double staining of paraffin mirror image sections of human pancreas. **a** MHC class II-positive cells are stained *brown* (*arrows*) and islet endocrine cells are stained *red* for synaptophysin. **b** LCA-positive cells are stained *brown* (*large arrow*) and islet endocrine cells are stained *red* for synaptophysin. In the islet, the MHC class II-positive cells (*small arrows*) are not positive for LCA. Also note that islet capillaries do not express MHC class II. *Bar* 10 μm


1


2


3a


b

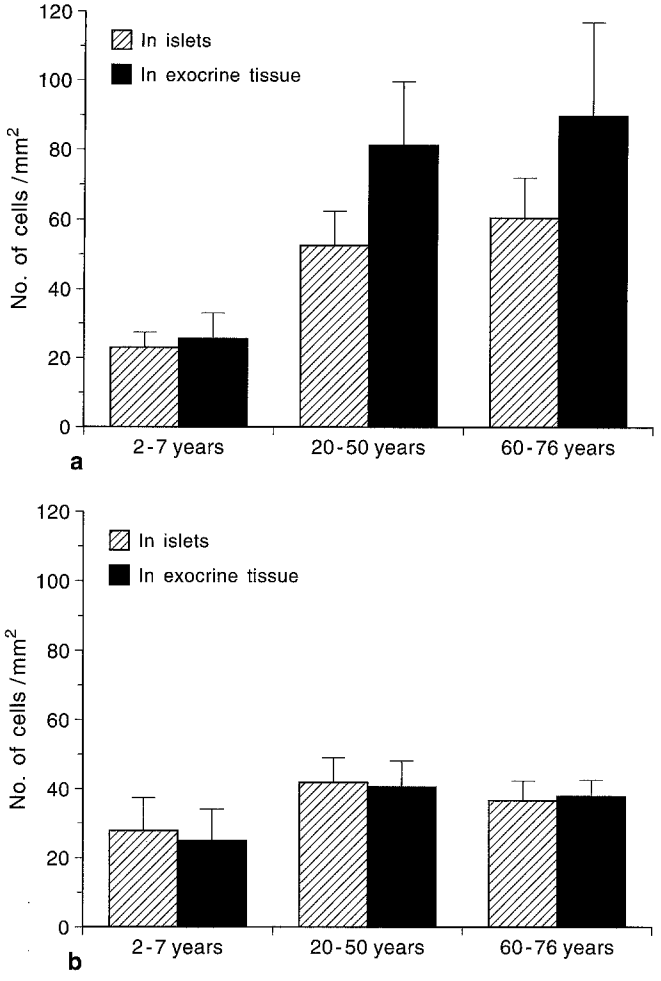


Fig. 4 Density of **a** MHC class II- and **b** LCA-positive interstitial cells in donor pancreas. The density of MHC class II-positive interstitial cells in adult donors is significantly higher than in donors under age 7. (Means ± SEM are shown; Wilcoxon rank sum test, $P < 0.05$)

Endothelial cells were Factor VIII positive (not shown). MHC class II-positive interstitial cells were scattered throughout connective tissue, islets of Langerhans and exocrine (inter-acinar) tissue. MHC class II-positive vascular endothelial cells were seen in exocrine tissue in 17–67% of donors, depending on age. MHC class II expression was not observed on endocrine, acinar, or duct cells. In exocrine tissue, MHC class II expression on endothelial cells of capillaries and venules differed between young and older donors. Under age 7, only 1 of the 6 donors showed very weak MHC class II staining on endothelial cells of some capillaries and venules. This proportion was much lower than in the adult donor groups, in which 8 of the 12 donors aged 20–50 years and 4 of the 9 aged 60–76 years had positive staining on the capillaries and venules. In islets, capillary endothelial cells were always negative for MHC class II in all donors (Fig. 3a, b).

The tissue density (no./mm²) of MHC class II-positive interstitial cells varied widely among the different donors. However, within a given donor the MHC class II-positive interstitial cells were homogeneously distributed and their density was similar throughout the exocrine and islet tissue. A higher density, with heterogeneous distribution, was noted in the connective tissue surrounding large ducts and blood vessels (not quantified). No difference was observed in the numbers of MHC class II-positive interstitial cells between adult donor groups in the age range 20–50 years or the age range 60–76 years, but a significantly (Wilcoxon rank sum test, $P < 0.05$) lower number was found in children aged 2–7 years (Fig. 4). We noted no differences related to the sex of donors. In a single donor we found that the distribution of MHC class II in frozen, paraffin and Spurr semithin sections was similar (data not shown).

The majority of MHC class II-positive interstitial cells had the morphology and phenotypic markers of

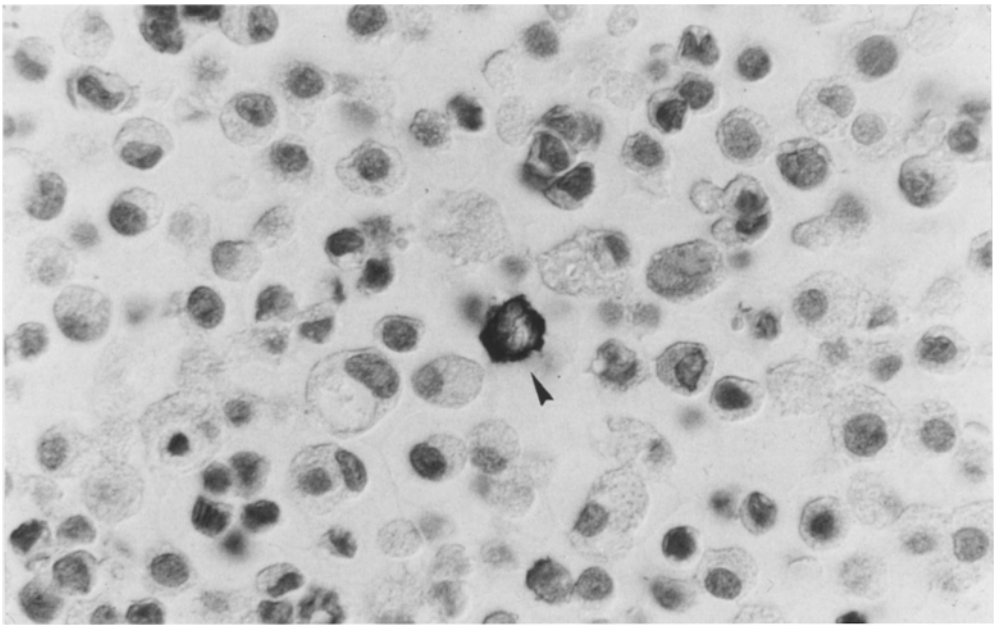


Fig. 5 Immunocytochemical staining for MHC class II in a paraffin section of isolated islet cells. Note one positive cell (*arrowhead*) and the absence of positivity on the majority of the cells. *Bar* 10 μm

Table 2 Frequency (%) of cells expressing MHC class II or other markers in isolated islet preparations (n = 10)

Markers	Percentage of positive cells (Mean±SEM)
Anti-human HLA-DR, CR3/43 (MHC class II)	0.44±0.15%
Anti-human leucocyte common antigen	0.42±0.14%
Anti-human myeloid /histiocyte antigen (MAC-387)	0.24±0.12%
Anti-Factor VIII	0.87±0.47%

macrophages or dendritic cells. As previously described by others [17, 23], macrophages frequently showed cytoplasmic vacuoles containing acid phosphatase cytochemical activity (Fig. 1), whereas dendritic cells have no such vacuoles. In double stainings most MHC class II-positive cells co-expressed the CD68 histiocytic marker, while only some of them expressed either the macrophage markers MAC-387 and Ham-56 or leucocyte common antigen LCA (Fig. 2). For donors under the age of 7, tissue densities of interstitial cells expressing MHC class II and LCA were similar (Fig. 4). However, in the adult groups, there was a significant difference between the density of MHC class II-expressing and of LCA-expressing cells, with a higher proportion of MHC class II-positive interstitial cells that did not express LCA. As a result, the density of LCA-expressing cells did not increase with age, in contrast to the number of MHC class II-positive cells.

Isolated cell preparations from enriched islets were analysed in 10 donors in the adult group (20–50 years). We measured the percentage of cells positive for MHC class II (Fig. 5), LCA, MAC-387 and Factor VIII (Table 2). A low percentage of MHC class II-positive cells was found (mean ± SEM = 0.44 ± 0.15%). When the percentages of MHC class II-positive and of LCA-positive cells in these isolated preparations were compared with the values obtained for islets in intact tissue from the same donors, there were no statistical differences (paired t-test). The frequencies of MHC class II- and LCA-positive cells in islets within intact tissue were 0.45 ± 0.17% and 0.42 ± 0.07%, respectively (mean ± SEM, adults aged 20–50 years). The number of MHC class II-positive cells in isolated cell preparations (mean = 0.44%) was too small to allow a detailed analysis of their cellular composition.

Discussion

We analysed the tissue distribution and type of cells expressing MHC class II (HLA-DP, -DQ, DX and DR) in 27 pancreases from organ donors. MHC class II expression was not detected on endocrine, acinar, or ductal epithelial cells, which confirms previous studies on human [9] and rat pancreas [14, 30]. MHC class II was found to be expressed on interstitial mesenchymal cells and on endothelial cells. In all donors, the interstitial cells of exocrine and endocrine tissue represented the major site of MHC class II expression. Not all donors showed expression of MHC class II on endothelial cells; this was particularly the case for donors under age 7. Interestingly, MHC class II (HLA-DP, -DQ, DX and DR beta chain) was not detected on intra-islet capillaries, irrespective of the age of the donors. It has been previously reported that intra-islet capillaries were HLA-DR negative in human fetal pancreas, whereas endothelial cells in exocrine tissue were positive [24, 25]. However, in adults HLA-DR alpha chain was detected on islet capillary endothelium [1, 10, 28]. The discrepancy between these results and our study at the islet endothelium level is perhaps explained by the different specificities of the antibodies used, e.g. class II alpha versus class II beta, but the functional importance of this is not clear. Other studies have shown that intra-islet endothelial cells also differ from acinar endothelial cells in other types of antigen expression (e.g. factor VIII) [10].

The MHC class II-expressing interstitial cells were evenly distributed throughout the islet and exocrine parts of the glands. Most of them were identified as histiocytes on the basis of their positivity for LCA and/or CD68 markers. They were further subdivided into macrophages, if they were positive for acid phosphatase and MAC-387 and/or Ham-56 markers, or dendritic cells, which lack acid phosphatase, LCA and macrophage differentiation markers (except for CD68). The anti-LCA antibody used in this study contains two monoclonal antibodies, PD7/26 directed against CD45RB and 2B11 directed against CD45 common [15, 33, 36]. As previously noted by Wood et al. [36], we observed that these antibodies did not react with dendritic cells in pancreas tissue.

Densities of MHC class II-expressing interstitial cells were significantly lower in tissues from donors under 7 years of age, which may reflect an incompletely developed immune system [7]. In these children virtually all MHC class II-positive cells were also LCA positive and thus correspond to macrophages. In adults, the density of MHC class II-expressing cells increased significantly as a result of an increase in LCA-negative dendritic cells, the latter becoming twice as numerous as the macrophages.

The density of MHC class II-positive cells in freshly isolated islet preparations was comparable to that in islet tissue in situ. They most probably represented resident histiocytic cells (macrophages and dendritic cells), but not endothelial cells or leucocytes. Our data are thus in contrast with a previous study, in which MHC class II expression was reported both on normal endocrine cells and on "passenger" leucocytes [22].

Since macrophages and dendritic cells are considered to be "professional" antigen-presenting immunocytes [31], their presence in the graft is highly undesirable [20, 30]. MHC class II expression characterizes the stimulator cells that mediate immunogenicity [21]. MHC class II molecules function as antigen-binding molecules and play a decisive part in antigen recognition by immuno-

competent T-lymphocytes [2, 6, 13, 32]. After islet allotransplantation, it was reported that MHC class II-positive cells with macrophage and dendritic morphology formed a large proportion of the inflammatory infiltrate [30]. Most of these cells were recruited from the recipient, but donor-type MHC class II-positive dendritic cells were also present in the islet surroundings [30]. Although the density of MHC class II-expressing cells was less than 1% in our freshly isolated human islet preparations, it is difficult to exclude the possibility that they may have a role in graft rejection. Culturing the cells for a certain period of time may further reduce their presence in the donor tissue [18, 34]. The majority of pancreases from adult donors contained MHC class II-positive endothelial cells in capillaries and venules. Such cells were not present in isolated islet preparations. It is not known whether this difference is responsible for a lower immunogenicity of isolated islet grafts. The absence of dendritic cells in islets of donors under age 7 years also raises the question as to whether islet preparations from these donors are less immunogenic.

Acknowledgements We thank Mrs. Sylvie Duys and Mr. Geert Stange from the Central Unit of Beta Cell Transplant for their help. We also thank Mrs. Nicole Buelens and Emmy De Blay for their expert technical support. This work was supported by grants from the Belgian Fund for Scientific Research (FGWO nos. 3.0128.93 and 3.0093.90), Biomed Concerted Action no. CT92-0805, Flemish Community nos. 3.0075.88 and 3.0132.91 and Concerted Actions nos. 86/91-102 and 92/97-1807.

References

1. Alejandro R, Shienvold FL, Hajek SV, Ryan U, Miller J, Mintz DH (1982) Immunocytochemical localization of HLA-DR in human islets of Langerhans. Diabetes 31 [Suppl 4]:17–22
2. Atkinson MA, Maclaren NK (1994) The pathogenesis of insulin-dependent diabetes mellitus. N Engl J Med 331:1428–1436
3. Bedossa P, Bacci J, Lemaigre G, Martin E (1990) Lymphocyte subsets and HLA-DR expression in normal pancreas and chronic pancreatitis. Pancreas 5:415–420
4. Bottazzo GF, Todd I, Mirakian R, Belfiore A, Pujol-Borrell R (1986) Organ-specific autoimmunity: a 1986 overview. Immunol Rev 94:137–169
5. Brunicardi FC, Mullen Y (1994) Issues in clinical islet transplantation. Pancreas 9:281–290
6. Buus S, Sette A, Grey HM (1987) The interaction between protein-derived immunogenic peptides and Ia. Immunol Rev 98:115–141
7. Caillat-Zucman S, Garchon H-J, Timsit J, Assan R, Boitard C (1992) Age-dependent HLA genetic heterogeneity of type 1 insulin-dependent diabetes mellitus. J Clin Invest 90:2242–2250
8. Chesnu RW, Grey HM (1985) Antigen presenting cells and mechanisms of antigen presentation. Crit Rev Immunol 5:263–316
9. Daar AS, Fuggle SV, Fabre JW, Ting A, Morris PJ (1984) The detailed distribution of MHC class II antigens in normal human organs. Transplantation 38:293–298
10. Dib SA, Vardi P, Bonner-Weir S, Eisenbarth GS (1988) Selective localization of factor VIII antigenicity to islet endothelial cells and expression of class II antigens by normal human pancreatic ductal epithelium. Diabetes 37:482–487
11. Federlin KF (1993) Islet transplantation. The connection of experiment and clinic expemlified by the transplantation of islets of Langerhans. Exp Clin Endocrinol 101:334–345
12. Foulis AK, Farquharson MA, Hardman R (1987) Aberrant expression of class II major histocompatibility complex molecules by B cells and hyperexpression of class I major histocompatibility complex molecules by insulin containing islets in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 30:333–343
13. Hanafusa T, Miyazaki A, Miyazaki J, Tamura S, Inada M, Yamada K, Shinji Y, Katsura H, Yamagata K, Itoh N, Asakawa H, Nakagawa C, Otsuka A, Kawata S, Kono N, Tarui S (1990) Examination of islets in the pancreas biopsy specimens from newly diagnosed type 1 (insulin-dependent) diabetic patients. Diabetologia 33:105–111
14. Hiller WFA, Steiniger B, Klempnauer J (1993) The role of histocompatibility antigens in transplantation of isolated islets of Langerhans in the rat. Diabetes 42:90–97
15. Inghirami G, Knowles DM (1992) The immune system: structure and function. In: Knowles DM (ed) Neoplastic hematopathology. Williams & Wilkins, Baltimore, pp 43–44
16. Jaffe R (1993) Review of human dendritic cells: isolation and culture from precursors. Pediatr Pathol 13:821–837
17. Kabel PJ, Voorbij HAM, De Haan M, Gaag RDVD, Drexhage HA (1987) Intrathyroidal dendritic cells. J Clin Endocrinol Metab 65:199–207
18. Ketchum RJ, Moore WV, Hegre OD (1992) Increased islet allograft survival after extended culture by a mechanism other than depletion of donor APCs (lack of correlation between the elimination of donor MHC class II-positive accessory cells and increased transplantability). Transplantation 54:347–351
19. King PD, Katz DR (1990) Mechanisms of dendritic cell function. Immunol Today 11:206–211
20. Lacy PE (1995) Treating diabetes with transplanted cells. Sci Am 273:40–46
21. Lafferty KJ, Prowse SJ, Simeonovic CJ (1983) Immunobiology of tissue transplantation: a return to the passenger leukocyte concept. Ann Rev Immunol 1:143–173
22. Lautenschlager I, Inkinen K, Taskinen E, Charles MA, Hayry P (1989) Major histocompatibility complex protein expression on pancreas and pancreatic islet endocrine cell subsets. Am J Pathol 135:1129–1137
23. Leprini A, Valente U, Celada F, Fontana I, Barocci S, Nocera A (1987) Morphology, cytochemical features, and membrane phenotype of HLA-DR+ histiocytic cells in the human pancreas. Pancreas 2:127–135
24. Motojima K, Matsuo S, Mullen Y (1989) DR antigen expression on vascular endothelium and duct epithelium in fresh or cultured human fetal pancreata in the presence of gamma-interferon. Transplantation 48:1022–1026
25. Oliver AM, Thomson AW, Sewell HF, Abramovich DR (1988) Major histocompatibility complex (MHC) class II antigen (HLA-DR, DQ, and DP) expression in human fetal endocrine organs and gut. Scand J Immunol 27:731–737
26. Pipeleers DG, In't Veld PA, Van De Winkel M, Maes E, Schuit FC, Gepts W (1985) A new in vitro model for the study of pancreatic A and B cells. Endocrinology 117:806–815
27. Pulido R, Cebrian M, Acevedo A, De Landazuri MO, Sanchez-Madrid F (1988) Comparative biochemical and tissue distribution study of four distinct CD45 antigen specificities. J Immunol 140:3851–3857
28. Shienvold FL, Alejandro R, Mintz DH (1986) Identification of Ia-bearing cells in rat, dog, pig, and human islets of Langerhans. Transplantation 41:364–372
29. Somoza N, Vargas F, Roura-Mir C, Vives-Pi M, Fernández-Figueras MT, Ariza A, Gomis R, Bragado R, Martí M, Jaraquemada D, Pujol-Borrell R (1994) Pancreas in recent onset insulin-dependent diabetes mellitus. J Immunol 153:1360–1377

30. Steiniger B, Hiller WFA, Klempnauer J (1990) Identical pattern of acute rejection after isolated islet and vascularized whole-pancreas transplantation in the rat. Am J Pathol 137:93–102
31. Steinman RM (1991) The dendritic cell system and its role in immunogenicity. Annu Rev Immunol 9:271–296
32. Thorsby E, Rønningen KS (1993) Particular HLA-DQ molecules play a dominant role in determining susceptibility or resistance to type 1 (insulin-dependent) diabetes mellitus. Diabetologia 36:371–377
33. Warnke RA, Gatter KC, Falini B, Hildreth P, Woolston R-E, Pulford K (1983) Diagnosis of human lymphoma with monoclonal anti-leucocyte antibodies. N Engl J Med 309:1275–1281
34. Warnock GL, Ellis D, Rajotte RV, Dawidson I, Baekkeskov S, Egebjerg (1988) Studies of the isolation and viability of human islets of Langerhans. Transplantation 45:957–963
35. Wilders MM, Drexhage HA, Kokje M, Verspaget HW, Meuwissen SGM (1984) Veiled cells in chronic idiopathic inflammatory bowel disease. Clin Exp Immunol 55:377–387
36. Wood GS, Freudenthal PS, Edinger A, Steinman RM, Warnke RA (1991). CD45 epitope mapping of human CD1a$^+$ dendritic cells and peripheral blood dendritic cells. Am J Pathol1 38:1451–1459