Vet. Res. (2008) 39:54
DOI: 10.1051/vetres:2008030

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Review article

Membrane markers of the immune cells in swine: an update

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(Received 6 February 2008; accepted 16 July 2008)

Abstract – Besides their breeding value, swine are increasingly used as biomedical models. As reported in three international swine clusters of differentiation (CD) workshops and in the animal homologue section of the last workshop for the determination of human leukocyte differentiation antigens (HLDA 8), characterisation of leukocyte surface antigens by monoclonal antibodies and other molecular studies have determined the cell lineages and blood leukocyte subsets implicated in the immune response, including cell adhesion molecules involved in cell trafficking. This review focusses on the current state of knowledge of porcine leukocyte differentiation and major histocompatibility complex (SLA) molecules. Examples of porcine particularities such as the double-positive T lymphocytes with the phenotype $CD4^{+}CD8^{low}$ and $CD4^{-}CD8^{low}$ $\alpha\beta$ T cell subsets and the persistence of SLA class II after T-lymphocyte activation are illustrated, as well as the shared characteristics of the Artiodactyla group, such as the high proportion of $\gamma\delta$ TcR (T cell receptor) T cells in blood and other lymphoid tissues. Furthermore, discrepancies between swine and humans, such as CD16 expression on dendritic cells and CD11b (wCD11R1) tissue distribution are outlined. The rapidly growing information should facilitate manipulation of the swine immune system towards improving disease control, and open new avenues for biomedical research using the pig as a model.

cluster of differentiation (CD) / monoclonal antibody / immune system / histocompatibility system / pig

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Article available at http://www.vetres.org or http://dx.doi.org/10.1051/vetres:2008030

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1. INTRODUCTION

Specific identification of the various subpopulations of leukocytes enables improved investigations of the immune response to various porcine infections such as *Actinobacillus pleuropneumoniae*, African swine fever virus, classical swine fever virus, porcine reproductive and respiratory syndrome virus (PRRSV) and Aujeszky disease virus [6, 41, 76, 110, 116, 127, 137, 213]. An understanding of these interactions is essential for the development of new generations of vaccines. This field has also been promoted by the potential values of the pig as a model for biomedical studies due to anatomical and physiological similarities with humans and as an important source of tissues or organs for xenotransplantation [106, 178]. This has led to an increase in the number of scientists interested in this species, well beyond the restricted numbers focussing on the pig due to its economical importance. The unique aspect of T cell biology in the pig makes this species particularly suitable for

studying the generation of T cell subset diversity and tissue distribution. Pigs have been used, since 1966, to study the ontogenesis of the immune response [41, 156, 201, 227] within a foetal development not influenced by maternal antibodies and antigens. These studies concluded that piglets are immunocompetent at birth [22], albeit with a largely 'immature' immune system that has not been previously in contact with antigens, resulting in a primary immune response, a less developed mucosal immune response and lower repertoire diversity than in adults [182]. Piglets also constitute a unique material for studying the development of the postnatal immune response [120] without any other antigenic stimulus, since they can be reared in germ-free [179, 222] and antigen-free environments [108, 129]. However, certain characteristics of the porcine lymphoid system may affect the immune system, and thus require the development of appropriate cellular and molecular reagents and tools [184].

The recent development of monoclonal antibodies (mAb) directed against membrane molecules of porcine leukocytes has made it possible to improve the characterisation of the phenotype and functions of various porcine leukocyte populations. Various international workshops have been organised for the identification of porcine cell surface proteins, classified as clusters of differentiation (CD) using mAb. The first international workshop on differentiation markers was held in 1992 in Budapest (Hungary), the second in 1995 in Davis, CA (USA) and the third in 1998 in Ludhiana (India) [89, 118, 122, 157, 174]. The different workshops made it possible to produce an inventory of the various antibodies and molecular reagents available for the same reactivity cluster or differentiation group, specifically in pigs (Table A, available online only at www.vetres.org)[1]. Cross-reactivity studies have been made with well defined mAb directed against human leukocyte differentiation antigens showing species-overlapping reactivities [33, 171]. In these studies, care was taken to include a broad panel of lymphoid cells and specialised cell populations in order to ensure that the mAb were clustered appropriately. Thus, in addition to analyses of peripheral blood mononuclear cells (PBMC) and lymphoid tissues, analyses of representative cell subsets and cell lines, such as B-cell lines, [98, 99], alveolar macrophages, $\gamma\delta$ TCR-expressing cell lines foetal liver cells, SLA I-transfected mouse fibroblasts and T-cell lines have been carried out [164].

The assignment of mAb reactivity to CD has been standardised, using the following criteria: (i) the binding to the cluster of two or more mAb resulted in a pattern of reactivity that was typical of the same CD on human cells; (ii) the molecular weight (MW) of the antigen was similar to that of the human antigen; (iii) finally, the reactivity with the gene product or functional studies of the identified molecule were required to obtain official swine CD number assignment [122]. Antigens recognised by mAb without fulfilling all of these criteria were labelled with the prefix 'w' (workshop, see Table A). If the pattern of cell binding reactivity for the cluster of pig mAb differed from that of any known human CD antigen, then the cluster of mAb was assigned a swine workshop cluster number (SWC number, see Table A). Where detailed epitope analyses were performed, identified epitopes were denoted by a letter following the CD or SWC number (e.g. CD172a or CD8a, b, c, Table A) [122, 160, 174, 251]. The lack of a letter means that no epitope was

[1] Informative websites on swine immune markers: Porcine Immunology and Nutrition (PIN) database [online] http://www.ars.usda.gov/Services/docs.htm?docid=6065 [consulted 08/04/2008]; Veterinary Immune Reagent Network [online] http://www.umass.edu/vetimm/swine/index.html [consulted 08/04/2008]; and Porcine Immunology Resources [online] http://eis.bris.ac.uk/~lvkh/donors.htm [consulted 08/04/2008]; commercial websites such as RDI [online] http://www.researchd.com/pigcdabs/pigcdabs.htm [consulted 08/04/2008]; and eBioscience [online] http://www.ebioscience.com/ebioscience/whatsnew/humancd-chart.htm [consulted 08/04/2008].

assigned for that mAb. It is important to note that cross reactivity with CD from other species does not necessarily imply that positive mAb recognise the identical CD in swine [33, 171].

2. LYMPHOID AND MYELOID CELLS

2.1. Markers of T and/or NK (natural killer) cells

2.1.1. CD2

Swine CD2 (LFA2), a 50 kDa type I transmembrane glycoprotein[2] [167] is an adhesion molecule, the ligand of which LFA-3 (CD58) is found on many cells [34]. It is originally the sheep red blood cell receptor [167] and the anti-CD2 mAb block formation of the T-cell rosette [83]. In peripheral blood, most of the TcR-$\alpha\beta$ T cells express CD2, like $CD2^+CD4^+CD8^-$, $CD2^+CD4^+CD8^{low}$, $CD2^+CD8^{low}CD4^-$, $CD2^+CD8^{high}CD4^-$, in contrast to TcR-$\gamma\delta$ T cells which are $CD2^-CD4^-CD8^-$, $CD2^+CD4^-CD8^{low}$ and $CD2^+CD8^-CD4^-$ [92, 168, 239]; in addition, there is a large proportion of non-T ($CD3^-$), non-B (sIg-) lymphocytes expressing CD2, ($CD2^+CD4^-CD8^{low}$) and exhibiting a natural killer activity [239], as well as a subset of B lymphocytes albeit with CD2 at low level [196]. In foetus cells with a high level of MHC (major histocompatibility complex) class II and a low level of CD2 and CD25 expression may represent B cell precursors [194, 197]. On the contrary, in the spleen, most TcR-$\gamma\delta$ T cells express CD2 and/or $CD8^{low}$ whilst in the blood the majority of TcR-$\gamma\delta$ T cells are $CD2^-CD8^-$ [239].

2.1.2. CD3-T cell complex

The CD3-TcR is a multi-polypeptide membrane complex on T lymphocytes that is composed of the highly variable, antigen-binding TcR heterodimer ($\alpha\beta$ or $\gamma\delta$) and invariant signalling CD3 peptide chains [113]. However, the assembly of the CD3 complex on $\gamma\delta$ T cells is probably more complex, since unlike the conventional anti-CD3, the mAb anti-purified porcine CD3 molecule of $\gamma\delta$ T cells reacted specifically with peripheral $\gamma\delta$ T cells but not with $\alpha\beta$ T cells and failed to induce antigenic modulation, T cell proliferation and CD3-redirected cytotoxicity [243]. However, no anti-pig $\alpha\beta$ T cell mAb have been produced. The NK cells are enriched in the $CD3^-CD21^-CD172a^-$ fraction [150] and their activities stimulated by IL-2/IL-12/IL-18 cytokine, inducing IFN-gamma, perforin production and cytotoxicity against target cells.

2.1.2.1. CD3ε

The porcine CD3ε chain has been cloned, sequenced and transiently expressed in COS cells (cells being CV-1 (simian) in Origin, and carrying the SV40 genetic material) [111]. A panel of 14 mAb (PPT 1-14) directed against the porcine CD3 molecule [142, 238] defines six groups of CD3ε epitopes; they coprecipitate two types of TcR expressed on the surface of TcR-$\alpha\beta$ and TcR-$\gamma\delta$ T cells which differ in antigenicity, signal transduction potential and structure. They revealed that the density of CD3 on $CD2^+$ or $CD8^+$ cells is relatively low and heterogeneous, whereas the $CD2^-$, $CD8^-$ or $SWC6^+$ T cells express CD3 at a higher and more homogeneous level [238]. Based on differing mitogenic effects, the 14 anti-CD3 mAb can be divided into three groups [241] (a) PPT3 requires both epitope ligation and some unknown additional signal(s); (b) PPT5, 6, 9, 12, etc. only requires epitope ligation, either by monocytes or by immobilisation; (c) PPT7 requires neither epitope ligation nor participation of APC (Ag-presenting cells).

2.1.2.2. TcR δ and γ-chain

Biochemical analysis revealed that one TcR δ-chain of 40 kDa MW and three distinct TcR γ-chains of 37, 38 and 46 kDa MW are distributed in different subsets of porcine $\gamma\delta$ T cells [92, 168, 221].

[2] The Human Protein Reference Database [online] http://www.hprd.org/ [consulted 08/04/2008] and Human Cell Differentiation Molecules (HCDM) [online] http://www.hcdm.org/ [consulted 08/04/2008] also provide background information on protein structure, function and expression.

MAb immunoprecipitating heterodimers of 37 and 40 kDa MW [60, 61, 242] recognised a constant region of the δ-chain [61] and first demonstrated that the majority of 'null cells' ($CD2^{-}sIg^{-}$) are TcR-γδ T cells [23, 243]. Some other mAb recognise different epitopes of the γ-chain [61], whereas 7G3 was demonstrated suitable for high-quality immunostaining on frozen sections [218]. In addition, PG83A and 86D specifically recognise the porcine γ-chain of the TcR [61]. Furthermore the expression of a phylogenetically conserved external epitope of TcR-γδ subdivides porcine γδ T cell lymphocytes into a minor $86D^{+}$ and a major $86D^{-}$ subset [92].

2.2. Markers of TcR-γδ T cells and 'null cells'

In swine, as well as in ruminants, there is a high proportion of null cells (≥30% in the blood of piglets [134, 180]). These cells were originally defined as cells which did not form a rosette with sheep red blood cells – thus devoid of CD2 and of membrane immunoglobulin (CD2- sIg- lymphocytes) [25, 180]. One population is similar in phenotype and distribution to the population identified in other mammals. The second population is distinguished by expression of WC1. Analysis of these two populations of γδ T cells have shown they differ in expression of other lineage restricted molecules as well, including CD2, CD6, CD8 and molecules with no known human or rodent equivalent [60].

It is now clear that this intriguing cell population comprises several distinct subsets encompassing γδ T cells, although not all γδ T cells are null cells. In fact, $CD3^{+}CD2^{-}CD4^{-}CD8^{-}$, $CD3^{+}CD2^{+}CD4^{-}CD8^{low}$ and $CD3^{+}CD2^{+}CD4^{-}CD8^{-}$γδ T cell subsets have been identified [216]. Interestingly, a subset of these circulating γδ T cells displays a phenotype similar to professional antigen presenting cells and are able to take up and present soluble antigen to $CD4^{+}$ T cells in a direct cell-cell interaction via MHC class II [217].

2.2.1. SWC4, SWC5 and SWC6

MAb that form the SWC4 cluster immunoprecipitate two heterodimeric molecules of 270–280 kDa, the largest of which is also recognised by the anti-SWC6 mAb. They label the majority of 'null' ($CD2^{-}SIg^{-}$) lymphocytes [23, 25, 60, 61].

MAb against SWC5 [24, 61] also bind to determinants found on null lymphocytes.

A single mAb Mac320 defines SWC6, a disulphide-linked heterodimer that is present in two isoforms of 270 and 280 kDa. In reducing conditions, it immunoprecipitated 2 or 3 polypeptide chains at 130–160 kDa MW the largest of which is also precipitated by MAC319 assigned as anti-SWC4 mAb [25, 61]. It effectively identifies all null T lymphocytes in the blood and the majority of these $SWC6^{+}$ cells also express the orthologue of WC1 [25, 60]. The second population is negative for SWC4, SWC5 and SWC6 and similar in phenotype and distribution to the $WC1^{-}$ population in cattle [59] but expresses CD2 and CD6. A subset co-expresses CD8. As in cattle, this population is low in concentration in peripheral blood and most lymphoid organs but high in the spleen [61].

2.2.2. Anti-WC1

The anti-bovine WC1 mAb CC101 recognises a conserved determinant of WC1 of sheep and cattle and cross-reacts with porcine lymphocytes [24, 61]. While WC1 is expressed on the majority of ruminant γδ T cells only the $CD2^{-}$ subset of porcine γδ T cells are labeled [44]. Porcine WC1 was identified as a new member of the scavenger-receptor cysteine-rich (SRCR) superfamily containing up to six extra-cellular SRCR domains, and being highly homologous to other members of the family. Interestingly, a striking feature of the porcine and ruminant WC1 gene is its presence as a multigene family with extensive sequence diversity, both at the nucleotide and predicted protein levels [101].

2.3. Accessory molecules

2.3.1. CD4

CD4 is expressed on 50% of thymocytes and extra-thymic Th (helper T cells) lymphocytes [144]. Furthermore, blood plasmacytoid DC (dendritic cells) (or NIPC natural interferon-producing cells) express high levels of CD4 in contrast to conventional (myeloid) DC [208]. Anti-CD4a epitope antibodies inhibit binding to MHC class II and block the activation of Th lymphocytes [140, 144].

CD4/CD8 double-positive (DP) lymphocytes were found to increase gradually in proportion with age (30–55% by 3 years of age) and were able to proliferate in response to stimulation with recall viral antigen consistent with the hypothesis that this population in swine includes memory/effector T cells [52, 173, 177, 248, 249].

Interestingly, a novel antigen recognised by mAb 2E3 is selectively expressed in the periphery by a subset of porcine $CD4^+$ T cells, on both $CD4^+CD8\alpha^-$ and $CD4^+CD8\alpha^{low}$. $CD4^+2E3^+$ T cells show phenotypical and functional characteristics of naive T cells with the majority of them being $CD29^{low}CD45RA^{high}CD49^{low}$ [152]. Accordingly, after mitogen activation $CD4^+2E3^+$ T cells express high levels of IL-2 mRNA, but only traces of IFN-γ or IL-4 mRNA.

2.3.2. CD5

CD5 is expressed on most thymocytes (92–97%), both immature and mature thymocytes at low and high levels respectively on 54–97% of peripheral blood T lymphocytes [161] with a heterogeneous distribution [166]; high levels of CD5 are found on $CD4^+$Th cells, $CD4^+CD8^+$ memory T cells and $CD4^-CD8^{high}$ Tc (T cytotoxic) cells. In contrast, $CD4^-CD8^-CD2^-\gamma\delta$ T cells express low levels while $CD4^-CD8^-$ and $CD4^-CD8^{low}$ NK cells do not express CD5.

Thus, CD5 can also be used to distinguish MHC class I-restricted cytolytic T cells ($CD4^-CD5^+CD8^+$) from MHC-unrestricted, spontaneous cytotoxic NK cells ($CD4^-CD5^-CD8^+$) [138]. In addition, 10–30% of porcine blood B lymphocytes are $CD5^+$ of low density [161]. This population could represent the B1 cells of mice, man and other species based on frequency and lymphoid organ distribution and the high frequency in neonates [7].

2.3.3. CD6

The homologous of human CD6 [159] has three cystein-rich domains and belongs to the family of SRCR as CD5 and other peptide-binding receptors [135, 138]. Differences in N- and O-glycosylation sites may account for variations in MW between porcine CD6 molecules.

All thymocytes with the exception of $CD4^-CD8^-$ cells, and 39–76% of peripheral blood T cells express CD6. CD6 is co-expressed with $CD4^+CD8^-$ Th cells and $CD4^-CD8^{high}$ Tc cells whereas $CD4^-CD8^{low}$ and $CD4^-CD8^-\gamma\delta$ T are devoid of CD6. Thus, $CD6^+$ T lymphocytes are responsible for MHC class I-restricted T-cell cytotoxicity (TcR $\alpha\beta$) whereas the $CD6^-$ T lymphocytes support spontaneous and un-restricted MHC cytotoxicity [138, 173]. CD6 is not expressed nor by B cells nor by cells of the myeloid lineage.

2.3.4. CD8

CD8 is expressed as a homo-dimer ($\alpha\alpha$) or a hetero-dimer ($\alpha\beta$) [97, 144]. CD8α is expressed on the surface of most thymocytes, and is present at high ($CD8\alpha^{high}$) or low ($CD8\alpha^{low}$) cell density on porcine T cells. $CD8\alpha^{high}$ cells are generally Tc cells whereas the co-expression of low levels of CD8α with $CD4^+$ identifies memory Th cells [145, 146, 175, 177, 246]. Most $\gamma\delta$ T cells are $CD8^-$ with a minor subset $CD8\alpha^{low}$ [239, 240]. The mAb specific for the β-chain can be used to distinguish between $CD8^{low}$ and $CD8^{high}$ cells, with only the latter expressing CD8β [251]. MAb directed against the CD8a or b epitopes, block cell-mediated lysis in allogeneic T cell responses [97, 144, 162]. MAb that recognise the wCD8c epitope bind to only the $CD4^-CD8\alpha^{high}$ representing the

classical Tc cells and not the $CD4^{+}CD8\alpha^{low}$ DP (double positive) Th-cell subset [251].

2.3.5. SWC2

SWC2 cluster closely to the CD6 group [162, 170]. The role of these molecules of 49–51 kDa [162] still remains unknown.

2.4. Differentiation antigens of B cells

B cells in mammals are lymphocytes that mature in the bone marrow and/or ileal Peyer patch [41] and, when stimulated by free antigen in solution, differentiate into plasma cells that secrete immunoglobulins (Ig) that inactivate/eliminate the antigens. This population is characterised by expression of the BcR representing a stable (i.e. not elutable) membrane immunoglobulin [180] that can be recognised by antibodies against the Ig light chain [193]. Extensive work on the antibody repertoire development was done and reviewed by the Butler laboratory [42].

2.4.1. CD1

MAb anti-CD1 antibody 76-7-4 [86] recognises the product of porcine pCD1. One gene, a class I-like protein, with a 40 kDa heavy chain and a 12 kDa light chain [86], thus highly similar to human CD1a [55]. In both humans and pigs, CD1 group I (CD1 a, b and c) markers are expressed on cortical thymocytes, a fraction of B cells, thymic dendritic cells, some macrophages and Langerhans cells [147, 167, 183].

2.4.2. wCD21 (complement receptor 2, CR2)

wCD21 is expressed primarily on B cells and follicular dendritic cells. It is recognised by the mAb IAH-CCR1, a cross-reacting anti-bovine CD21 [133, 171], BB6-11C9, and C35 [29, 63]. The broad species-overlapping reactivity of mAb directed against CD21 as well as CD9, CD11, CD14, CD18, CD29, CD44, CD45, CD47, CD49d, CD61, CD86, CD91, CD172a, is interesting, indicating evolutionary highly conserved epitopes on these surface molecules but reactivity alone is not sufficient. These data have to be confirmed by molecular analyses, e.g. immunoprecipitation studies and/or analyses on transfectants [171].

2.4.3. SWC7

SWC7 is expressed on a subset of B cells and on follicular dendritic cells in the germinal centers of different lymphoid organs (tonsil, lymph-node, spleen, Peyer patches [37]) and on a large fraction of B cells in the thymus and bone marrow [192]; but it is not expressed on resting circulation B cells [37]. Nevertheless, after phorbol ester activation, SWC7 is induced on most blood B cells and on a subset of T cells [37, 192].

Although anti-SWC7 mAb are related to bovine CD19 according to patterns of flow cytometry profiles these mAb immunoprecipitate a 40 kDa molecule instead of the expected 90 kDa molecule [62, 63].

2.4.4. Cross-reacting anti-human (anti-h) B cell mAb

2.4.4.1. CD19

CD19 is a type I transmembrane protein of the immunoglobulin super family (IgSF). It is present on B lymphocytes but not plasma cells and it is a co-receptor involved in B cell signalling. The swine CD19 gene has been cloned, sequenced and expressed in bacteria; only 60% sequence similarity was in the extracellular region explaining that only one of 17 anti-hCD19 mAb recognised swine B cells (B-D3 from Diaclone reactivity with CD19 to T1) [212].

2.4.4.2. CD79

Human CD79a and CD79b are two small 22 kDa type I IgSF proteins that are associated with the BCR. The commercial mAb anti-human CD79α seems to label the intracellular portion of the swine molecule in cytometry but not in immunohistochemistry [75]. It is claimed as a pan-B cell but as ascertained by phenotypes warrants further confirmation.

2.4.4.3. CD72

Swine CD72 is highly transcribed in the lymph-node, thymus, lung tissues and pulmonary alveolar macrophages, perhaps due to the known expression of this gene into B cells, some T cell macrophages and DC cells [18]. Compared to CD72 sequences from other species, the extracellular part of the swine polypeptide is less conserved than the intracellular part, explaining the absence of identified cross-reacting mAb [18].

2.5. Differentiation antigens of monocytes, macrophages and dendritic cells

2.5.1. CD14

Swine CD14 is a marker of monocytes and macrophages [68, 85, 209, 220] with a maturation-dependent expression for the monocytic-bone marrow haematopoietic cell population [210]. The intensity of CD14 labelling depends on the cell type: PMN (polymorph nuclear leukocytes) neutrophils express low levels of CD14, whereas monocytes/macrophages (macrophages less than monocytes [128]) express higher levels of CD14. CD14 can also be found on monocyte- and bone marrow-derived GM-CSF-driven DC, although functional differences are found when compared to monocyte CD14. Furthermore, the continued presence of CD14 and CD16 [87] on mature and immature porcine DC was a notable difference with other species including humans [46].

The mAb anti-hCD14 cross-react with porcine CD14 expressed on alveolar macrophages [107], on 60–70% swine monocytes but few granulocytes (6–13%) [69]. Inversely mAb anti-swine CD14 cross-react with human monocytes and granulocytes, in a pattern similar to that of human CD14 [209]. The gene encoding CD14 has been recently cloned in swine [148], showing that the different reactivity patterns described by anti-CD14 mAb may be due to differences in affinity of these antibodies [68].

2.5.2. CD16

The CD16 gene has been cloned, and the gene product is recognised by the mAb G7 [57, 82, 109, 214]. MAb has been shown to abolish PBL (porcine blood leukocytes)-mediated Ab-dependent cellular cytotoxicity almost entirely and to inhibit PMN-mediated Ab-dependent cellular cytotoxicity by about 50% [232]. All blood monocytes and all NK lymphocytes bear CD16 [185, 232]. This receptor is also found on immature and mature monocyte-derived DC as well as on blood DC in pigs, contrasting to the human expression pattern [46] and in gut DC [87].

2.5.3. CD123

CD123, a type I cytokine receptor family, associates with the common CD131 signalling chain. CD123 is expressed on haematopoietic progenitors and most myeloid cells including basophiles and mast cells. Although no CD123 cross-reactive mAb was identified, the molecule can be detected using his-tagged IL-3 [208]. IL-3 is required for the survival of the DC subset as blood myeloid DC and NIPC, the latter expressing particularly high levels of this receptor [208].

2.5.4. CD163

The mAb anti-swine CD163 recognises a 120 kDa protein with a sequence similar to that of human CD163 [38, 185, 220]. This receptor is restricted to cells of the porcine monocyte/macrophage lineage and more specifically, to macrophages and tissue DC [53] and confers susceptibility to PRRSV [43]. $CD163^+$ monocytes produce more TNF-α, express high levels of adhesion molecules and are better at presenting antigens to T cells when compared to $CD163^-$ monocytes [48]. In addition, the DC derived from $CD163^+$ monocytes, express higher levels of MHC class II and CD80/86 and are more efficient antigen presenting cells [49].

2.5.5. CD172a

CD172a, an α member of SIRP (signal regulatory protein) of 90–115 kDa MW [4, 5] also known as CD172a [28, 147, 220] is associated with the protein-tyrosine phosphatase SHP-1 after tyrosine phosphorylation. This cluster is present on monocytes/macrophages, neutrophils [86], bone-marrow derived DC, blood monocyte-derived DC and plasmacytoid DC [46], thymic DC [181] skin DC [14] gut DC [21, 90] and as NIPC [126, 155]. Monocytes express high levels of CD172a, whereas the two blood DC, conventional and plasmacytoid DC express only low levels [208].

2.5.6. CD203

Swine CD203, (SWC9) of 130 and >205 kDa MW is orthologue of human CD203a (NPP1/CD203a) [148]. It is present on thymocytes but disappears during T cell development, since most mature peripheral lymphocytes do not express this marker. As monocytes differentiate into macrophages, they rapidly start to express CD203 [12]. On this basis, CD203 has been proposed as a useful marker for studies of myeloid differentiation or maturation. Most prominent expression of CD203a was found in lung macrophages and liver sinusoids.

2.5.7. SWC8

SWC8 [85, 91] is present on all PMN cells in blood, macrophages and PMN cells in the gut lamina propria [220]. This antigen is not restricted to $CD172a^+$ myeloid cells, since MIL3 also labels B cells, a subset of $CD8^{high}$ T cells, epithelial and fibroblastic cells [91]. SWC8 has been used to discriminate blood and bone-marrow granulocytes ($SWC8^+$) from monocytes ($SWC8^-$). This epitope is associated with the differentiation of cells, such as monocytes and macrophages [192]. A minor fraction of $CD4^+$ T cells also expresses this antigen at a low level [91]. Through SWC3/SWC8 double-labelling, three cell populations committed to the myeloid lineage can be discriminated: (i) early myeloid progenitors are $CD172a^{low}SWC8^-$; (ii) cells committed to the granulocytic lineage are $CD172a^+SWC8^+$ and (iii) monocytic cells are $CD172a^+SWC8^-$ [210].

2.5.8. Other anti-macrophage mAb

Two mAb (clones 2G6 and 2B10) directed against porcine macrophages [17], immunoprecipitating under non-reducing conditions a 140–150 kDa and a 140–145 kDa antigen, respectively, identify cell populations of the mononuclear phagocytic system. While 2G6 detected tissue macrophages, 2B10 stained scattered cells in the lymph node and in the lung interstitium.

2.6. Differentiation antigen of activated cells

CD25 is expressed on activated T and B lymphocytes [11, 143] and on regulatory T cells [29, 103] (personal communication, C. LeGuern[3]).

2.7. Common T or B cell Ag

2.7.1. CD45 and CD45R

As in almost all species, anti-CD45 antibodies recognise common epitopes present in all isoforms (named CD45), whereas anti-CD45R antibodies react with restricted antigenic determinants CD45RA, CD45RB or CD45RC encoded by exons A, B and C displaying alternative splicing. The isoform devoid of all these antigenic determinants is called CD45RO.

MAb anti-CD45 (or leukocyte common antigen) were based on their broad reactivity patterns with lymphoid and myeloid cells and their ability to immunoprecipitate three polypeptides with an apparent MW of 226, 210 and 190 kDa whereas mAb anti-CD45R were based on their restricted reactivity against lymphoid and myeloid target cells, and their ability to immunoprecipitate either

[3] LeGuern C., Role of MHC Class II in regulatory tolerance to class II-matched transplants, Transplantation Biology Research Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02129, USA.

two polypeptides with an apparent molecular weight of 226 and 210 kDa or a single polypeptide with an apparent molecular weight of 210 kDa [52, 247].

As a prelude to defining the specificity of anti-porcine CD45 mAb for this purpose, Chinese hamster ovary cells were transfected with constructs containing cDNA encoding the extracellular and transmembrane domains of four pig CD45 isoforms, CD45RO, CD45RC, CD45RAC and CD45RA [188].

CD45 is present on more than 95% of PBL, 90% of thymocytes and 95% of granulocytes and monocytes in pigs. CD45RA (exon A) reacted with 65–85% of PBL and only 25% of thymocytes, but is absent from granulocytes [250]. Only between 10% and 50% of monocytes express this marker. All B cells express CD45RA, whereas most $CD4^+$ T cells express this marker only weakly (ten times lower), if at all. A reverse pattern was observed with CD45RC (exon C): a significant proportion of $CD4^+$ T cells was stained at a level 10 times higher than that of B cells whereas in humans it is the CD45RB which is expressed at a high level onto $CD4^+$ T cells [250]. In mice and humans, CD45RA identifies naive cells whereas CD45RO (i.e. an isoform devoid of all these antigenic determinants) identifies memory cells. Accordingly, CD45RA is gradually down-regulated after the stimulation of swine T cells with a mitogen [39, 70]. The polymorphism of CD45 was used to detect donor lymphocytes during migration experiments [20, 26].

2.7.2. SWC1

SWC1 has two subunits, of 41 and about 15 kDa, under reducing conditions [124, 169]. SWC1 is expressed on thymocytes [163], resting T cells, monocytes and neutrophils but is absent from B lymphocytes [144]. This relates to the observation that monocytes gradually downregulate SWC1 during their differentiation to macrophages [12]. Similarly, T lymphocytes also down-regulated SWC1 expression following in vitro activation [163].

2.8. Costimulatory molecules

2.8.1. wCD40

Human mAb CD40 cross-react with porcine cells and show similar cellular reactivity onto B cells, B cell line L14, pulmonary alveolar macrophages and endothelial cells with increased expression on activated cells [29]; however the MW reported by the mAb STH224 of 35 kDa is lower than that reported for human CD40 (48 kDa), and one-color flow cytometry results of PBMC and mesenteric lymph node (MLN) cells showed only partial co-expression of the ligands, hence wCD49 [19, 29, 86]. Cholera toxin promoted the development of semi-mature DC phenotype with decreased levels of MHC class II and CD40, but increased CD80/86 expression [19]. Porcine membrane CD40L, a ligand of the CD40 receptor, was cloned and sequenced [231] with 88% AA sequence similarity to human CD40L. Human soluble CD40L may be used to stimulate the $CD40^+$ swine cells [16].

2.8.2. CD69

Swine CD69 mRNA was detected in activated PBL, NK cells, macrophages, monocytes and granulocytes, but not in resting cells. These results indicate that CD69 can be used as an activation marker in pig cells of innate as well as acquired immune systems [244]. No antibody against porcine CD69 is yet available.

2.8.3. CD80/86 and CTLA-4 (CD152)

Porcine co-stimulatory molecules CD86 (also known as B7-2) soluble ([74] or transmembrane [54, 125] and CD80 (also known as B7-1) soluble [58] or transmembrane [215, 228] have been characterised molecularly, structurally and functionally, as well as their porcine receptor CTLA-4 (CD152) [226]. Sequence analysis showed a high degree of conservation in residues involved in pCD80/86 with hCD28 and CTLA-4 so that to detect expression of CD86, human CTLA-4 mu-Ig fusion protein was used [19, 132].

Cross-reacting anti-hCD80 blocks the stimulation of human lymphocytes by porcine splenic lymphocytes [215].

2.9. Cell adhesion molecules

Adhesion molecules belong to four main protein families, integrins, selectins and proteoglycans and members of the immunoglobulin superfamily. In this chapter, we will focus on adhesion molecules more specifically implicated in leukocyte trafficking [20] and susceptible to play a role in xenotransplantation [71, 187, 191].

2.9.1. Molecules of the integrin family

Integrin heterodimers composed of non-covalently linked α and β transmembrane subunits act as cell surface receptors that mediate cell-cell interactions and attachment to the endothelium.

2.9.1.1. The β2 integrin subfamily CD11a-c/CD18

MAb anti-hCD18 or anti-pCD18 [109] recognise an epitope CD18a on the common integrin β2-chain (CD18, 95 kDa) and react with 80–96% of porcine PBMC and PMN. In association with CD11a (180 kDa), CD11b (170 kDa) or CD11c 150 kDa) CD18 form the heterodimers CD11a/CD18, CD11b/CD18, CD11c/CD18 which differ in their pattern of expression and in cellular distribution as compared to humans [67, 220].

2.9.1.1.1. CD11a/CD18

CD11a, (LFA-1, lymphocyte-functional antigen-1) is found on all leukocytes with high levels on monocytes, granulocytes and a $CD8^{+}$ subset but low levels on B cells and various levels inversely correlated with CD3 expression on T cells, $CD3^{low}CD11a^{high}$ and $CD3^{high}CD11a^{low}$ [3]. Memory Th cells ($CD45RA^{-}$) express higher levels of CD11a than naive T cells probably in relation to their greater capacity to migrate from the lymphoid tissues to inflammatory sites [3]. MAb anti-CD11a inhibit the ConA mitogenic response, the NK cell-cell mediated lysis of K-562 cells and the mixed lymphocyte reaction [3].

2.9.1.1.2. wCD11R1/CD18

The cross-reactive mAb anti-hCD11b (TGM6-5) had a similar pattern of reactivity to mAb MIL-4 raised against porcine leukocytes [85]: both mAb label ∼50% porcine PMN, all eosinophils, but not monocytes or alveolar macrophages [67, 85, 204, 220], whereas in humans CD11b is expressed on all monocytes and macrophages and granulocytes. Consequently, the molecule recognised by the cross-reactive anti-hCD11b was named wCD11R1. A recent study using the cannulated pseudo-afferent lymph model, has demonstrated that large numbers of DC, expressing CD11R1 (CD11b) and CD172 are found in efferent lymph [21] and are phenotypically similar to DC from the diffuse lymphoid tissue [21, 87].

Inversely, mAb anti-swine CD11b defines a cluster of differentiation that corresponds to the expression of CD11b similar to that observed on human cells but with a different MW so that they were designed as wCD11R3 [67, 69, 209, 220].

The CD11b/CD18 herodimer binds to a fragment of the complement (iC3b) and contributes to PMN and monocyte adhesion to the endothelium, so that mAb anti-wCD11R3 inhibits phagocytosis of iC3b opsonised particles and adherence of activated PMN to plastic [35].

2.9.1.1.3. CD11c/CD18

While in humans CD11c is found on all myelo-monocytic cells, NK cells and some T and B cell subsets, in the pig the distribution with cross-reactive anti-hCD11c is different, with expression on most monocytes but not on granulocytes [67, 86, 204]. Hence, we call the prefix w for wCD11R2 recognised by the cross-reactive anti-hCD11c (S-cHl3).

2.9.1.2. The β1 integrin subfamily, CD49 a-f/CD29 heterodimers: the VLA family

The structure of CD29 (the β1 integrin subunit) is highly conserved among species and

includes 12 potential N-glycosylation sites. Punctual changes between human and swine CD29 molecules within the ligand binding domain, and/or the regulatory domain suggest potential differences between human and porcine CD29 relative to the human CD29 ligand [94]. CD29 mRNA were expressed in a variety of porcine tissues with different intensities [95] and CD29 integrin is widely distributed and found on all the cell lines tested in one study [91]. The anti-hCD29 mAb cross-react with porcine cells and have been assigned to the wCD29 group due to differences in MW [91]. In immunohistochemistry, rabbit antibody anti-porcine recombinant CD29 displayed a morphological pattern associated with smooth muscle, epithelium and myeloid cells [136].

The CD29 non-covalently associated to one of the six α integrin subunits (CD49 a to f, 150 to 200 kDa) form the VLA heterodimer, which stands for 'very late activation antigens' reflecting their late upregulation after activation [205].

VLA-4 (the α4β1 integrins, CD49d/CD29) forms the adhesion molecule, which mediates adhesion to the extracellular matrix components and provides an important stimulus during interactions between B and T lymphocytes, or between Th and Tc cells. Furthermore this adhesion molecule is the major ligand for VCAM-1 (vascular cell adhesion molecule-1), which is expressed on inflamed endothelia and certain endothelial cells of the respiratory tract [30]. In all organs except the Peyer patches, α4β1 (heterodimer detected by mAb anti-h α4β1 PAG) has been shown to be more frequently expressed on sIgA$^+$ and CD3$^+$ T cells of the pharyngeal than palatine tonsil [31]. Variations in the level of wCD49d expression [9] demonstrate a relationship between the activity of blood and spleen Th cells, but not Tc cells. Ag- or IL-2-activated Th CD25$^+$ and memory Th cells display higher levels of wCD49d than naive cells. Differences in CD49d expression between blood and lymph node cells, and between Tc cells from different organs, show that CD49d levels are high on blood T cells emigrating from the lymph nodes and spleen [9]. The anti-hCD49e (Sam-1) was the only mAb cross-reacting with the majority of swine monocytic cells, but not other bone-marrow hematopoietic cells [209].

2.9.1.3. β3 integrin: CD61

The mAb anti-CD61 [115] shows a broad expression in all tissues of the pig with a strongest expression in epithelial cells from tubules in the kidney [130].

2.9.1.4. β7 integrin

β7 integrin associates non-covalently to α4 to form the homing receptor of T and B lymphocytes for the gut-associated lymphoid tissue and mammary gland [30, 31, 219]. It binds and mediates cell attachment to MAdCAM-1 (mucosal cell adhesion molecule-1) [15]. The mAb against murine β7 integrin and as well as the mAb against an epitope present on the human α4β7 dimeric molecule cross-react with β7 and α4β7 in swine [30, 31]. Similar to murine studies, retinoic acid also mediates the induction of α4β7 on porcine lymphocytes [186].

2.9.2. Selectins

Selectins (L-, E-, and P-selectins) belong to a family of cell adhesion molecules and are type I transmembrane proteins with a lectin, an epidermal growth factor and variable numbers of SCR (short consensus repeat) domains. Initial leukocyte rolling on the vascular endothelium is mediated by selectins.

2.9.2.1. L-selectin

L-selectin, CD62L or leukocyte endothelial cell adhesion molecule-1 (LECAM-1) is a glycoprotein that is constitutively expressed and functional on all leukocytes. An antibody directed anti-h L-selectin LAM1-3 ([102] labels porcine lymphocytes [31]. L-selectin ligands include glycosylated cell adhesion molecule-1 (Glycam-1), glycosylated MadCAM-1 and CD34, a sialomucin

of 120 kDa which is expressed on vascular endothelial cells and appears as the swine L-selectin binding receptor [190]. MECA-79, an anti-rat mAb reacting with peripheral node addressin (the counter-receptor for L-selectin on lymph node high endothelium venules), cross-react with porcine lymph node high endothelium venules [31, 230].

2.9.2.2. P-selectin

P-selectin, CD62P or platelet granule membrane protein-40 is stored preformed in endothelial cells. The porcine P-selectin cDNA has been cloned and used to generate mAb 12C5 [206]. The high degree of conservation of this lectin and EGF domain – particularly in regions involved in ligand binding – explains the ability of human leukocytes to bind to P-selectin. MAb anti-hP-selectin (G3) cross-reacts with porcine P-selectin and labels 30–60% of blood macrophages and granulocytes [114].

2.9.2.3. E-selectin

Swine E-selectin, CD62E or ELAM-1 is a glycoprotein of 92 kDa and 71% homologous with human E-selectin but missing SCR. It is recognised by the human cross-reacting mAb 12B6 [105, 224]. It is expressed on the activated vascular endothelium, and mediates attachment of neutrophils, monocytes and some lymphocytes [27, 112, 224].

2.9.3. Molecules of the immunoglobulin superfamily

The immunoglobulin superfamily adhesion molecules are involved in leukocyte-endothelial cell interactions. These proteins include ICAM (intercellular adhesion molecule), VCAM-1 and PECAM-1 (platelet endothelial cell adhesion molecule). ICAM-1, -2 and -3 are a group of type I transmembrane molecules within the IgSF having a variable number of Ig constant region-like domains, which are expressed by endothelial cells and bind to the β2 (leukocytes) integrins, LFA-1 and Mac-I.

2.9.3.1. ICAM

In swine, the gene structure and endothelial expression of pig ICAM-2 (CD102) are strikingly similar to the human and mouse counterparts: mRNA transcripts were detected in cultured pig endothelial cells and in the lung, spleen, kidney, liver and heart [79]. However, in contrast to humans and mice, ICAM-2 is not down-regulated on cultured endothelial cells after treatment with inflammatory cytokines such as IL-1β and TNF-α. The mature protein sequence is 55% identical to human ICAM-2, with conservation of 5 out of 6 residues critical for binding of the human protein to its ligand LFA-1 [79]. The anti-hCD102 mAb (CBR-IC2/2) labels blood leukocytes and T lymphoblasts [114].

Other mAb directed against human CD54 (ICAM-1, with ~41% degree of identity between human and porcine ICAM-1 [207]), CD31 (PECAM-1), CD50 (ICAM-3) do not cross-react with pig cells [114]. However, specific mAb anti-swine ICAM-1 have been developed [207]. HEV (high-endothelial venule) express higher levels of ICAM-1 [20].

Similarly, the expression of CD50 (ICAM-3), although ubiquitous for the majority of human leukocytes, was more restricted on pig cells with the cross-reacting anti-hCD50 (HP2/19). Most pig granulocytes were negative, but monocytes were positive and subsets of T and B cells showed variable expression. This work illustrates the importance of carrying out a thorough characterisation of reagents raised and characterised for cells of one species for use in another species [86]. However, specific mAb anti-swine ICAM-1 have been developed [207].

2.9.3.2. VCAM-1

Porcine VCAM-1 (CD106) has five Ig domains and an overall 77% homology with the human protein [223]. Several mAb have been developed against porcine VCAM-1 to specifically block leukocyte adhesion in xenografts [84, 131, 154]. It is highly expressed after cytokine activation of cultured vascular endothelial cells [13, 223], and by

skin endothelial cells during inflammatory skin reactions [84]. As a vascular addressin, VCAM-1 is present constitutively in pharyngeal tonsil and lymph-nodes, but neither in the palatine tonsil nor in Peyer patches and intestinal vascular cells [30, 31].

2.9.4. CD44

Swine CD44 (also known as Pgp-1, Hermes antigen or H-CAM, gp 85) is a type I transmembrane glycoprotein of 80 to 90 kDa MW with a soluble form present in porcine intestinal efferent lymph [235]. Variants exist due to alternative RNA splicing [104]. Four mAb have been shown to react with the porcine equivalent of human CD44 [236]. The human mAb Z062 recognise another epitope (wCD44a) [247]. CD44 is strongly expressed by nucleated cells (leukocytes, [9] fibroblasts, epithelial cells) but not on red blood cells (at variance with humans, [247]) and platelets. The expression of CD44 in the lymphoid tissues tested appeared to be related to their level of cell migration capacity [234]. Although CD44 has been ascribed as a receptor involved in lymphocyte recirculation by binding to high endothelial venules, cell-cell and cell-extracellular matrix interactions, in swine it is not directly involved in such binding [233].

3. MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGENS (MHC) IN SWINE

3.1. Introduction

$CD3^{+}\alpha\beta$ T lymphocytes recognise antigens only if they are presented in the MHC context of Ag-presenting cells. The T cell receptor reacts simultaneously with MHC antigenic peptides (MHC-Ag peptides) and with CD4 or CD8 molecules. Depending on their origin and size, antigenic peptides are either presented by MHC-class II and recognised by Th CD4 lymphocytes or presented by MHC-class I and recognised by CD8 Tc lymphocytes. MHC-class I presents antigenic peptides of eight to nine amino-acids following endogenous degradation in the cytosol, whereas MHC-class II present peptides of 12 to 25 amino-acids following exogenous degradation in phagolysosomes [65, 200]. Using synthetic pentadecapeptides, classical swine fever virus-specific T cell epitopes of SLAd/d mini-swine were identified. These represent class II- and class I-restricted Th and cytolytic T cell epitopes, respectively [8]. Moreover, foot and mouth disease virus-specific pentapeptides which stimulated class II-restricted Th cells were identified [78] as well as nonameric peptides able to reconstruct the swine SLA class I protein complex [77].

MHC class I is expressed on all cells of the body, except those of the neural system and red blood cells, whereas in the adult, MHC class II is expressed on the surface of APC such as macrophages, B lymphocytes, microglial and dendritic cells [12, 46, 225]. In developing organisms, MHC II expression is also observed on other types of cells such as endothelium cells of blood vessels and thymic epithelial cells [90].

The pig MHC[4] or swine leukocyte antigen (SLA) has been mapped on both sides of the centromere of chromosome 7. The SLA complex is about 2 000 kilobases (kb) long, with the SLA class II region locus spanning 500 kb and the SLA class I and SLA class III regions spanning about 1 500 kb. Despite their division by the centromere, the spatial relationships between regions II and III and between the well conserved class I and non-class I are similar to those observed for the human HLA complex [50].

3.2. Major histocompatibility complex class I

MHC class I is a dimer (α and β subunits) of non-covalently associated type I transmembrane proteins – the α (44 kDa)

[4] Table A and text also report information available through websites: for SLA the Immuno Polymorphism Database-MHC (IPD-MHC) website [online] http://www.ebi.ac.uk/ipd/mhc/sla/stats.html [consulted 24/06/2008]; for Swine genome project [online] http://www.ncbi.nlm.nih.gov/sites/entrez?db=genomeprj&cmd=Retrieve&dopt=Overview&list_uids=10718 [consulted 24/06/08].

and β (β2-microglobulin, 12 kDa) chains expressed on most nucleated cells.

The classical class-I SLA genes are designated as SLA-1, SLA-2 and SL-3; the non-classical as SLA-6, SLA-7 and SLA-8 and the pseudogene SLA-4, SLA-5, SLA-9 and SLA-11. The SLA-1, SLA-2 and SLA-3 locus are highly polymorphic. For the SLA-1 locus, there are 44 alleles. The SLA-3 locus has 26 alleles and the SLA-2 locus has 46 alleles.

In contrast, the SLA-6 locus has limited polymorphim. Only two polymorphisms occur within the alpha-1 or alpha-2 domains. The limited polymorphism of SLA-6 is similar to the limited polymorphism of 'non-classical' MHC class loci, such as HLA-E, HLA-F and HLA-G in humans [199]. SLA-6 mRNA has been found in many tissues with the highest level found in lymphoid tissue, which is a pattern of expression more similar to HLA-E than to HLA-F or HLA-G [72].

Lunney [119] and Ivanoska et al. [93] summarise the large set of mAb to SLA I and II antigens. Two antibodies [145] react with SLA class I. MAb 74-11-10 is specific for a polymorphic MHC class I determinant (haplotype d), and mAb 76-3-2, precipitates two chains of 43 kDa and 11 kDa and β2-microglobulin. Haverson et al. [91] described several monoclonal antibodies that appeared to recognise SLA class I antigens (1D10, 4B7/8, UCP1E9 and UCP1F9).

3.3. Major histocompatibility complex class II

SLA class II antigens, the second major group of histocompatibility antigens, are dimers of α (33–35 kDa) and β (28–30 kDa) type I transmembrane proteins. The two chains are non-covalently associated.

The SLA class II region has been fully sequenced [51, 151, 198]. The SLA class II genes demonstrate high strong sequence homology with their human leukocyte antigen (HLA) counterparts. The overall arrangement of genes in the class II region is very similar to the HLA class II region, except that the length of the region is much shorter, there are no DP genes and it is separated from the class III region by the centromere. Two independent groups of class II MHC molecules are found in pigs: SLA-DR, a 28/35 kDa heterodimer similar to the murine I-E complex and human HLA-DR, and SLA-DQ, a 27/34 kDa heterodimer corresponding to human HLA-DQ.

The class II loci comprise the SLA-D region and, consistent with human nomenclature, are designated as SLA DRA, SLA-DRB1, SLA-DQA (α-chain) and SLA-DQB1 (β-chain). In the SLA-DRA locus, only two polymorphic sites were found in the α1 domain. The limited polymorphism in this region is of interest because the DRA locus in most species does not show any polymorphism in the peptide-binding portion of the protein, the α1 domain. In contrast, the SLA-DRB1 alleles show a highly polymorphic locus with 82 published alleles. The SLA-DQA corresponds to a moderate polymorphic locus with 20 representing alleles belonging to at least 4 groups. The SLA-DQB1 is a highly polymorphic locus with 44 published DNA sequences that represent alleles belonging to at least 9 groups [199].

SLA class II is expressed on dendritic cells, B cells, monocytes and macrophages and certain T cell subsets, whether resting or activated [49, 80, 197]. Expression may be induced or downregulated following the activation of epithelial and endothelial cells. Whilst the $CD4^-CD8^-$ TcR-γδ and the $CD4^+CD8^-$ TcR-αβ T cells lack MHC II, the $CD4^-CD8^+$ and $CD4^+CD8^+$αβ T cell subsets (the latter of which is unique to swine) do express MHC II. As opposed to human T cells, expression of porcine MHC II is not transient and restricted to lymphoblasts but is immanent in small, resting T lymphocytes of the two $CD8^+$ subsets [170, 172, 176].

Mab MSA3 recognises a monomorphic determinant on the 28/30 kDa SLA-DRw heterodimer [91], whereas mAb 2F4 and FQ1D7 recognise 33 kDa antigens that probably correspond to the α chain. An overview of the various mAb reacting with SLA class II antigens has been provided by Lunney and Pescovitz [121] and these antigens have also been the subject of another review [117, 119].

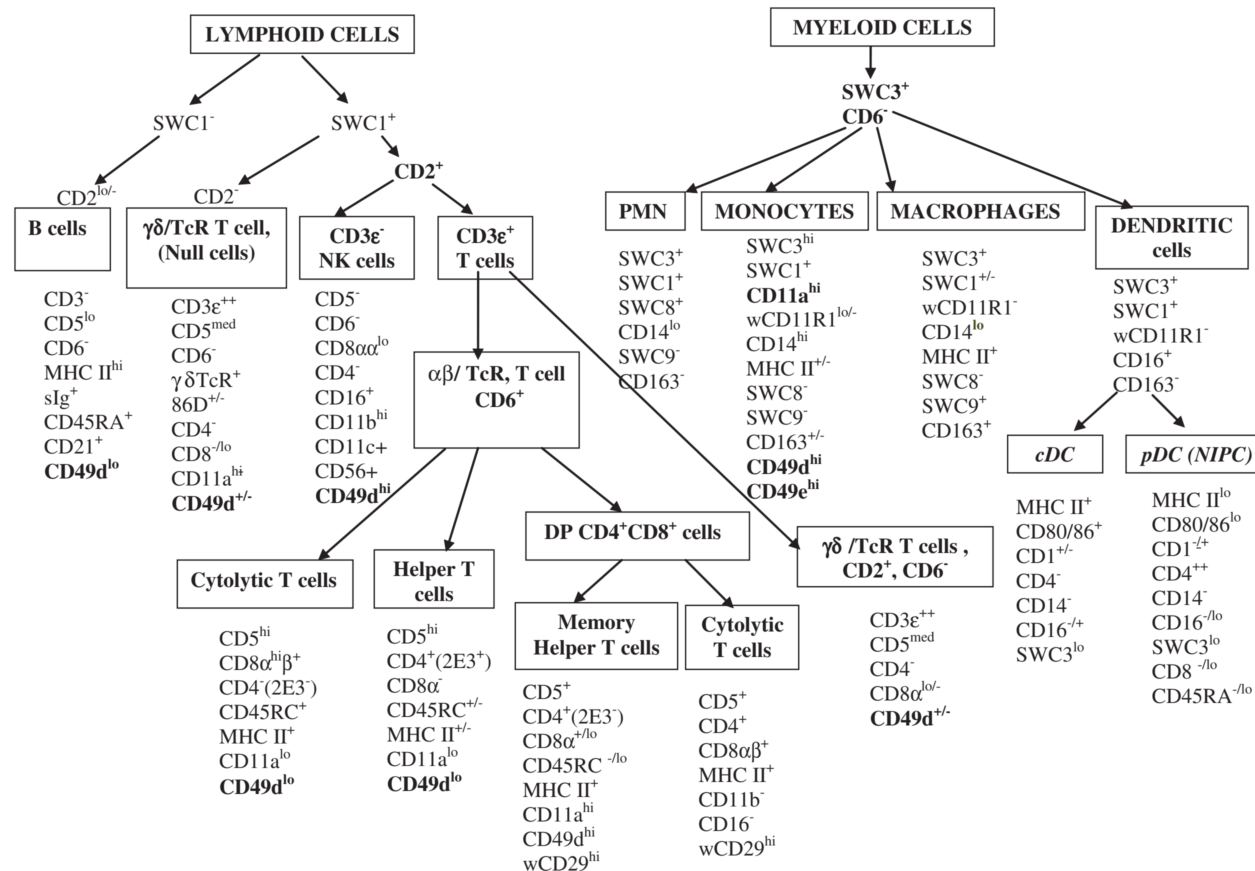

Figure 1. Phenotype of blood swine leukocytes, macrophages and dendritic cells as ascertained by discriminatory CD. Discriminatory CD are indicated as bold letters. (+) CD/SWC expressed; (−) CD/SWC not expressed; (+/−) variable expression; (hi) high density expression; (lo) low density expression. Note that: (i) most γδ-T cells are $CD2^-$ (and correspond to the Null cells according to the old definition) but some are $CD2^+$γδ-T cells; (ii) αβ-T cell, $CD4^-CD8^{lo}$ cell subset is not represented per se but among the $CD2^+$γδ-T cells; (iii) among DP (double positive) $CD4^+CD8^+$, cytolytic T cell [64].

4. CONCLUSION

Even with the limited resources available in porcine immunology, the various mAb identifying porcine CD on cells of the immune system listed in Table A dress the differences in binding distribution with respect to other species including humans and mice, and demonstrate the impact of new SWC marker on cell lineage and on function characterisations (Fig. 1). The various swine CD workshops have facilitated the development of collaborative interactions between immunologists, enabling the designation of new mAb as well as cross-reacting mAb to particular CD and SWC. This effort continues to improve porcine biomedical research, in particular a better knowledge of the porcine immune system. Furthermore, during the recent HLDA8 many more cross-reactive mAb have been identified as being directed against a wide range of CD antigens of different species including CD1b, CD9, CD14, CD18, CD41, CD44, CD47, CD59, CD68, CD80, CD86, CD91, CD95, CD163, CD172a, CD247 [158, 171]. On the contrary, certain commercially available human polyclonal antisera may also represent useful tools [195]. This will improve our understanding of porcine immunology.

Acknowledgements. We thank Arthur Summerfield for valuable criticisms.

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