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ANNUAL REVIEWS

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Importance of the Major Histocompatibility Complex (Swine Leukocyte Antigen) in Swine Health and Biomedical Research

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Keywords

Sus scrofa, swine leukocyte antigen, SLA polymorphism, allogeneic, xenogeneic, vaccine responses

Abstract

In pigs, the major histocompatibility complex (MHC), or swine leukocyte antigen (SLA) complex, maps to *Sus scrofa* chromosome 7. It consists of three regions, the class I and class III regions mapping to 7p1.1 and the class II region mapping to 7q1.1. The swine MHC is divided by the centromere, which is unique among mammals studied to date. The SLA complex

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spans between 2.4 and 2.7 Mb, depending on haplotype, and encodes approximately 150 loci, with at least 120 genes predicted to be functional. Here we update the whole SLA complex based on the Sscrofa11.1 build and annotate the organization for all recognized SLA genes and their allelic sequences. We present SLA nomenclature and typing methods and discuss the expression of SLA proteins, as well as their role in antigen presentation and immune, disease, and vaccine responses. Finally, we explore the role of SLA genes in transplantation and xenotransplantation and their importance in swine biomedical models.

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1. OVERVIEW

Pigs are a major source of animal protein worldwide. To ensure swine health and food safety, it is essential to prevent infectious diseases via biosecurity and use of well-designed vaccines and therapeutics. Advances in genomics have informed our understanding of the complexity of the immune system and the genes that influence disease and vaccine responses, with the most important being the swine major histocompatibility complex (MHC) genes, the swine leukocyte antigens (SLA). Gene sequencing data have advanced efforts to define the polymorphisms of class I and class II SLA genes, setting the foundation for probing the role of these genes in swine health and disease.

Owing to their physiological similarity to humans, pigs are an important biomedical model, particularly in the areas of heart and gut function, toxicology, and drug screening. SLA-defined pigs have served as a significant transplantation model and, with gene editing, a potential source of xeno-organs.

This review summarizes the current knowledge of the genomics of the SLA region, dissects the polymorphisms of each locus, and discusses the methods now used to more effectively identify these alleles and their assembly into haplotypes. We discuss the role of SLA gene regulation in swine disease and vaccine responses. Finally, we explore the importance of SLA genes in allogeneic and xenogeneic transplantation and their importance in swine biomedical models.

2. ORGANIZATION OF THE SLA COMPLEX

2.1. SLA Complex Genome Map

The SLA complex corresponds to a genomic region of 2.40 (haplotype Hp-1.1) to 2.66 Mb (genome assembly Sscrofa11.1) that maps to chromosome 7 (SSC7) and spans the centromere (1) (**Figure 1*a***; **Supplemental Figure 1**). It consists of three regions, the class I and class III regions mapping to 7p1.1 and the class II region mapping to 7q1.1 (**Figure 1*a***). The split of the MHC complex by the centromere in swine is unique among mammals studied to date. By convention and in agreement with reports on other vertebrate species, the class I and class II regions include the MHC class I and II gene series, respectively, together with many non-MHC genes with various functions. The class III region, located between the class I and II regions, does not contain MHC genes but comprises key immunity-related genes. Thus, as shown in **Figure 1*a*** (more detail in **Supplemental Figure 2**), the SLA complex includes clusters of MHC gene series embedded among non-MHC genes that were well conserved during evolution across mammals and are referred to as anchor genes (2). The MHC gene clusters correspond to the hot spots of functional polymorphisms from which SLA complex haplotypes in class Ia and II are defined (**Figure 1*b***).

MHC: major histocompatibility complex

SLA: swine leukocyte antigen

Hp: haplotype

SSC: *Sus scrofa* chromosome

Sequencing and mapping of the entire SLA complex of the very common SLA haplotype Hp-1.1 (H01) was completed in 2006, starting with the ubiquitin D gene (*UBD*) in the extended class I

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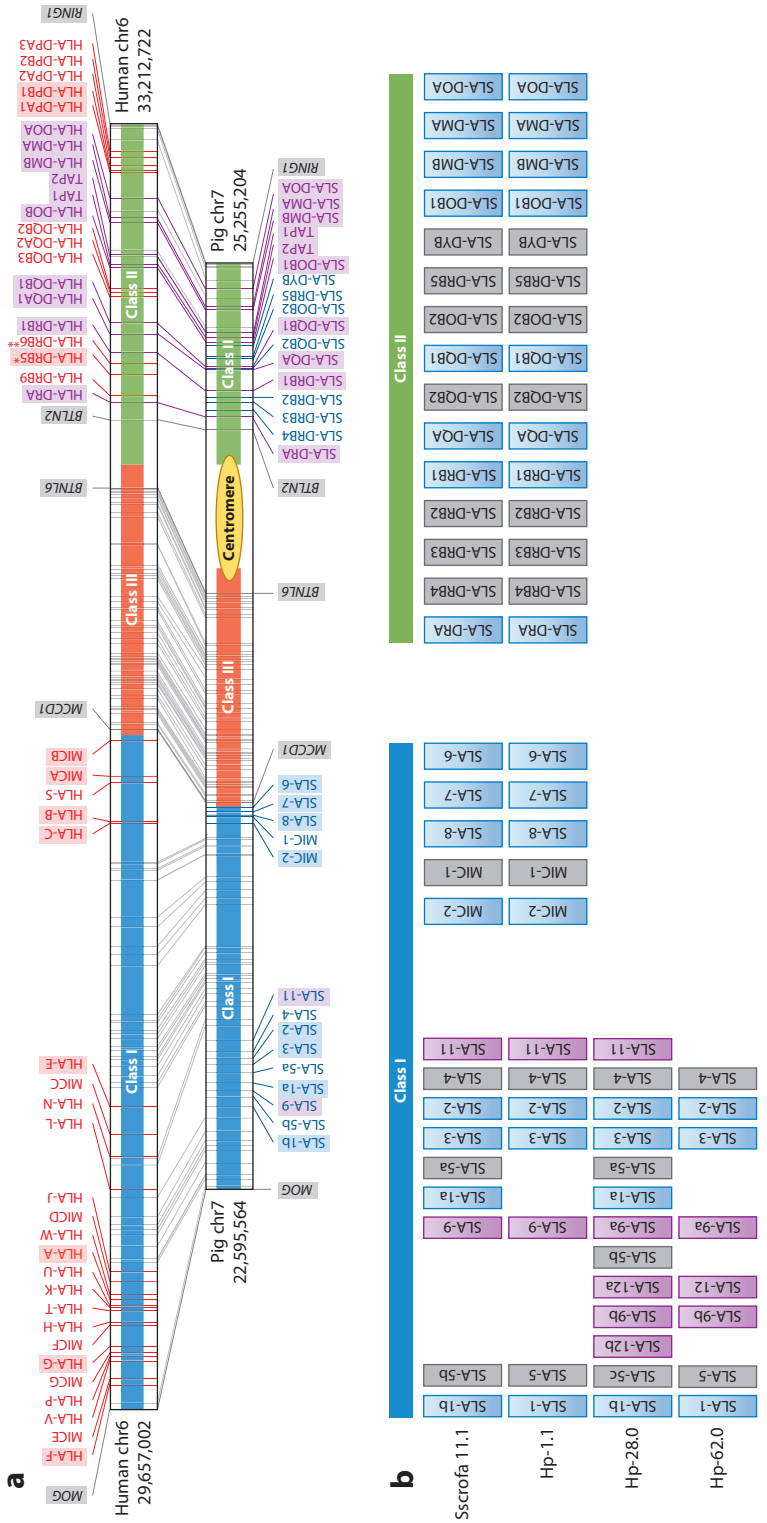


Figure 1

Genomic organization of the swine leukocyte antigen (SLA) complex. (*a*) Comparative maps between human leukocyte antigen (HLA) and SLA complex on human chromosome 6 and swine chromosome 7, respectively. The two genomic regions are delimited by *MOG* upstream from the class I region and *RING1* downstream to the class II region. The nucleotide positions refer to the human genome assembly GRCh38.p12 (Ensembl Release 96) and to the swine genome assembly Sscrofa11.1 (Ensembl Release 96). The anchor genes that delimit the three regions referred to as class I, class III, and class II are gray-shadowed. These regions span, respectively, 1.06 Mb, 0.67 Mb, and 0.46 Mb of the 2.66 Mb of the SLA region (centromeric region accounts for 0.47 Mb). Orthologies between human and pig genes are indicated by gray lines (anchor genes) and purple lines (MHC genes) (full gene list available in **Supplemental Figure 2**). The class I and II HLA genes are indicated on top of the figure, and the SLA class I and II genes at the bottom of the figure. The functional MHC genes predicted to encode proteins are highlighted. No orthologies are identified between the HLA and SLA class I genes that are organized in three clusters in human and two clusters in swine. In the class II region, the orthologous functional MHC class II genes are in purple, and the other loci correspond to species-specific genes and pseudogenes. In common human haplotypes, DRB3, DRB4, and DRB8(ψ) are found instead of DRB5 (denoted by the * symbol) and DRB6(ψ), DRB2(ψ), and DRB7(ψ) are found instead of DRB6 (denoted by the ** symbol). (*b*) Variability in the number of SLA loci by haplotype with only class I genes noted for HP-28.0 and Hp-62.0. The functional genes predicted to encode proteins are in blue, and the pseudogenes in gray. Highlighted in purple are SLA-9, SLA-11, and SLA-12 as putative genes that have been shown to express at the transcript level (8; M. Charles, B. Rosen, C.K. Tuggle, D. Ciobanu, A. Ando, S. Hammer, J.K. Lunney & Rogel-Gaillard, manuscript in preparation), with SLA-9 annotated to be a pseudogene (1), whereas SLA-11 and SLA-12 are annotated to bear the potential of protein coding.

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region and ending with the Ring finger protein 1 (*RING1*) gene in the extended class II region (1). To date, 151 loci have been manually annotated, and at least 121 genes are predicted to be functional in swine genome build 11.1 (**Supplemental Figure 2**). These annotations have confirmed that the SLA complex is one of the most gene-dense regions in the swine genome. The refined swine genome assembly Sscrofa11.1 has provided a second sequence of the entire SLA complex, spanning 2.66 Mb from the *MOG* gene upstream from the class I region to *RING1*. The whole region is generally well assembled in the Sscrofa11.1 build and confirmed the order of the anchor non-MHC genes between human leukocyte antigens (HLA) and SLA (**Figure 1*a***). However, because the reference Duroc female genome assembled in Sscrofa11.1 is not homozygous at the SLA, the annotations of the class I SLA genes based on automated annotation pipelines were incomplete and could be misleading. Manual curation was necessary, particularly for assembling the cluster of highly polymorphic classical class I genes within a 150-kb region. The annotation of the SLA complex in Scrofa11.1 has been updated, and the individual loci are listed in **Supplemental Figure 2** (M. Charles, B. Rosen, C.K. Tuggle, D. Ciobanu, A. Ando, S. Hammer, J.K. Lunney & C. Rogel-Gaillard, manuscript in preparation).

HLA: human leukocyte antigen

2.2. The SLA Class I Region

The class I region (from the *MOG* gene to the *SLA-6* gene) of the Hp-1.1 and Sscrofa11.1 assemblies spans 1.01 Mb and 1.06 Mb, respectively, in which 55 and 54 loci have been annotated (**Figure 1*a***). The MHC class I gene series is separated into two groups, referred to as classical class I (class Ia) and nonclassical class I (class Ib) genes. The class Ia genes are highly polymorphic, whereas the class Ib genes present limited polymorphisms. The class Ib genes have splice variants that may lead to various protein isoforms (3). The SLA class I region also contains the MHC class I chain-related (MIC) genes. These three gene sets are organized in two genomic clusters in pigs, whereas they are organized in three clusters in humans (**Figure 1*a***). Indeed, the genomic organization of the SLA class I gene series is quite different from that of the HLA class I genes, despite a well-conserved overall organization of the whole class I region between human and swine (**Figure 1*a***). Phylogenetic analyses showed that the SLA class I genes displayed much more sequence homology to each other than to the HLA class I genes. As such, the SLA class I genes were designated with numbers to avoid misinterpretation that any of these loci are direct orthologs of the HLA genes (4).

There are three functional class Ia genes, *SLA-1*, *-2*, and *-3*, and three class Ib genes, *SLA-6*, -7, and *-8*. The genes *SLA-4*, *-5*, *-9*, and *-11* have traditionally been annotated as pseudogenes owing to lack of intact coding regions; however, transcription of *SLA-9* and *SLA-11* has been reported (5, 6). Recent data on alignment between genomic DNA and transcript sequencing results have shown that *SLA-11* is predicted to encode a functional protein (GenBank Accession No. AK233371, AK395354, AK235068). Further studies are required to characterize the expression and function of this putative protein-coding gene. Only the *MIC-2* gene is predicted to be functional, whereas the *MIC-1* gene appears to be a pseudogene.

As in the bovine leukocyte antigen complex (7), the number of MHC genes may differ according to haplotypes; differences between the Hp-1.1 haplotype and others have been reported (**Figure 1*b***). An additional SLA-Ia gene, referred to as *SLA-12*, was found with either a single copy (Hp-62.0) or two copies (Hp-28.0). Two copies of class Ib *SLA-9* were detected for Hp-28.0 and Hp-62.0 (8), and two copies of *SLA-1* and *SLA-5* were found for Hp-28.0 and in the Sscrofa11.1 assembly. Further analyses are required to assess whether the duplicate copies of SLA-1 present in the Sscrofa11.1 assembly and other haplotypes are functional.

The three functional SLA class Ia genes (*SLA-1*, *-2*, and *-3*) have eight exons (**Supplemental Figure 3**). After removal of the peptide leader (exon 1), they code for 45-kDa glycoproteins

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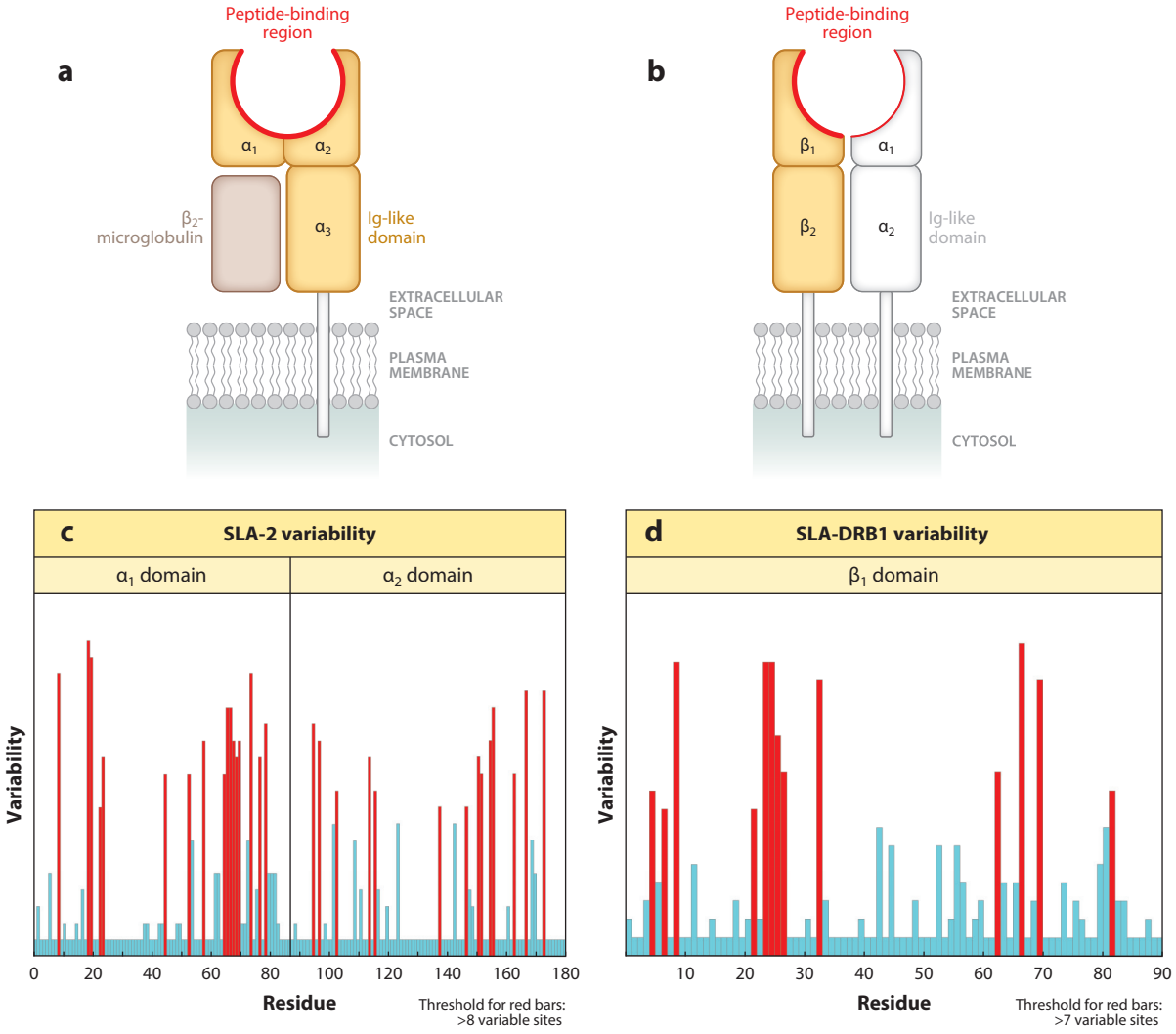


Figure 2

Model structure of class I and II proteins and exon polymorphisms. (*a*) Protein structure of swine leukocyte antigen (SLA) class I (SLA-2); (*b*) protein structure of SLA class II (SLA-DRB1); (*c*) allelic variation within SLA class I molecules; and (*d*) allelic variation within class II molecules. Allelic variation occurs at specific sites within SLA molecules (highlighted in red). Variability plots of the amino acid sequences of SLA molecules show that the variation arising from genetic polymorphism is restricted to the amino-terminal domains (α1 and α2 domains of SLA class I molecules and mainly β1 domain of SLA class II molecules). For the SLA class I molecule, the variability of 20 SLA-2 allele sequences (one representative sequence for each allele group) is shown. For the SLA class II molecule, the variability of 17 SLA-DRB1 allele sequences (one representative sequence for each allele group) is shown.

(**Figure 2*a***) consisting of three extracellular domains, α1 (exon2), α2 (exon 3), and α3 (exon 4); a transmembrane domain (exon 5); and a cytoplasmic tail (exons 6 to 8). The extracellular domains are noncovalently bound to 12-kDa β2-microglobulin that has been mapped to SSC1 (9). The α1 and α2 domains form the peptide-binding groove, and the α3 domain is a binding site for the CD8 co-receptor on porcine T cells (**Figure 2*a***). The extreme polymorphism of SLA class Ia genes resides mainly in exons 2 and 3; **Figure 2*c*** illustrates the degree of polymorphism of each nucleotide residue in the α1 and α2 domains of class Ia genes.

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The functional SLA-Ib genes (*SLA-6*, -7, and -*8*) were reported to have full-length transcripts with seven or eight exons (**Supplemental Figure 3**). Additional work is needed to affirm whether *SLA-11* is a functional class Ib gene. *SLA-8* was found to be the most transcribed SLA-Ib gene, followed by the *SLA*-7 and *SLA-6* genes (10). *SLA*-7 has full-length transcripts with either seven (11) or eight exons and splice variants that may lead to isoforms with a shorter exon 4 (α3 domain) (3). *SLA-6* alternative transcripts may encode isoforms lacking exon 3 (ACC GU322912) or exons 3 and 6 (ACC GU322913). These alternative splicing events seem to be specific to class Ib genes, as reported in humans.

2.3. The SLA Class II Region

The class II region (*BTLN2* to *RING1*) of the Hp-1.1 and Sscrofa11.1 assemblies spans 0.46 Mb, in which 28 and 26 loci have been annotated, respectively (**Figure 1*a***). The SLA class II region is more condensed than the class I region and mainly contains genes relating to peptide presentation of the adaptive immune system. This region includes the loci for both protein chains of each of the expressed SLA class II antigens (**Figure 2*b***), i.e., the α- and β-chain genes for SLA-DR, -DQ, -DM, and -DO proteins. The gene structures are detailed in **Supplemental Figure 3**. The polymorphism of class II proteins is limited for the α-chain and most prominent in the β-chain genes forming the peptide-binding groove (**Figure 2*d***). In contrast to the HLA system, there are no loci encoding DP proteins. There are several class II β-chain pseudogenes (*SLA-DRB2*, *-DRB3*, *-DRB4*, *-DRB5*, *-DQB2*, *-DOB2*, and *-DYB*) in the SLA class II region (**Figure 1*a***).

The SLA class II region includes genes involved in antigen presentation, transporter-associated with antigen processing genes (*TAP1*, *TAP2*), and proteasomes (*PSMB8*, *PSMB9*) (**Supplemental Figure 2**). The overall genomic organization of the SLA and HLA class II regions is well conserved, except that the SLA class II region is much shorter. Phylogenetic analyses showed that the SLA class II genes had strong sequence homology with their HLA counterparts (12); therefore, the functional SLA class II genes were designated after their human counterparts to reflect this orthology (**Figure 1*a***).

2.4. The SLA Class III Region

The class III region (*MCCD1* to *BTNL6*) of the Hp-1.1 and Sscrofa11.1 assemblies spans 0.67 Mb and 0.68 Mb, respectively, in which 61 and 59 loci have been annotated (**Figure 1**). This region includes genes important for immune defense mechanisms and inflammation, such as the tumor necrosis factor gene families (*TNF*, *LTA*, and *LTB*), the steroid cytochrome P450 21-hydroxylase (*CYP21A2*) enzyme, components of the complement cascade (*C2*, *C4A*, and *CFB*), and allograft inflammatory factor 1 (*AIF1*). This region also includes genes for heat shock proteins (*HSP1A*, *HSP1B*, and *HSP1L*); six distinct *BAT* (orthologous to HLA-B associated transcript) genes; and genes with complex functions, such as tenascin XB (*TNXB*), and Notch homolog 4 (*NOTCH4*). Among the 61 loci annotated in Hp-1.1, the main divergence occurs in a RCCX module consisting of four genes (*C4B*, *CYP21A2*, *TNXA*, and *STK19P*), possibly unique in SLA but known to vary depending upon haplotype in humans (13, 14).

3. SLA NOMENCLATURE SYSTEM

3.1. IPD-MHC SLA Sequence Database

The SLA system is among the most well-characterized MHC systems in nonhuman animal species. A systematic nomenclature for the genes, alleles, and haplotypes of the swine MHC is critical to the research in swine genetic diversity, immunology, health, vaccinology, and organ and

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cell transplantation. The SLA Nomenclature Committee was formed in 2002 as a joint committee of the International Society for Animal Genetics and the Veterinary Immunology Committee of the International Union of Immunological Societies (15). The primary objectives of this committee are (*a*) to validate newly identified SLA sequences, according to the guidelines established for maintaining high-quality standards of the accepted sequences; (*b*) to assign appropriate nomenclatures for new alleles as they are validated; and (*c*) to serve as a curator of the Immuno Polymorphism Database (IPD)-MHC SLA sequence database (**https://www.ebi.ac.uk/ipd/mhc/group/SLA**), the repository for all recognized SLA genes and their allelic sequences and haplotypes (16–18). The IPD-MHC website has also added new sequence submission tools that allow continuous updating of new allele sequences.

SSP: sequence-specific primer

SBT: sequence-based typing

NGS: next-generation sequencing

The IPD-MHC website provides investigators with a centralized platform to access the most recent information in the field of SLA research, such as the nomenclature reports and lists of SLA genes, alleles, and haplotype assignments (4). It serves as a convenient site to submit both new and confirmatory allele sequences and their associated studies for consideration of allele name assignments. A major update to the IPD-MHC SLA website was completed in February 2018 (16).

3.2. The SLA Alleles

The underlying principle of the SLA nomenclature system is assignment of alleles at each locus into groups based on sequence similarity (identification of group-specific polymorphic sequence motifs) (4). The allelic group assignments correspond to the polymorphisms in the exon 2 and 3 sequences for class I alleles and exon 2 sequences for class II alleles (**Figure 2*c*,*d***), which encode the peptide-binding domains and interact directly with the immune cell receptors and are therefore considered to be functionally important (**Supplemental Figure 3**).

In 2016, the Committee decided to fully adopt the HLA Nomenclature System and redesignated each allele with an official number, with colons as field separators (e.g., SLA-1*01rh28 → SLA-1*01:03). Phylogeny will remain the primary approach for assigning *SLA-1*, *-2*, *-3*, *-DRA*, *-DRB1*, *-DQA*, and *-DQB1* alleles into allele groups with similar sequence motifs, whereas alleles of the other loci, including *SLA-4*, *-5*, *-6*, -7, *-8*, *-9*, *-11*, *-12*, *-DMA*, *-DMB*, *-DOA*, *-DOB1*, *-DOB2*, *-DQB2*, *-DRB2*, *-DRB3*, *-DRB4*, *-DRB5*, *-DYB*, *-MIC-1*, *-MIC-2*, *TAP1*, and *TAP2* are designated sequentially as they are discovered. Currently 266 class I, 227 class II, 2 SLA-related (*MIC-1*, *MIC-2*), and 2 non-SLA (*TAP1*, *TAP2*) alleles are officially designated.

Recent evidence has suggested certain loci in the SLA system, previously defined as pseudogenes (e.g., *SLA-9*, *-11*, *-DQB2*, *-DOB2*), may be expressed at the transcript level; e.g., *SLA-11* is considered a putative protein-coding gene. The Committee will consider reclassifying some of these loci as additional evidence accumulates. Continuous efforts to characterize SLA alleles and haplotypes and their diversity in various pig populations will further our understanding of the architecture and polymorphism of the SLA system and the role of SLA alleles in disease, vaccine, and transplant responses.

3.3. SLA Typing Methods

The SLA genotyping methods are summarized and compared in **Supplemental Table 1**; earlier serological and cellular typing methods have been replaced by more accurate molecular methods. They include polymerase chain reaction (PCR)-based sequence-specific primers (SSPs) (19–24), sequence-specific oligonucleotides using bead-based methodologies (25), and sequence-based typing (SBT) by traditional Sanger methods and/or next-generation sequencing (NGS) (26–28) or a

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SNP: single-nucleotide polymorphism

combination of SBT and PCR-SSP (22, 29–33) (**Supplemental Table 1**). SLA typing by PCR is fast with reasonable costs and can be designed for high throughput; however, results are limited to alleles with previously known DNA sequences for which SSPs or probes have been designed. Although SBT is the most direct and accurate approach, it usually requires cloning of the alleles to resolve heterozygous sequences, which makes it time consuming and cost prohibitive; hence, this methodology is not typically adopted for large-scale studies, e.g., in outbred pig herds. Based on our collective experience, SBT is most suitable for characterizing the SLA types of parental or founder breeding animals of pedigreed pig populations (29, 32).

Alternatively, single-nucleotide polymorphism (SNP)-based genotypes from a high-density SNP chip were tested for their potential to predict haplotypes within the MHC region of the swine genome. By genotyping 920 pigs with the Illumina SNP60 BeadChip, SNP haplotypes corresponding uniquely to a MHC haplotype defined by a PCR-based method were found (34). However, these methods often detect more than one pair of SLA alleles because of chromosomal phase (*cis*/*trans*) ambiguity (35). The combination of PCR amplification of targeted SLA genomic regions with NGS platforms is expected to produce genotyping results that detect new and null alleles efficiently without phase ambiguity and imprecise results (36–39). The latest SLA typing approaches in human and nonmodel vertebrate species combine long-range PCR with high-throughput NGS and Oxford Nanopore MinION sequencing technologies. This efficiently achieves both the genotyping and assembly of complex genomic regions in multiple individuals in the absence of a reference sequence and allows haplotype phasing (40–42).

3.4. Polymorphism and Recombination Within the SLA Class I and Class II Regions

Numbers of confirmed SLA class I and class II alleles and proteins are summarized and compared in **Table 1**. To date, 228 SLA class Ia alleles and 18 class Ib alleles have been identified; the highest polymorphism was found for the *SLA-1*, *-2*, and *-3* genes (4; C.S. Ho, A. Ando, S.E. Hammer, J.H. Lee, C. Rogel-Gaillard, L.B. Schook & J.K. Lunney, manuscript in preparation) (**Table 1**). As expected, exons 2 and 3 of the coding regions, which form the class I protein peptide-binding groove, harbor the extreme polymorphisms of the SLA class I genes (**Figure 2*a*,*c***).

To date, 277 SLA class II alleles have been identified (156 β-chain and 49 α-chain alleles), with polymorphisms mainly located in exon 2 of the coding sequences (4; C.S. Ho, A. Ando, S.E. Hammer, J.H. Lee, C. Rogel-Gaillard, L.B. Schook & J.K. Lunney, manuscript in preparation) (**Table 1**). Similar to HLA, the porcine *SLA-DRB1* and *-DQB1* loci display a very high degree of polymorphism (**Figure 2*b*,*d***). As with *HLA-DRA*, the *SLA-DRA* locus shows very limited polymorphism, with 14 alleles representing three allele groups, despite the fact that it also encodes part of the domain for binding antigenic peptides (**Figure 2*b***).

For several SLA alleles for both class I and II, sequence length variations have been described (C.S. Ho, A. Ando, S.E. Hammer, J.H. Lee, C. Rogel-Gaillard, L.B. Schook & J.K. Lunney JK, manuscript in preparation). Although the functional role of these sequence length variations is still unclear, they most likely would affect the structural integrity of the proteins and thus modify their surface expression.

Owing to strong linkage disequilibrium, it is sometimes more appropriate and convenient for researchers to communicate and present findings in terms of haplotypes (a specific combination of alleles of genes on the same chromosome) rather than individual allele specificities (4). The SLA Nomenclature Committee has established a nomenclature system for SLA class I and II haplotypes based on high-resolution DNA sequencing. These high-resolution SLA haplotypes are noted with the prefix Hp-, followed by a number for the class I haplotype, separated by a

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Table 1 Numbers of confirmed swine leukocyte antigen (SLA) alleles and proteins

Category	Locus	Allele	Protein
SLA class I (classical)	SLA-1	90	88
	SLA-2	97	94
	SLA-3	41	39
SLA class I (nonclassical)	SLA-6	10	10
	SLA-7	3	3
	SLA-8	5	5
SLA class I (unclassified)	SLA-12	6	6
SLA class I (pseudogene)	SLA-4	3	0
	SLA-5	4	0
	SLA-9	5	0
	SLA-11	2	0
Total class I alleles		**266**	**245**
SLA class II	DRA	14	6
	DRB1	99	92
	DQA	26	24
	DQB1	53	48
	DMA	7	5
	DMB	1	1
	DOA	2	2
	DOB1	3	3
SLA class II (pseudogene)	DRB2	12	0
	DRB3	5	0
	DRB4	1	0
	DRB5	1	0
	DQB2	1	0
	DOB2	1	0
	DYB	1	0
Total class II alleles		**227**	**181**
Other non-SLA genes	MIC-1	1	0
	MIC-2	1	1
	TAP1	1	1
	TAP2	1	1
Total SLA-related alleles		**4**	**3**

period, then a number for the class II haplotype (e.g., Hp-1.1). The number 0 is assigned if there is no information on the associated class I or class II haplotype (e.g., Hp-1.0). Further, a lowercase letter is added to the haplotype numbers to indicate that they are closely related (e.g., Hp-1a.0 versus Hp-1b.0). As of July 2019, there are 73 independent class I (*SLA-1*, *-2*, *-3*) and 51 class II (*-DRB1*, *-DQB1*) assigned haplotypes.

The overall recombination frequencies were reported to be 0.05% within the SLA class I region (reviewed in 43). In a herd of more than 400 Sinclair/Hanford crossbred miniature pigs established for melanoma research, 3 animals with recombination between the SLA class I and class II region, and 3 with recombination within the class I region, were described, corresponding

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to crossover frequencies of 0.56% and 0.39%, respectively (29). Recombination within the SLA class II region has not yet been reported. In general, recombination is believed to be repressed in the genomic regions that are in close proximity to the centromeres, which include the SLA complex (1, 44). With the SLA complex spanning the centromere, the recombination rates reported thus far have nevertheless been comparable to the MHC of other species, e.g. HLA, that are not at, or near, the centromere (45).

IFN: interferon

APC: antigen-presenting cell

DC: dendritic cell

PAM: porcine alveolar macrophage

IL: interleukin

mo: monocyte

4. SLA EXPRESSION AND REGULATION OF SWINE IMMUNE AND PATHOGEN RESPONSES

4.1. SLA Expression on Immune Cell Subsets

Expression of SLA antigens was reviewed earlier (43), so this report summarizes critical basic information and focuses on selected new data. As with HLA class I antigens, the class Ia proteins are constitutively expressed on the surface of virtually all nucleated cells. They present peptides to $CD8^+$ cytotoxic T cells and interact with natural killer (NK) cells to prevent NK-mediated cytotoxicity (46). Kita et al. (36) used high-resolution, massively parallel pyrosequencing to estimate gene-level expression of SLA class I genes, affirming the relative class Ia gene expression as *SLA-2* > *SLA-1* > *SLA-3* in white blood cells. Using high-density tiling arrays encompassing the whole SLA complex, Gao et al. (5) affirmed alterations in expression of numerous SLA class I and II genes following activation of B and T cell proliferation.

It is generally believed that the three functional SLA class Ib genes, *SLA-6*, *-7*, and *-8*, play specialized roles similar to the nonclassical HLA genes (*HLA-E*, *-F*, *-G*). The three genes were shown to be expressed in a less-restricted manner than the HLA-Ib genes (11) but predominantly transcribed in the lymphoid organs, the lung, and the digestive tract, with each gene presenting tissue-specific expression (10). *SLA-8* is the most transcribed SLA-Ib gene, followed by the *SLA-7* and *SLA-6* genes (10). Transfection experiments have revealed that the promoters of *SLA-7* and *SLA-6* genes do not respond to interferon (IFN), suggesting distinct regulatory systems for pig MHC class Ia and Ib genes (47). It is not yet known whether SLA Ib proteins have peptide presentation functions.

SLA class II antigens function mainly in presenting exogenous peptides to $CD4^+$ helper T cells (48–50). Swine B cells and macrophages express both SLA-DR and -DQ antigens. Unexpectedly, swine T cell subsets express SLA-DR and -DQ antigens, with preferential expression of class II antigens on $CD8^+$ T cell subsets ($CD4^-CD8^+$ and $CD4^+CD8^+$ T cells) (48–50). The importance/relevance of this unusual class II T-cell expression has yet to be fully explained. A minority of the circulating porcine $CD2^+CD8^+$ γδ T cells coexpress MHC class II (51). In fact, a subset of circulating γδ T cells displays a phenotype similar to professional antigen-presenting cells (APCs) and is able to present soluble antigen to $CD4^+$ T cells in a direct cell–cell interaction via SLA class II (52) (see sidebar titled Genomic Regulation of SLA Genes Including Noncoding RNAs and Regulatory Variants).

Normal pig endothelial cells express SLA class I and upregulate class II in response to IFNγ (53–55). Induced pluripotent stem cells (iPSCs) express only low levels of SLA class I antigens and barely express SLA class II antigens; even with IFNγ treatment, expression of SLA class I but not SLA class II increased (56). Porcine intestinal and renal vascular endothelia, as well as epidermal skin dendritic cells (DCs) and Langerhans cells, are SLA class II^+ (57–59). SLA-DQ expression is found at the maternal–fetal interface (60).

Porcine alveolar macrophages (PAMs) are SLA-DR^+, but poor APC with low secretion of interleukin-1β (IL-1β), when compared with peripheral blood monocytes (mos); they may, though, be important immunoregulatory cells with cytokine suppressor activity (61). Summerfield et al.

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GENOMIC REGULATION OF SLA GENES INCLUDING NONCODING RNAS AND REGULATORY VARIANTS

MicroRNAs are known to regulate posttranscriptionally the expression of several protein-coding genes and play important roles in fine-tuning immune mechanisms and disease responses. As demonstrated for different porcine tissues and several SLA genes (e.g., *SLA-1*, *SLA-6*, *SLA-DQA*, and *SLA-DQB1*), certain variants of the 3′-UTR (untranslated region) microRNA target sites are linked to antigen processing and presentation functions. This is now known to be associated with disease traits as reported for altered microRNA binding to major histocompatibility complex (MHC) genes in humans (149). Interestingly, a whole blood transcriptome study detected numerous distant and local regulatory relationships within the swine leukocyte antigen (SLA) complex, revealing allele-specific expression for most SLA class I and II genes (6). In *Salmonella typhimurium*–infected porcine mesenteric lymph node cells, four microRNAs were identified as potential regulators of MHC-class I genes and suggested to be associated with the induction of MHC-I and MHC-II antigen presentation pathways (150). In mock- versus porcine reproductive and respiratory syndrome virus (PRRSV)-infected pig endometrial epithelial cells, differentially expressed microRNAs targeting *SLA-DQB1* were found. These genes are known to participate in the apoptosis signal, an indication of increased susceptibility to PRRSV infection (151). Thus, noncoding RNAs and regulatory variants are critical regulators of pig antigen presentation and immune response networks.

(62) delineated porcine blood APC subsets: the blood mos, which are SLA class II^+CD14^+, and the blood DC, which are SLA class II^+ but $CD4^-CD14^-$. Plasmacytoid DCs (pDCs) are strong type I IFN secretors after virus stimulation and are typically $CD4^{high}$MHC II^{low}. Flow cytometry demonstrated that both the cDC1 and cDC2 subsets expressed very high levels of SLA-DQ (63) (**Figure 3*a***). The majority of mos were SLA-DQ^+, whereas pDCs displayed a more variable expression profile. The mRNA sequencing data confirmed this very high expression of many SLA class II genes by the cDC1 and cDC2 subsets, with an intermediate expression in mos and the lowest expression in pDCs and mo-derived macrophages (63, 64) (**Figure 3*b***).

4.2. T-Cell Antigen Epitopes Bound by SLA Molecules

The Saalmüller lab performed initial molecular analyses of T-cell antigen epitopes bound by SLA molecules using foot-and-mouth disease virus (FMDV) synthetic pentadecapeptides. Unfortunately, no common epitope was found, but they predicted that an overlapping peptide may prove useful for FMD vaccine design (65). Later work has focused on swine influenza A virus (SwIAV) responses (66). With the immuno-informatics tool PigMatrix, Gutiérrez et al. (67) identified several epitopes from representative US SwIAV strains binding SLA class I and II antigens and used its predictions to distinguish nonimmunogenic from immunogenic peptides and to identify promiscuous class II epitopes. Holzer et al. (68) summarized T- and B-cell responses to flu infection and identified SLA alleles and the exact SwIAV epitopes they recognized. Franzoni et al. (69) used a peptide library spanning the classical swine fever virus (CSFV) proteome to identify conserved CSFV T-cell antigens and the corresponding antigenic regions/epitopes and assess the restricting MHC class I haplotypes found on CSFV-specific T cells.

Modulation of SLA antigen expression during viral disease responses is complex, dependent on tissue and time post infection [as previously reviewed (43)]. Transcriptomic approaches are revealing important details of host–pathogen interactions on SLA class I and II allele expression, along with relevant immune regulators. Susceptibility of DC subsets varies with different African swine fever virus (ASFV) strains; for immature mo-derived DC (moDC) after maturation with

FMDV: foot-and-mouth disease virus

SwIAV: swine influenza A virus

CSFV: classical swine fever virus

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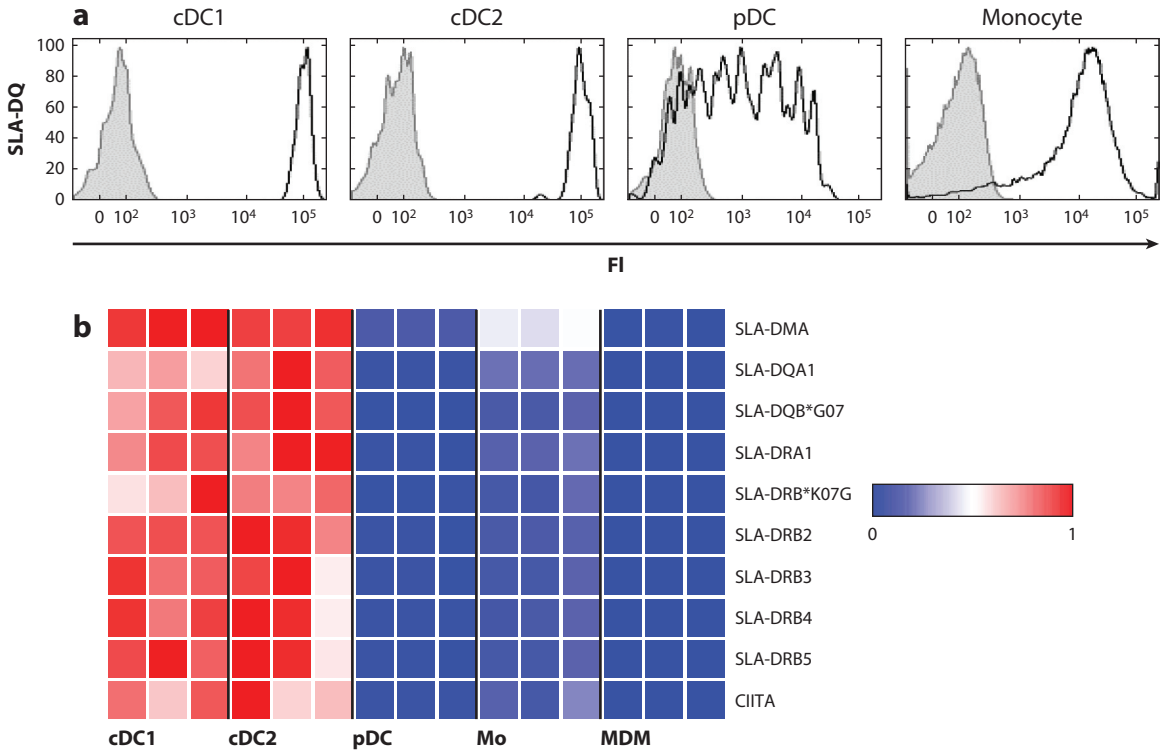


Figure 3

Expression of swine leukocyte antigen (SLA) class II by porcine blood dendritic cell (DC) subsets and monocytes. (*a*) Cell surface expression of MHC class II (SLA-DQ) by porcine blood DC subsets and monocytes was assessed by multicolor flow cytometry. The Fluorescence Minus One Control fluorescence intensity (histograms in gray) was used as a negative control, and the corresponding staining is shown in open bold histograms. Data shown were obtained from one pig and are representative of three independent experiments. (*b*) Expression of major histocompatibility complex (MHC) class II–related genes determined from RNA-seq data and displayed as a heat map. For each gene, the heat map ranges from the lowest number of reads (*blue*) to the highest number of reads (*red*). For each class II gene, the results from three different pigs are shown. Abbreviations: MDM, monocyte-derived macrophage; Mo, monocyte. Figure adapted with permission from Auray et al. (63).

IFN-α, there was increased susceptibility to infection with ASFV virulent strains but reduced susceptibility, and downregulation of SLA-I, with low-virulent strains (70). Van Chanh Le et al. (71) have analyzed peptide-SLA binding by transfecting primary PAMs with both hTERT and SV40LT to establish immortalized PAM cell lines with different SLA class II haplotypes.

Mokhtar et al. (72, 73) hypothesized that conserved porcine reproductive and respiratory syndrome virus (PRRSV) antigens would be prime candidates for the development of a novel PRRS vaccine and screened cells from SLA typed pigs to prove reactivity. Burgara-Estrella et al. (74) used bioinformatic predictions to screen for potentially relevant T-cell epitopes. Similar approaches were used to identify porcine endogenous retrovirus–derived peptides presented on porcine and human MHC class I molecules to test their role in xenograft rejection (75).

PRRSV: porcine reproductive and respiratory syndrome virus

4.3. Molecular Analyses of SLA Class I Genes and Tetramers

In China, several groups have cloned and expressed single SLA class I proteins and used X-ray crystallography to evaluate cytotoxic T-cell epitopes for PRRS (76). For H1N1 flu peptides, a single

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Arg (156) in SLA-1*0401 may provide a unique binding groove (77). Further SLA class I structures have identified different SLA-1 and SLA-3 binding pockets (78). Analyses of SLA-2 proteins with Asia 1 and O serotype FMDV peptides are underway (79, 80). A modified in vitro refolding method indicated cross-reactivity between swine and human MHC I specificities for IAV peptides (81). All of these efforts will provide critical data for viral peptide selection and vaccine design.

MHC class I and II tetramers have become essential tools for identifying protective immune cells in response to vaccination and pathogen challenge. Pedersen et al. (82) used SLA class I tetramers to prove the specificity of the $CD8^+$ T cell response to Ad5-FMDV-T vaccine. Pedersen et al. (31) used cells from outbred SLA-1*0401 pigs to verify tetramer staining of porcine $CD4^-$ $CD8\alpha^{high}$ T cells with 4 SwIAV-derived peptides and tested the effects of sequence-substituted MHC ligands. Baratelli et al. (83) identified cross-reacting T-cell epitopes in structural and nonstructural proteins of swine and pandemic H1N1 influenza A virus strains in pigs. They used reverse vaccinology to identify cross-reacting MHC class I T-cell epitopes from two different SwIAV H1 lineages in pigs and showed that SLA-1*07:02 T-cell epitopes worked in heterologous SwIAV-infected pigs. Following viral infection, tetramer-specific T-cell populations were identified, suggesting that targeting cross-reactive T-cell epitopes could be used to improve vaccines against SwIAV in SLA-1*07:02-positive pigs. To date there are no reports of use of SLA class II tetramers.

Using the Babraham inbred pig model, Tungatt et al. (84) induced influenza-specific CD8 T cells in the respiratory tract after aerosol delivery of vaccine antigen or virus. Their team developed a tool set that included successful long-term in vitro pig T-cell cultures, which were used to identify immunodominant influenza-derived T-cell epitopes. They generated structures of two SLA class I molecules to define the primary epitope anchor points. Finally, they generated peptide-SLA tetramers to track influenza-specific T cells ex vivo in blood, lungs, and draining lymph nodes. Overall, they concluded that pigs are now an effective model for studying protective local cellular immunity against flu and other respiratory pathogens.

4.4. Vaccines and Disease Models

Alterations in swine vaccine and disease responses associated with SLA class I and/or class II genes or haplotypes have been reported for decades (reviewed in 43). With refinement in SLA typing methods, alleles at individual SLA loci have been identified. Imaeda et al. (85) verified associations between serum antibody titers to a swine erysipelas vaccine and reproductive and meat-production traits of SLA-defined Duroc pigs. Correlation of SLA haplotypes with serum-neutralizing antibody titers, T-cell activation, and protection were used to design and evaluate peptide vaccines against FMDV and to improve the humoral response against CSFV (86, 87; F. Sobrino, personal communication).

Cortey et al. (88) reported a lack of correlation between the length and titer of PRRS viremia in vaccinated pigs and the clustering of the sequences of CD163, four SLA class I, and two SLA class II allele groups. Hess et al. (89) revealed dynamic relationships between PRRS serum antibody at 42 days postinfection with 3-day weight gain, suggesting that animals that placed more emphasis on immune response early in infection reaped benefits of that later in infection by more effectively clearing the virus. Genome-wide association studies (GWAS) identified 3 SNPs in the SLA complex that explained 10–45% of the genetic variance associated with serum antibody but were not associated with viremia or weight gain. Walker et al. (90) used haplotype-substitution analysis to uncover potential DQB1 alleles associated with divergent effects. These studies reveal a possible biomarker for improved host response to PRRSV infection.

SLA-DR expression was correlated with reduced antigen-presentation capability and modified inflammatory/immunosuppressive cytokine expression of induced moDC from peripheral blood

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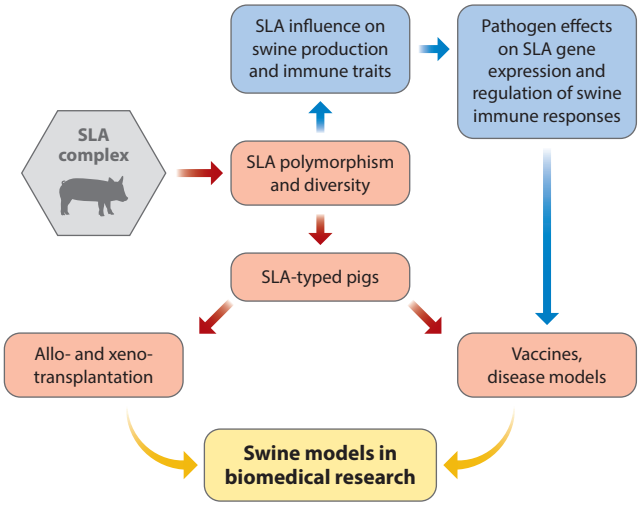


Figure 4

Swine leukocyte antigen (SLA) influence on breeding, disease, vaccine, and transplantation research. The SLA complex plays a key role for swine models in biomedical research. In pigs, production traits are influenced by SLA polymorphism and diversity. Pathogen effects on SLA gene expression drive the regulation of swine immune responses. SLA-typed pigs are used in vaccine design, disease models, and allogeneic and xenogeneic transplantation.

of piglets infected with porcine circovirus type 2 (91). Based on GWAS analyses, Walker et al. (92) verified that host genotype explained 64% of the phenotypic variation for overall PCV2 viral load, with two major quantitative trait loci (QTL), one identified on SSC7 near the SLA complex class II locus and, importantly, a missense mutation in the SYNGR2 on SSC12.

Overall, the influence of SLA encoded genes on immune and disease traits is broad. SLA alleles regulate antibody levels to defined proteins and vaccine antigens, effectiveness of cellular antibacterial and anti-viral reactions, and improved responses to foodborne pathogen challenges (**Figure 4**). As biosecurity improves, the range of pathogens to which pigs are exposed is altered, and consumers increasingly expect pork products free of antibiotics, the importance of disease-resistant breeding stock increases. Numerous groups have attempted to evaluate the relationship between SLA alleles and the level and function of circulating immune cells with average daily gain, live and carcass measurements, and feed conversion. These results could help guide breeders in selectively increasing the frequency of certain SLA alleles, i.e., those that are known to be associated with enhanced disease resistance or QTL effects, while maintaining SLA diversity.

4.5. Important Considerations for Evaluating SLA Associations

In decades past, associations between specific SLA haplotypes and production, immune, or reproductive traits were reported using serologically based SLA typing methods (reviewed in 43). Results typically indicated specific SLA haplotype associations with significant effects on each trait that differed among populations of pig breeds. However, it was difficult to define the corresponding SLA locus owing to limitations in serological reagents and technologies. This resulted in lack of ability to determine the exact locus and alleles within the proposed SLA haplotype responsible. Indeed, because the gene density of the SLA complex is very high, SLA alleles could only be markers in linkage disequilibrium with causal quantitative trait nucleotides. As outlined above, molecular-based SLA locus typing techniques now identify many SLA loci and their alleles

QTL: quantitative trait loci

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(4; C.S. Ho, A. Ando, S.E. Hammer, J.H. Lee, C. Rogel-Gaillard, L.B. Schook & J.K. Lunney, manuscript in preparation). These methods are now used for testing associations of growth, production, or reproductive performance and SLA alleles (85, 93–95). These new association data indicate that SLA alleles or haplotypes are useful genetic markers for improvement in pig breeding programs. However, for many of these studies, trait associations were evident with only one or a few SLA loci and/or found in limited pig populations and breeds. Indeed, multiple gene/trait associations have been mapped on several chromosomes, including SSC7 (see Animal QTLdb and CorrDB updates). QTL detection analyses for traits influencing growth and fatness mostly excluded SLA complex genes on SSC7 as important candidates due to limited number of animals or breeds analyzed (96, 97). To conduct a comprehensive assessment of involvement of the SLA complex on reproduction and production traits, future association analyses will need to be carried out using detailed SLA-DNA typing methods, including, if possible, NGS techniques and, importantly, testing in multiple breeds and broader pig populations.

HSC/BM: hematopoietic stem cell/bone marrow

5. SLA IN ALLOGENEIC TRANSPLANTATION

5.1. Rationale for Swine as a Model in Allotransplantation

Swine are anatomically and physiologically more similar to human than almost any other animal species. With the existence of significant amounts of background data, swine have been the preferred preclinical large animal model for transplantation, xenotransplantation, and regenerative medicine research (98). In human allogeneic transplantation [solid organ and hematopoietic stem cell/bone marrow (HSC/BM)], HLA matching has proven to be the most significant variable influencing graft function and longevity. Thus, the use of swine as transplantation models requires the understanding and control of SLA complexity. SLA-inbred/-defined pig lines have been established around the world, including the National Institutes of Health/Massachusetts General Hospital (NIH/MGH) miniature swine model (99, 100), Westran pigs (101), Yucatan miniature pigs (102), Korean Native pigs (21), Japanese Microminipigs (26), CLAWN miniature swine (103), Göttingen minipigs (104), MINI-LEWE pigs (105), and British Babraham pigs (33). These have been invaluable for studying the impact of SLA compatibility on allotransplantation. Recently, a model of acute kidney allograft rejection was established using primarily outbred Yorkshire farm pigs (106, 107) with 17 unique SLA haplotypes. Here, we briefly discuss recent data on the use of swine as relevant preclinical allogeneic transplantation models. SLA typing provides information to select recipient and donor pair SLA allele matching or mismatching for testing. However, specific studies are needed to estimate and predict the level and speed of rejection caused by each SLA mismatch.

5.2. Solid Organ Transplantation

In solid organ transplantation, the benefits of HLA matching have been clearly established in various types of organs, primarily in kidney owing to the sheer volume of transplants performed worldwide, but also in heart, lung, liver, and pancreas (108). Among the routinely typed HLA loci, matching between donor and recipient *HLA-A*, *-B*, and *-DR* significantly contributes to improved graft survival and reduced incidence of rejection (109). As with HLA, SLA compatibility has been demonstrated repeatedly to mediate transplant rejection in swine solid organ transplantation. The recognition of SLA alleles as transplant determinants on allograft survival was first documented 40 years ago in the NIH/MGH miniature swine transplant model (110), a model that has resulted in the publication of numerous cutting-edge transplantation experiments worldwide (111–113).

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VCA: vascularized composite allograft

Without immunosuppressive conditioning, pigs receiving a kidney allograft with at least one SLA haplotype mismatch had moderate to severe cellular rejection, whereas a "perfect" SLA-matched kidney displayed normal renal allograft histology and serum creatinine with no evidence of rejection (106). It should be noted that the pig that received a blood group–incompatible kidney (A to O) experienced hyperacute rejection (114). In another swine renal allotransplant study, mismatched minor histocompatibility antigens had been associated with acute cellular rejection in SLA-matched pigs (115). SLA typing has been of utmost importance in the EU research program (FP7 DIREKT) on end-stage renal disease and has greatly contributed to a successful porcine transplantation model (M. Jensen Waern, personal communication).

5.3. Hematopoietic Stem Cell/Bone Marrow Transplantation

In HSC/BM transplantation, clinical data highlight the benefit of patient–donor matching of HLA determinants to promote engraftment and lessen risks of graft-versus-host disease (GVHD), incidence of disease relapse, and transplant-related mortality (116, 117). Currently, the gold standard in either related or unrelated HSC/BM transplants is the matching of *HLA-A*, *-B*, *-C*, *-DRB1*, and *-DQB1* at the allele level (i.e., perfect 10/10 match). For swine HSC/BM transplantation, crossing SLA barriers usually resulted in delayed engraftment and/or the development of severe GVHD. Such correlations between SLA compatibility and clinical outcomes have been established mainly in the SLA-inbred NIH/MGH swine model (118, 119). Recently, correction of a severe combined immunodeficiency (SCID), in four of nine pigs having mutations in the Artemis gene, was achieved by long-term engraftment of allogeneic bone marrow that was matched at all class I and class II SLA genes (120).

5.4. Vascularized Composite Allograft and Cellular Transplantation

Vascularized composite allograft (VCA) transplantation, such as face, hand, arm, and genitalia, is an emerging field of clinical transplantation. Owing to the small volume of VCA transplants performed worldwide, limited data are available on the impact of histocompatibility on human clinical outcomes. Despite the involvement of multiple tissue types in some VCAs, they have been treated in the same way as solid organ transplants with regard to histocompatibility and immunosuppression (121, 122). Swine are becoming the preclinical large model of choice for this research (123–126). SLA mismatches in Yucatan pigs drive the rejection of allogeneic musculocutaneous skin flap (127). In vascularized skin transplants using the NIH/MGH swine, SLA class I mismatching triggered rejection characterized by infiltration of recipient $CD8^+$ T cells, whereas SLA class II mismatching was tolerated (126). Swine allotransplantation models using SLA-mismatched Yucatan miniature pigs have been developed for orthotopic tibial bone (128, 129) and limb (130).

The impact of HLA matching on clinical cellular transplantation, such as islet cells, has not been fully elucidated. SLA-mismatched cellular transplants have been performed to examine their ability to treat (*a*) acute myocardial infarction (131–133), (*b*) errors of metabolism (134), and (*c*) spinal cord injuries using iPSC-derived neural precursor cells (135). The role of SLA antigens in cellular transplantation remains a topic of active investigation.

6. SLA IN XENOGENEIC TRANSPLANTATION

6.1. Rationale for Swine as a Model in Xenotransplantation

Xenotransplantation could potentially increase organ availability by using pig organ donors; however, numerous issues must first be addressed. Histocompatibility and donor-recipient cross-match testing are critical to avoid allotransplants with incompatible organs based on patients

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having preformed HLA antibodies that can cause tissue damage (136, 137). Given the structural similarities and >70% sequence identities between HLA and SLA genes, HLA-specific antibodies will likely cross-react with SLA. Until recently, little has been done to evaluate the role of SLA as a humoral barrier to clinical xenotransplantation. The abundance of human antibodies to pig glycans concealed the presence of SLA antibodies in cross-matching assays; those could preclude clinical application of xenotransplantation (reviewed in 138).

PBMC: peripheral blood mononuclear cell

TKO: triple knockout

Immunoadsorption studies with pig erythrocytes, to remove antiglycan antibodies, followed by cross match with pig peripheral blood mononuclear cells (PBMCs) suggested that anti-HLA class I antibodies could cross-react to SLA and form a barrier to xenotransplantation. The creation of Gal/SLA class I knockout pigs made it possible to evaluate whether patients had anti-SLA class I antibodies (139). Mixing human serum with triple knockout (TKO) pig PBMCs, followed by elution of antipig antibodies and then binding to HLA beads, revealed that patients with anti-HLA-A antibodies were more likely to cross-react with class I SLA (140). Similar studies indicated that anti-HLA class II antibodies could cross-react with SLA class II.

Recently developed GGTA1/CMAH/B4GALNT2 (triple knockout, TKO) pigs have eliminated multiple carbohydrate xenoantigens and improved the cross-match to the point where clinical xenotransplantation without the certainty of antibody-mediated rejection may be possible for at least 30% of waitlisted patients (140–142). HLA-sensitized patients who are unable to find a suitable cross-match with human donors make attractive initial candidates for xenotransplant clinical trials. The successful identification of patients who can receive TKO pig organs requires understanding whether or not anti-HLA antibodies in these patients bind to SLA and alter engraftment.

6.2. Anti-HLA-A and Class I SLA Cross-Reactivity

The presence of similar or identical epitopes in HLA and SLA makes it possible to predict which highly sensitized patients are likely to have a positive cross-match with pig cells. Testing human sera that bound to 16 specific class I HLA-A molecules identified lysine at position 144 of the class I amino acid chain as a key residue in the epitope that is common to all 16 HLA-A proteins. There are now 166 full-length class Ia SLA sequences in the IMGT SLA database. All of these SLA molecules also contain lysine at position 144. Serum from patients with alloreactivity to 144K had a positive cross-match to SLA-1*12. These same sera, when tested for reactivity to a mutated form of SLA-1*12 (having glutamine rather than lysine at amino acid position 144), exhibited reduced binding for some patients and no binding for others. This indicated that 144K is a key residue that can drive cross-reactivity of antibodies with HLA and SLA (140).

These results are exciting for two reasons: (*a*) They enable identification of patients for whom participation in initial trials will be unlikely to be successful, and (*b*) they indicate that simple genome-editing strategies may eliminate the cross-reactive epitope in donor pigs. Because these epitopes have been preserved for millions of years of evolution, it is not surprising that they are found in all class Ia alleles (*SLA-1*, *-2*, and *-3*) and in all pigs sequenced (i.e., there is no magic pig!).

6.3. Class II SLA Cross-Reactivity

Anti-class II HLA antibodies are implicated in transplant glomerulopathy, the most common form of late renal allograft failure (141, 143). The importance of anti-HLA DQ antibodies as a cause of graft failure has become clear in the past 5–10 years (144, 145). Earlier absorption studies showed that anti-HLA class II antibodies in patients could cross-react with class II SLA, and

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Ig: immunoglobulin

that immunoglobulin (Ig)M as well as IgG was reactive (146). More recent work using individual SLA-DR and -DQ antigens expressed in HEK cells confirmed these findings (147). Patients, both unsensitized and sensitized to HLA, had antibodies that bound to class II SLA, and this binding was to both SLA-DR and -DQ. Many anti-SLA-DR and -DQ antibodies were cytotoxic. Therefore, the humoral response to SLA class II antigens will need to be considered carefully to obtain acceptable outcomes in a clinical trial (148). Similar to the class I SLA epitope mapping described above, it has been possible to use differential class II HLA and SLA binding, along with site-directed mutagenesis, to define an epitope common to many SLA-DQB proteins (147).

7. CONCLUDING REMARKS

The last decade has seen major progress in swine immunology and genetics, and particularly in understanding of the SLA complex, its genetic loci, and the role of SLA in normal immunity and in infectious disease and vaccine responses (**Figure 4**). The stage is now set for deeper probing of the role of SLA alleles and haplotypes in controlling these responses, for determining specific antigenic epitopes that stimulate immune and vaccine responses, and for identifying critical immune cell subsets and the exact SLA loci that facilitate cellular interactions for effective immune responses. As biosecurity improves and consumers expect pork products free of antibiotics and swine pathogens, the need for vaccines will change. The relevance of disease-resistant breeding stock will become more important, along with pigs with improved vaccination responses.

Research using improved swine genome sequence and updated genomic and proteomic tools may reveal novel immune pathways regulated by SLA genes. It will help to verify the effects of specific SLA alleles on QTL and disease responses and to identify exactly which genes enable pigs to resist infection by specific pathogens. Detailed swine genomics, particularly of the SLA complex alleles and their diversity, will amplify the importance of the pig for allotransplantation and biomedical research. As appropriate genetically modified pigs are developed, the stage is now set for determining the critical role of SLA genes and proteins in cell and tissue xenotransplantation. The role of individual SLA antigens in swine biomedical models and for overall pig health and productivity will continue to be clarified.

SUMMARY POINTS

1. The SLA system is among the most well-characterized MHC systems in nonhuman animal species. A systematic nomenclature for the genes, alleles, and haplotypes of the SLA complex is critical to research in swine genetic diversity, immunology, health, and vaccinology, as well as organ and cell transplantation.
2. Based on our new, detailed annotation of the Sscrofa11.1 genome assembly, the SLA complex encodes approximately 150 loci, with at least 120 genes predicted to be functional.
3. Despite the ongoing domestication process, involving selection for favorable traits, pigs have still maintained a high degree of SLA diversity, as demonstrated by the presence of the 246 and 277 class I and class II alleles, respectively.
4. Pig disease models provide better understanding of host–pathogen interactions. Pathogen effects on SLA gene expression drive the regulation of swine immune responses. Novel trait association data indicate that SLA alleles or haplotypes may be useful genetic markers for use in improving pig breeding programs.

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5. Swine have become the preferred preclinical large animal model for biomedical studies, transplantation, xenotransplantation, and regenerative medicine research. Allogeneic transplantation research in pigs has improved understanding of rejection mechanisms of both host-versus-graft and graft-versus-host disease.
6. Improved cross-matched genetically engineered pigs could reduce antibody-mediated rejection of pig xenografts in highly HLA-sensitized patients. Modifying SLA genes could improve pigs as donors for xenotransplantation.

FUTURE ISSUES

1. The impact of SLA genes on swine production and health traits needs to be attributed to individual SLA locus alleles and not just haplotypes.
2. Renewed typing methods, from PCR SSP to NGS, will enable reliable typing of outbred pigs. To truly explore diversity, data based on large cohorts of pigs are necessary.
3. Functional studies on MHC effects on cell interactions and on microbiota diversification are needed to understand the impact of SLA genes on the education of the pig immune system.
4. In-depth analysis of peptide presentation via major SLA genes will identify the broad range of functionally relevant vaccine targets.
5. Identification and maintenance of important SLA-defined pig lines (e.g., NIH/MGH, Yucatan, or Babraham pigs) are essential as resources for pig biomedical models.
6. Future tool development is needed for the swine biomedical model; this includes SLA class I and first SLA class II tetramers, T-cell receptor profiling, SLA-informed SNP chips, and panels of monoclonal antibody reagents to swine immune proteins.
7. Availability of well-characterized, genetically engineered pigs for human disease models will lead to development and validation of novel therapeutics and improvements in xenotransplantation research.
8. Human cross-matching with SLA class I and II will facilitate xenotransplantation. Histocompatibility testing of pigs needs to be improved in analogy to human allogeneic transplantation.

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DISCLOSURE STATEMENT

A.J.T. has founded and has significant financial holdings in a company (Makana Therapeutics) and has applied for and been awarded patents related to xenotransplantation. M.T. is now employed by Makana Therapeutics with stock options. The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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There is a vast literature on the MHC, SLA, and HLA complex structure and methods to assess alleles and their effects on immune responses. Due to citation limitations, we have included only

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the most recent publications. The authors are indebted to Shirley Ellis and Armin Saalmüller for their critical review and valuable comments on this manuscript.

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15. Role of comparative MHC nomenclature committee for dissemination of MHC-related information to the scientific community.

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RELATED RESOURCES LIST

Based on the International Society for Animal Genetics guidelines, all swine gene locus symbols are based on the Human Genome Organization Gene Nomenclature Committee: **http://www.genenames.org**

Animal QTLdb and CorrDB updates: **https://www.animalgenome.org/QTLdb**

European Bioinformatics Institute (EMBL-EBI): **https://www.ebi.ac.uk/services**

Functional Annotation of Animal Genomes (FAANG): **https://www.faang.org/**

IPD-MHC SLA sequence database: **https://www.ebi.ac.uk/ipd/mhc/group/SLA**

NetMHCpan 4.0 Server: **http://www.cbs.dtu.dk/services/NetMHCpan/**

NetMHCIIpan 3.2 Server: **http://www.cbs.dtu.dk/services/NetMHCIIpan/**

NIH Tetramer Core Facility: **https://tetramer.yerkes.emory.edu/**

Pig Genome: The latest genome build (build 11.1) for the pig can be found at NCBI (**https://www.ncbi.nlm.nih.gov/assembly/GCF_000003025.6**) or Ensembl (**https://useast.ensembl.org/Sus_scrofa/Info/Index**).

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