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Current Genomics, **2015**, *16,* 47-59

Genetics and Vaccines in the Era of Personalized Medicine

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Abstract: Vaccines represent the most successful and sustainable tactic to prevent and counteract infection. A vaccine generally improves immunity to a particular disease upon administration by inducing specific protective and efficient immune responses in all of the receiving population. The main known factors influencing the observed heterogeneity for immune responses induced by vaccines are gender, age, co-morbidity, immune system, and genetic background. This review is mainly focused on the genetic status effect to vaccine immune responses and how this could contribute to the development of novel vaccine candidates that could be better directed and predicted relative to the genetic history of an individual and/or population. The text offers a brief history of vaccinology as a field, a description of the genetic status of the most relevant and studied genes and their functionality and correlation with exposure to specific vaccines; followed by an inside look into autoimmunity as a concern when designing vaccines as well as perspectives and conclusions looking towards an era of personalized and predictive vaccinology instead of a one size fits all approach.

Keywords: Vaccine, Personalized medicine, Genetics, HLA, Autoimmune ecology, Infection, Autoimmunity and systems biology.

1. INTRODUCTION

Vaccines represent the most successful and sustainable tactic to prevent and counteract infection [1]. A vaccine, typically containing one or several antigens from or similar to a disease-causing microorganism, generally improves immunity to a particular disease upon administration by inducing specific immune responses. Over the last century, the availability of vaccines reduced the incidence and mortality for polio, smallpox, diphtheria, mumps, pertussis, polio, tetanus, measles, rubella, pneumococcus, meningitis and hepatitis B [2].

Although the field has been successful, there is an empty space ready to be occupied by effective vaccines to abate new and old foes [3]. Moreover, the historic development of the field is usually divided in generations: the first generation stands for the administration of live attenuated or inactivated infection vectors [2, 4]; while the second refers to vaccines assembled from isolated cellular or structural components (e.g., polysaccharides and/or protein antigens) [5]. The second-generation takes advantage of the constant development DNA molecular technology and carbohydrate chemistry.

Conventional methods of vaccine development deal with obstacles such as non-cultivable pathogens, pathogens with-hypermutable and highly variable antigens [6], opportunistic pathogens [7], and rapid evolving adaptable pathogens. The main goal of every vaccination is to initiate protective and efficient immune response in all of the receiving population; however, a wide-ranging and effectual protection is rarely observed and reflects the fine and composite interactions between the host and pathogen immune system and genetic counterparts. On top of this, tools to accurately identify vaccine outcomes are currently lacking [3]. The main known factors influencing the observed heterogeneity for immune responses induced by vaccines are gender, age, co-morbidity, immune system, and genetic background [3, 8]. The effect of the genetic status, in defining the response generated directly or indirectly with an innate or adaptative immune response, has been demonstrated across multiple viral vaccines (e.g., smallpox, influenza, measles, rubella, and mumps) [8].

A new momentum to vaccine research surfaced as the genomics field bloomed over the last decades. With the completion and availability of the first draft for the genome sequence of a living microorganism in the mid 90s, genomic knowledge refreshed the field's point of view [9]. Now the complete genomic information for about 300 microorganisms has been obtained and finalized, including those capable of causing disease to humans [10]. Thus, the advent of high throughput sequencing technologies has enabled new and more sophisticated approaches to further expand genomic information, becoming key drivers to disentangle vaccine-induced immune response hoping for an era of personalized and predictive vaccinology instead of a one size fits all approach [8, 11]. Personalized medicine is committed to survey and monitor risks to provide patients with a specific treatment taking into account their particular genetic profile and molecular phenotype. Thus evaluation, comparison, cor-

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1875-5488/15 $58.00+.00

relation, cross-matching and interaction of the nascent omic information would aid in the prediction, diagnosis, and treatment at the individual level but at the same time would provide a better understanding of the physiopathological mechanisms of disease and infection onset and progression [12].

Studying the genome of pathogens and the host using experimental and computational approaches has broadened the field to mechanistic and functional insights targeted to the development of potential novel diagnostic, therapeutic and vaccine candidates [13, 14]. Concepts such as "vaccinomics" describe the common ground where a systems biology approach takes into account immunogenetic, immunogenomic, metagenomics, immune profiling and functional studies directed towards understanding and predicting immune responses induced by vaccine exposure, using this information to engineer and test new vaccine candidates [15]. Thus new and innovative technology-driven approaches are starting to take genomics and a whole set of ongoing and developing omics (i.e., transcriptomics, metagenomics, metabolomics, adversomics, among others) into play in order to decipher and disentangle functionality and organization [16]. These new approaches are taking even a step into describing and correlating matching layers of genome-wide information to explain and explore mechanisms taking into account ways of interaction from the genetic to the environmental factors (i.e., genomics and epigenomics, respectively) [17, 18].

The main objective of a vaccine is to identify a specific immunological profile to be later customizable and able to provide a long term protection against a pathogen [19]. A systems biology approach to decipher novel mechanisms of vaccine response could allow the forecast of immunogenicity and efficiency of candidate vaccines [20]. The advent of high-throughput approaches is allowing exploring the acting layers of connected networks that control and define an immunological event enabling the field to roam from the search of correlates to the identification of protection signatures related to an immunological protective response.

New tools for vaccine diagnostics could be aimed to customize new candidates in subpopulations with better accuracy and safety. Likewise, moving the field towards a more therapeutic framework accompanied by the preventable classic approach will broaden the application and treatment to chronic pan-diseases like obesity or cancer [21]. A needed makeover on the design and application of vaccines will benefit health worldwide in this present time of data availability, globalization and integrative biology. This review is focused on the genetic status and effects to vaccine immune response and how this could contribute to the development of novel vaccine candidates that could be better directed and predicted relative to the genetic history of an individual and/or population. The text guides the reader through a brief history of vaccinology as a field, from the stepping stones to Pasteur's principles; then a genetic focus on the most relevant and studied genes, their functionality and correlation with exposure to specific vaccines. The review closes with an inside look into a main concern when designing vaccines, which is autoimmunity and exposure to the vaccine components and their possible secondary effects and role into a protection onset for a specific pathogen. Perspectives and conclusion leave hopefully more questions to be answered in this immense field of data and information we are heading to.

2. BRIEF HISTORY OF VACCINOLOGY

Vaccines antedate the vaccinology field by a long time. Origins are traced to Asia where smallpox lesions were used to transmit a mild infection to induce protection [22]. Documented smallpox vaccinations go back as early as the 17th century in the United States and England by using variolation, the method for purposefully infecting a person with smallpox (Variola), as the vehicle of inoculation.

Variolation became more accepted and safer when Edward Jenner demonstrated protection against smallpox infection by inoculation of cowpox in 1796, leading to the formulation of the vaccine concept [23]. By the 19th century –once the germ theory of disease was proven and several bacteria species related to infection and viruses discovered – Louis Pasteur described the process of microbial attenuation and how it would affect immunization. Then, Pasteur developed the rabies vaccine which is the first vaccine created in a laboratory [23]. He also laid the rationality to vaccine development and the first rules and principles, as per isolation, inactivation and administration of a disease-causing microorganism [2].

Ever since, the field focused on vaccination as the best strategy against bacterial and viral pathogens affecting human health. By the mid-20th century, toxoid based vaccines brought diphtheria and tetanus under control; followed by partially successful vaccines for cholera and typhoid, the first inactivated influenza vaccine and an attenuated yellow fever vaccine [24]. Then newly develop tissue culture techniques permitted the first *ex vivo* culture of poliovirus, leading to an effective polio vaccine [25]. After polio, other important childhood disease vaccines were developed against measles, mumps, rubella and varicella.

Current vaccines are either made of killed, live attenuated and/or purified subunits, such as detoxified toxins, purified antigens or conjugated polysaccharides of the disease causing microorganisms (Table **1**). These vaccines were developed using Pasteur's principles and became landmarks and tools that led to the control and elimination of some of the most devastating infectious diseases worldwide. Despite their success, vaccine development takes time for those non-cultivable pathogens or the ones where there is not an obvious antigen or structure to use as a candidate for a vaccine. On top of the former, variation between individuals in vaccine responses remains a complex trait that needs further attention given that a high proportion of vaccinated individuals lack complete protection after routine immunizations [26].

Finalizing the 20th century, technologies to develop vaccines were coming to an overuse since all plausible vaccines to develop were described already; the field needed new approaches to counteract the problematic pathogens at hand. Then, the introduction of newly develop technologies – such as recombinant DNA and chemical conjugation of proteins

Table 1. Different approaches to vaccine design in the pre-genomic era: application of Pasteur's principles. Adapted from Serruto *et al.* [10].

Microorganism Status	Pathogen Treatment	Advantages	Drawbacks	Vaccine Example
Killed	Agent is inactivated	Efficacious	Difficult to cultivate in a scalable setting	Polio virus; Influenza; Rabies; Oral cholera.
Live attenuated	Agent live do not cause disease			Polio virus; Intranasal influenza vaccine; Measles, mumps and rubella (MMR).
Subunit	Purified portions of agents	No risk of disease No need to culture	Identification of components complex and time consuming	Diphtheria toxoid; Tetanus toxoid; Pertussis toxoid; Hepatitis B vaccine.
Subunit – conjugated	Polysaccharide component agent is linked to a protein carrier	The conjugated polysaccharide that is poorly immunogenic on its own becomes immunogenic	Need to culture *in vitro* to obtain its capsule	Haemophlius influenza; Meningococcus A, C, Y, W135 Pneumococcus

to be used as new adjuvants – leveled the field to keep going forward. By 1995, Craig Venter published the first draft genome of a microorganism [9]. This led the way to initiate a technological revolution allowing to use computational approaches to design vaccines by extracting the information from the genomic information without even growing the pathogen, this is known as "reverse vaccinology" [27].

Reverse vaccinology serves to develop protein-based vaccines and has been applied to many bacterial pathogens. The first pathogen tackled was group B streptococcus which by using eight available genomes, allowed the expression of 312 candidate antigens and the development of a vaccine based on four proteins able to protect against all serotypes [27]. For group A streptococcus another vaccine was developed by cross-matching homology to make sure the selected antigens for the vaccine differed from human encoded proteins. By using the entire protein repertoire of a pathogen, reverse vaccinology selects the best antigen vaccine candidates, to confection new candidate vaccines that can lead to the discovery of unique antigens that may improve existing vaccines. A parallel between conventional and reverse vaccinology is presented on (Table **2**).

3. VACCINE RESPONSE AND GENETICS

The immune system is responsible for the surveillance, recognition and generation of a response based on a presented exposure. Recognition of foreign and hazard signals stems from the capability of antigen-presenting cells to expose pathogen-derived peptides in the HLA peptide-binding grooves determined by the genetic constitution of the individual, providing a useful frame work to understand variability of the immune response [28].

Population genetic studies provide the tools to understand the underlying genetic factors responsible for the variation in susceptibility to pathogen infection, and also further clues for the interactions between host and pathogen that define the host response. However, the diversity and heterogeneity of the immune response to vaccines remain primary obstacles to offer vaccines to the general public. This variability originates from the genetic history of each individual and it is believed to be related at least in part to polymorphisms in the immune response genes [29]. There are a growing number of reports documenting clinically relevant infectious differences in clinical outcomes depending on the status of genes related to the immune response. Just until recently, the idea of genetics influencing the response to vaccine exposure began to be further explored. It is not for lack of trying that a response has not been attained but for multiple factors defining and interacting to reach an outcome after the system is perturbed; this implies a vaccine response is defined by the articulation of a plethora of genetic and environmental components such as genes promoting/suppressing a response due to the presence of a polymorphism; environmental modifications such as epigenetic modifications; and interaction of host and non-host genes at the genetic and environmental level [30].

There is increasing interest in understanding the genetic influence of polymorphisms associated with the effect to define humoral, adaptative, and innate responses to vaccines from the perspective of an individual and at the population level. This area of study is growing due to the fact that genomic tools and technological advances –such as high-throughput, low-cost platforms and methodologies – are pushing the field towards deciphering the role of genetic variants involved from the time of exposure to receptors such as Toll-like receptors (TLRs), to cytokine and their receptors, to the human leukocyte antigen (HLA) molecules, and others that may skewed the immune processes to originate and complete a response. The introduction of genetics, epidemiology and genomics to vaccine design has been denominated vaccinomics [29]. Perhaps this path would offer important allelic gene variants, which would allow defining how likely an individual respond to a vaccine challenge.

Table 2. Comparison between traditional and reverse vaccinology. Adapted from Sette *et al.* [20].

	Traditional	**Reverse**
Antigens available	Only 10-25 identified.	Virtually all antigens encoded by the genome.
Property of antigens	Most abundant antigens, immunogenic during disease only from cultivable microorganisms.	Antigens from non-cultivable microorganisms can be identified.
Immunology of the antigens	Highly immunogenic antigens Some may contain domains mimicking self-antigens and may induce autoimmunity.	Conserved protective antigens can be identified. The novel antigens are screened against the human genome to avoid homology.
Polysaccharide antigens	A major target of traditional bacterial vaccines.	Cannot be identified by reverse vaccinology; however, operons coding for the biosynthesis of polysaccharides can be identified.
T cell epitopes	Known epitopes limited to the known antigens.	Virtually every single T cell epitope is available.

Still, vaccine development for multifactorial complex traits (i.e., complex diseases), including HIV, malaria, dengue fever, tuberculosis, among others is in its infancy and would require a shift in vaccine strategies [31, 32]. Several reports present data for the effect of genetic factors in vaccine-induced immunity. Next, we provide a brief recapitulation of the genetic factors associated with immune response mainly for groups of genes related with HLA alleles and other genetic variants.

3.1. Epidemiology and Genetics

Due to response heterogeneity, vaccines can either elicit partial, complete and/or fail to protect individuals treated under the same conditions. Approximately, 5 to 10% of vaccines fail to induce long term antibody protective levels [33]. Twins studies support the role of genetics in vaccine response. For measles, mumps, and rubella, a 89%, 39%, and 46% of the variation of IgG titers in humoral immunity after vaccination is attributed to genetic factors rather than by chance, respectively [34]. Moreover, early vaccination in twins showed high heritability (40—70%) for antibody responses in oral polio, tetanus, diphtheria and hepatitis B vaccines [35]. The estimated genetic attributed contribution of the HLA genes is about 40% and 60% as per non-HLA genes [36]. Interferon-gamma and interleukin-13 responses to tetanus, pertussis and some BCG vaccine antigens show also high heritability (39-65%). Sibling and twin genetic heritability approaches for vaccine response support a genomic approach to interindividual variation in vaccines response [37].

Epidemiological and family vaccine studies have shown familial aggregation. Subsequently, many association studies have identified both HLA and non-HLA candidate gene markers, including genes in close linkage disequilibrium with a putative causative marker [31]. These HLA and polymorphism findings emphasize the importance of identifying and replicating initial reports of genetic associations with vaccine-induced immune responses, as well as understanding the functional consequences of each gene/ polymorphism association. The most common approaches to evaluate the effect between vaccination and variation in immune response related genes are the candidate gene approach and genome-wide association studies (GWAS) [38]. As example of these genome-wide approaches Crosslin *et al.* analyzed 22,981 participants exposed to the varicella zoster virus and identified a genomic region mapping to the non coding gene *HCP5* (HLA Complex P5) located in the HLA region and associated previously with regulatory viral activity, suggesting a clinically actionable variant for the shingles vaccine [39]. Kenney *et al.* assessed cellular responses in healthy individuals and performed a GWAS on their immune responses following rubella vaccination [40]. Their results indicate that rs16928280 in protein tyrosine phosphatase delta (*PTPRD*) and a collection of SNPs in *ACO1* (encoding an iron regulatory protein) are associated with interindividual variations in interferon-gamma (IFN-γ) response to rubella virus stimulation [40].

An additional component is host variability and includes the multiplicity of immune response genes, as well as the diversity of HLA haplotypes, allowing human populations an almost limitless immune response repertoire [41]. Vaccine efficacy can be impacted by a number of host factors as possible confounders [42]. It is now clear that pathogen and host variability, as well as the interactions between them, must be considered in vaccine design.

3.2. Polymorphism of the HLA Region

Immune responses after the exposure to vaccination by measles, mumps and rubella (MMR), influenza, hepatitis B, and vaccinia vaccines are influenced by the HLA region and other immune regulatory genes [31]. The HLA region, located on the short arm of chromosome 6 (6p21.3), is considered the most polymorphic region of the human genome with more than 220 genes contributing to the genetic susceptibility to infectious diseases and variations in immune responses to vaccines [30]. Genes in this region are usually taken as candidate genes in association studies of infectious diseases due to their role in immune function. The HLA region is divided into three regions: the class I region where the *HLA-A*, *-B*, and *-C* genes are located and involved in antigen-presentation to CD8+ T cells to define cell-mediated immune responses; next is the class II region, containing genes like *HLA-DR*, *-DQ*, and *-DP*, associated with the presentation of

exogenous antigens to helper CD4+ T cells, active players in humoral immune responses. Finally, there is the class III region where immune non-HLA related genes are located (See Fig. **1**). HLA genes play a key role in determining the response to specific T-cell antigens [43]. HLA class I and class II genes represent one of the main focal points due to their biologic role of presenting pathogen-derived peptide epitopes to T cells and their extraordinary polymorphism.

Genes located in the HLA region are inherited as a block (haplotype) and are codominantly expressed. Every individual receives a maximum of two alleles per each locus, meaning that a heterozygous individual inherits per parent one haplotype of three HLA class I (A, B, and C) and three of class II (DP, DQ and DR) loci. Since, each chromosome is found twice (diploid) in each individual, a normal individual will have at least a set of 12 HLA antigens [44]. Haplotypes are inherited in chromosomal blocks, making antigens at different loci to be segregated together. Sometimes, crossing over between parental chromosomes generates new loci combinations resulting in new recombinant haplotypes (See Fig. **1**) [45].

A growing list of genes has been associated with immune related functions critical to the immunological response. Class I and II HLA genes, chemokines and chemokine receptor genes, cytokines and their receptor genes, immunoglobulin-like receptor genes, signaling molecules, and over all genes associated with the onset maintenance and control of the innate, humoral and adaptative immune response. Below a brief introduction to the HLA structure and biological role is provided followed by a description of the genetic correlates, reported for HLA Class I, II and non-HLA genes, to specific vaccines.

3.2.1. Functions of HLA Class I and II

Class I and class II molecules are essential for T cell-mediated adaptive immunity. T cell receptors recognize foreign antigens peptides produced by intracellular protein degradation, which are bound to class I or class II molecules at the surface of human cells. The process of foreign protein degradation is refer to as antigen processing, while the binding of peptides by HLA molecules to form ligands for binding to the T cell receptor is called antigen presentation. When the T cell receptor recognizes HLA-associated pep-

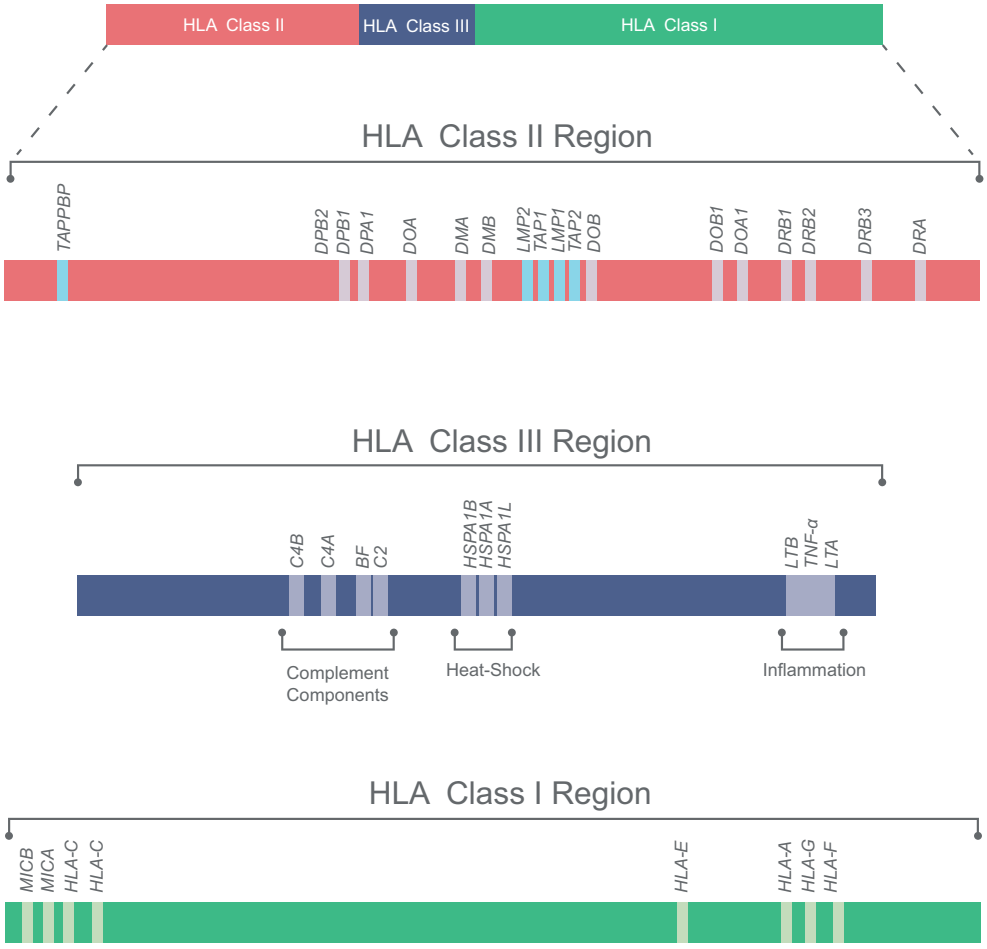

Fig. (1). Map of the human HLA. The region is conventionally divided into three classes: I, II, and III. Each region contains numerous genes, only a few of the most relevant are shown. Abbreviations: Tapasin (*TAPBP*); large multifunctional proteases 1 and 2 (*LMP1* and *LMP2*); transporter associated with antigen processing 1 and 2 (*TAP1* and *TAP2*); complement components 2, 4A and 4B (*C2*, *C4A* and *C4B*, respectively); complement factor B (*BF*); heat-shock protein 1A A-type (*HSPA1A*); heat-shock protein 1A B-type (*HSPA1B*); heat-shock protein 1A–like (*HSPA1L*); lymphotoxins A and B (*LTA* and *LTB*); tumor necrosis factor α (*TNFA*); and major histocompatibility complex class I chain genes A and B (*MICA* and *MICB*). With permission from [105].

tides on an antigen-presenting cell, several T cell surface proteins and intracellular signaling molecules are rapidly mobilized to the site of T cell and antigen presenting cell contact.

3.2.1.1. Antigen Processing in the Class I Pathway

For the most part, endogenous antigens presented by class I molecules are originated from intracellular infection caused by viruses, proteins synthesized in the cytosol, mature proteins or defective ribosomal products [46]. Assembly of class I molecules with antigenic peptides requires coordination of multiple processes to generate, transport and load the peptides into the peptide-binding groove structure of nascent class I molecules in the endoplasmic reticulum [47, 48]. Many of these polypeptides are ubiquitinated and thus are degraded by the proteasome [46] (See Fig. **2**).

Peptides to be presented are transported into the endoplasmic reticulum by TAP (transporter associated with antigen processing), where they associate with heterodimers of HLA class I heavy chain and β2-microglobulin. Tapasin loads the HLA class I molecules to TAP in association with chaperone molecules (calreticulin and ERp57) forming the peptide-loading complex. Once the peptide is loaded the HLA class I-peptide complex is transported to the cell surface via the ER and Golgi network to be recognized by the specific T cell receptor CD8+ T cell [48] (see Fig. **2**).

3.2.1.2. Antigen Processing in the Class II Pathway

Usually, exogenous antigens are presented by class II molecules and are derived from pathogens located in the extracellular spaces. Antigen presenting cells have specialized receptors to bind and internalize microorganisms into phagosomes, which will fuse with lysosomes, producing phagolysosomes or secondary lysosomes.

Less often, cytoplasmic and membrane proteins may be processed and displayed by HLA class II molecules. In this pathway, cytoplasmic proteins are trapped within membrane bound vesicles called autophagosomes; these vesicles fuse with lysosomes, and the cytoplasmic proteins are degraded by proteolysis. In both cases, degraded proteins are then able to bind to HLA class II molecules [46] (see Fig. **2**).

HLA class II α and β chains assemble in the ER with a non-polymorphic protein called invariant chain (Ii). The interaction with the Ii stabilizes the structure of the HLA class II molecule while preventing the binding of peptides within the ER. Ii is anchored in the ER membrane, and the cytosolic portion of the molecule directs intracellular sort-

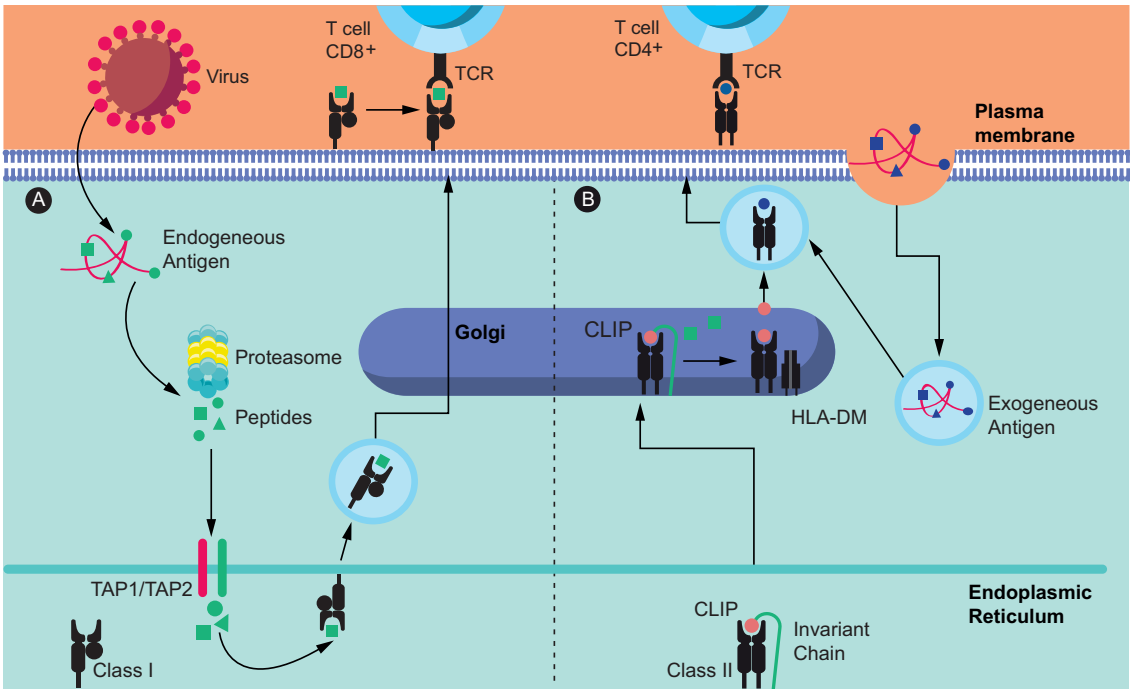

Fig. (2). Antigen processing by HLA Class I and II molecules. A. Class I antigen processing and presentation occurs when proteins in the cytosol are degraded by the proteosome into small peptides then they are transported by TAP into the ER lumen. HLA class I molecules are synthetized, translocated and assembled into the lumen of the ER where they load the peptide; HLA class I and peptide complexes leave the ER and move through the Golgi apparatus to the plasma membrane where they present the joined peptide to the T cell receptor of CD8+ T cells. **B.** Class II presentation occurs when extracellular proteins are phagocytized and then degraded to small peptides. These peptides are then sorted into vesicles where they interact with the HLA class II molecules. HLA class II α and β chains, CLIP and the invariant chain (Ii) molecules are located and assembled in the lumen of the ER, where they cannot bind peptides because the complex occupies the peptide-binding site. Heterotrimers leave the ER and pass through the Golgi apparatus to fuse with vesicles. The Ii is degraded and with the help of HLA-DM and HLA-DO a peptide can be joined. Complexes of HLA class II and peptide are relocated to the plasma membrane where they can be recognized by CD4+ T cells. With permission from [105].

ing of class II molecules through the Golgi to the HLA class II compartment; Ii is degraded and can be replaced by a peptide derived from degradation in the endosomes or lysosomes of endocytosed material. Proteolytic enzymes such as cathepsins that generate peptides from internalized proteins degrade the Ii, leaving only a 24 amino acid remnant called class II-associated invariant peptide (CLIP), which sits in the peptide-binding groove [49]. CLIP is removed by the action of the HLA-DM. Complexes of HLA II together with the peptide are then taken to the plasma membrane where they can be recognized by CD4+ T cells [50] (see Fig. **2**).

3.3. HLA Class I Vaccine Effects

For the measles vaccine, *HLA-B*8, HLA-B*13* and *HLA-B*44* alleles associate with IgG seronegativity after a single dose [51]. For the rubella vaccine response, low-rubella IgG antibody levels associate with *HLA-B*27:05*, while *HLA-B*45:01* alleles associate with high antibody levels after two doses of rubella vaccine [52]. *HLA-B*35:03* and *HLA-C*15:02* alleles associate with high levels of lymphocyte proliferation to rubella virus, and *HLA-B*13:02*, *HLA-B*37:01*and *HLA-B*38:01* alleles associate with high levels of cellular proliferation to the mumps virus following two doses of the MMR vaccine [53].

The association between HLA alleles and rubella-specific IFN-γ (Th1) and IL-10 (Th2) cytokine responses among healthy children following two doses of rubella vaccine has been studied. Several class I *HLA-A (*02:01, *24:02, *68:01)* alleles associate with rubella vaccine-induced IFN-γ secretion [54]. Both *HLA-A*02:01and HLA-A*68:01* alleles associate with IFN-g and IL-10 secretion. *TAP1*, *TAP2*, *LMP2*, *LMP7* and *Tapasin* genes are involved in antigen processing for HLA class I presentation and suggested to contribute to susceptibility to human papillomavirus (HPV) type-16-associated cervical cancer [55, 56]. *IL-10* gene polymorphisms are associated with infection clearance and with high-risk HPV types among immunosuppressed adolescent females with varying degrees of HIV-1-induced CD4 immunosuppression [57]. This type of associations create a compelling argument for the importance of cytokine gene regions and/or a cluster of genes in the HLA region regulating host immune responses to HPV infection in a manner that results in inherited susceptibility or resistance to the transforming properties of oncogenic papillomaviruses [30]. There are over 100 HPV types of which 40% are usually transmitted by sexual intercourse. The HPV vaccine avoids infection of certain types of HPV and two vaccines are available in the global market (i.e. quadrivalent and bivalent) [58]. Prevention is the general approach to HPV infection. Currently, new and better ways to increase cross-protection towards different type with less vaccination are moving forward. Implementation of immunization in national programs is becoming more frequent and gaining ground targeting young adolescent girls defined by age groups. Usually, vaccination is recommended for females between 11 to 26 years old, and has also started to being offered to males in different countries (For a more in depth review the reader is referred to Kim *et al.* [59]).

The contribution of HLA genes to the immune responses generated by the rubella vaccine have been evaluated. As an example, when genotyping was performed in a group of 346 healthy school children and young adults vaccinated with two doses of the MMR vaccine [53], *HLA-B*35:03* and *HLA-Cw*15:02* weakly associated with lymphoproliferative responses to rubella virus, suggesting that class I HLA alleles may have limited associations with humoral and cellular immune responses to rubella vaccine [53].

3.4. HLA Class II Vaccine Effect

For the mumps vaccine, *HLA-DQB1*02:01, HLA-DQB1**04:02, *HLA-DQA1*04:01, HLA-DRB1*03:01, HLA-DRB1*08:01, HLA-DRB1*12:01*, and *HLA-DRB1*13:02* alleles associate with low cellular proliferative responses in healthy children [60]; while the alleles positively associate with rubella-specific lymphocyte proliferation were *HLA-DQB1*05:01, HLA-DRB1*01:01*, and *HLA-DRB1*11:04*. Conversely, the *HLA-DQB1*02:02* and *HLA-DRB1*07:01* alleles negatively associate with rubella-induced cellular proliferation [61].

*HLA-DQA1(*01:03, *03:01, *03:03*) and *HLA-DQB1(*02:02, *03:02, *06:03)* associate with rubella virus-induced IL-2 [62]. *HLA-DPA1*02:01* associate with low levels of rubella-induced antibodies, whereas *HLA-DPB1*04:01* alleles associate with high-antibody levels [52]. Immune response to other vaccines associates with specific HLA class II alleles [63]. *HLA-DRB1*07* alleles are more prevalently observed in individuals failing to respond to the trivalent influenza vaccine compared with responders to the vaccine [64]. HLA gene polymorphisms and non-responsiveness to the HBV vaccine has been proposed in multiple studies [29].

3.5. HLA Haplotypes

Associations between HLA haplotypes after a second dose of the MMR vaccine are reported [29]. Lower IgG antibody levels associate with class I *HLA-A*29-Cw*16-B*44* haplotype to measles and mumps vaccine viruses [65]. Higher cellular immune responses associate with the *HLA-A*26-Cw*12-B*38* haplotype when examining measles and mumps response. The class II *HLA-DRB1*03-DQB1*02-DPB1*04* haplotype presents higher levels of cellular proliferation to measles and mumps [65]. Association with low IgG antibody levels to rubella virus is observed with the *HLA-DRB1*15/16-DQB1*06-DPB1*03* haplotype, whereas *HLA-DRB1*04-DQB1*03-DPB1*03* haplotype is associated with high levels of cellular proliferation to measles and rubella vaccine viruses [51]. Mumps-specific humoral and cell-mediated immune responses associate with the *HLA-A*26-Cw*12-B*38* haplotype. A deeper characterization of HLA profiles could nurture the design of novel epitope-based vaccines, in order to move forward prediction at the individual and at the population level [29].

Immune responses to vaccines are also affected by extended haplotypes in the class III region. Associations involving haplotypes expanding across the HLA class I region, plus ten polymorphisms for *LTA-TNF-LST1* and the HLA class II region are reported involving rubella-specific

antibodies [66]. Likewise, HLA alleles supertypes are grouped according to their shared peptide-binding specificities [67].

Previously, the association of the immune response to the MMR has been examined taking into account the HLA supertypes and the shared epitopes between HLA molecules [68]. Lower measles vaccine-induced levels associate with HLA class I B44 and B58 supertypes, while the most common HLA supertypes, B7 and DR, associate with higher measles antibody response. Moreover, lower mumps-specific cellular immune responses significantly associate with the DR supertype. Higher levels of measles virus-induced IFN-γ and IL-4 immune responses associate with the A3 supertype. Differential associations between measles and mumps, the rubella vaccine response and the HLA supertypes suggest that HLA molecules are less effective in peptide presentation [68]. Through the identification of naturally processed peptides combined with specific HLA supertypes, more efficient candidate adjuvanted vaccines with peptides most likely to be immunogenic could be tested [68]. For the measles virus, 13 peptides were identified for the HLA-DRB1 peptide-binding groove capable of binding across a common population HLA supertypes, these type of repertoires could be used to fine tune new candidate vaccines [61, 69].

3.6. Non-HLA Genetic Polymorphisms and Vaccine Response

Cytokines and their receptors give shape to the immune response [70]. Characterization of the genetic effects of their main molecules might ease the development of vaccine candidates that will incorporate them to counteract those lost or unbalanced natively in order to restore and facilitate and optimal cellular and humoral response onset [30].

3.6.1. Cytokine Genes

IL-2 and *IL-10* genes associations are suggested in the measles vaccine-induced immunity. Polymorphisms mapping to the *IL-2* gene (i.e., rs2069762 and rs2069763) associate with higher antibody and higher cellular immune responses to measles [71]. On the other hand, rs1800890, rs1800871, and rs1800872 from the *IL-10* gene influence lower antibody and cellular immune responses to the measles vaccine. Polymorphisms proximal to the promoter region of *IL-10* are known to contribute with lower production of secreted IL-10 [72]. Genetic variants rs3790567 and rs372889 at the *IL12RB2* associate with both lower antibody and lower cellular immune responses following two doses of measles vaccine [71]. Similarly, a lower mumps vaccine-induced cellular response associates with the minor allele of rs372889 within the *IL-12RB1* gene [60].

Polymorphisms at the *IL12B* promoter do not associate with responsiveness to HBV vaccine in North American adolescents. Nonetheless, polymorphisms mapping to HLA and cytokine genes independently associate with HBV vaccination [73]. Of importance, the immune response to HBsAg and hepatitis A vaccination is modulated by a *IL-10* polymorphism located at the promoter [74]. Recently, smallpox vaccinated individuals that presented fewer after live vaccinia virus vaccination showed an association with haplotypes in the *IL-1* and *IL-8* genes. On the other hand, a reduced susceptibility to the development of fever after vaccination for a haplotype in the *IL-4* gene is suggested as a genetic predisposition for adverse event after vaccination [29]. Lack of response to the hepatitis B vaccine is found independently associated with *HLA-DRB1*07* and with polymorphisms at the *IL-2*, *IL-12B* and *IL-4*genes [73]. Efforts to develop a new HBV vaccine that consists on a mixture of peptides with cytokine adjuvants to circumvent these immunogenetic restrictions have been put forward [30].

Rubella vaccine-induced humoral and cytokine responses are significantly modulated by cytokine and cytokine receptor genetic variants. For example, an increased representation of minor alleles for two promoter SNPs (rs2844482 and rs2857708) of the *TNFA* gene associates with two-fold increases in rubella-specific IgG levels. Furthermore, IL-6 production associates with intronic SNPs (rs5745993, rs17882988, rs472093, rs5746059, and rs590977) in the *TNFRSF1B* gene, while several promoter and intronic polymorphisms in the *IL12B* gene significantly associate with higher IL-6 production after rubella vaccination [75].

Cytokines play an essential role in the modulation of immune responses and cytokine production is influenced by the rate of transcription of their cytokine and cytokine receptor genes. As an example, polymorphisms in these cytokine genes can affect mRNA splicing, stability, and structure of RNA molecules or protein folding [70].

3.6.2. Innate and Cell-surface Receptor Genes

The TLR family of receptors play an essential role in the primary recognition of pathogens and in the initiation of adaptive immunity. TLRs are pattern recognition receptors that can contribute to viral detection by sensing RNA and viral proteins, leading to induction of cytokines and interferon response [76]. Poxvirus, herpesvirus, retrovirus, and paramyxovirus families activate T cells through TLRs triggering antiviral innate immune responses [77].

For the *TLR3* gene, rs3775291 and rs5743305 associate with low antibody and cellular proliferation responses after measles vaccination [78]. Variation in measles-vaccine induced humoral immunity response associates with both *TLR2* (rs3804100) and *TLR4* (rs5030710) genes in an allele dose-dependent manner [79]. Rubella-induced granulocyte macrophage-colony stimulating factor secretion, lower measles-specific antibody titer, and lower cellular proliferation to measles vaccine associate with rs5743305 [79].

Other associations of innate related genes have been identified between the vitamin A (*RARA, RARB, and RARG*), *RIG-I/DDX58, TRIM* (*TRIM5* and *TRIM22*), vitamin D receptor, and *RXRA* genes with rubella vaccine-specific immunity [79]. *TRIM5* gene variants associate with rubella-specific humoral response, TNF-α secretion (rs3740996) and IL-2/GM-CSF production (rs10838525) [31]. Genetic variants (rs3741981, rs1051042, rs2660) on the *OAS* gene associate with rubella-induced IL-2, IL-10, IL-6 secretion and antibody levels. These three variants are part of a haplotype associated with an increase in rubella-specific IL-2 production [79].

Upregulation of TLRs after infection with vaccine strains of measles virus trigger activation of TLR-responsive genes such as IL-1α/β, IL-6, IFN-α/β, and IL-12 [80, 81] and induction of its own receptor, SLAM [82]. Measles virus binds to SLAM and CD46. *SLAM* minor allele T of rs3796504 correlates with an allele dose-related decrease of measles antibody levels [83]. In addition, polymorphisms in *CD46* (rs11118580 and rs2724384) correlate with allele dose-dependent reduction in measles antibody levels [83].

4. VACCINES AND THE INDUCTION OF AUTOIMMUNE DISEASES

For the past 200 years, administration of safely and effectively vaccines to humans and animals has enable the control, elimination and safeguard of many of the emergent and generalized infectious diseases. Autoimmune diseases (ADs) develop through four stages [84]. First, heritable factors (that is, genetics, including ancestry, and epigenetics) impact over the life of the individuals. They converge and interact to create and increase or decrease the liability an individual would have to develop the phenotype depending on risk and protective effects. Women are more affected than men. Second, the autoimmune ecology, characterized by the interactions between an individual and its environment, which acting stochastically will also influences the risk and course of disease. The additive effects of heritable and environmental risk factors favor the loss of autoimmune tolerance. Then, a preclinical stage characterized by B and T cell dysregulation arises. This third phase may take months or years before the phenotype becomes clinically evident (i.e., fourth stage) [84]. Evidence of association with infection in the development of rheumatic fever with *Streptococcus pyogenes* [85], cardiomyopathy with *Trypanosoma cruzi* [86], Lyme disease with *Borrelia burgdorfeii* [87], Guillain-Barre syndrome with *Campylobacter yeyuni* [88], type 1 diabetes (T1D) with viral infections [89], multiple sclerosis with Epstein-Barr virus (EBV) and *Chlamydia pneumoniae* [90] and systemic lupus erythematosus with EBV [91], among others is reported.

Autoimmunity is a concern for many vaccines, though AD presentation among immunized individuals is rarely observed. However, because of relatively low baseline incidence of many autoimmune conditions, large post-marketing and adequately powered studies are required to evaluate any increased risk of ADs after vaccination [92]. In fact, in most of the clinical trials evaluating vaccines, a systematic screening for ADs is not performed.

Patients with autoimmune conditions often show decreased immune responsiveness, which in turn would make them vulnerable to infection given their underlying disease and frequent use of immunosuppressive drugs. Reports on vaccine-induced inflammatory myopathies are sporadic and have been observed after immunizations with HBV, BCG, tetanus influenza, smallpox, polio, and diphtheria [93].

An observational safety study for the quadrivalent human papillomavirus vaccine (qHPV) in women who received at least one dose of the vaccine reported a higher incidence rate for Hashimoto's disease in vaccinated females when compared to unvaccinated ones while Graves' disease, the other autoimmune thyroid condition evaluated, was not significantly elevated. Many confirmed "new-onset" events were likely pre-existing cases [94], suggesting that exposure to the vaccine might spark the overt of an autoimmune clinical condition. Moreover, a Swedish and Danish study disclosed a significant association between exposure to qHPV vaccine and Behcet's syndrome, Raynaud's disease, and T1D [95]. However, no genetic data favoring these occurrences has been published so far. In France, Grimaldi-Bensouda *et al.* [96] observed an association between personal and family history of autoimmunity and development of ADs post vaccination with qHPV, confirming the clustering of ADs [97]. The authors, nevertheless, acknowledged insufficient statistical power to allow conclusions to be drawn regarding individual ADs [97]. More recently, a small although non-significant increase in the risk of multiple sclerosis was observed after qHPV vaccination [98]. The authors argued that "the short-term increase in risk suggests that vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease", at the time they recognized that larger studies are needed to completely rule out an effect [98].

Macrophagic myofasciitis (MMF) is an intramuscular reaction against vaccines containing aluminum hydroxide [99]. Such adjuvant is commonly contained in the HBV and tetanus toxoid vaccines; although, there is still discrepancy in the data due to limited reports. Additional data support a genetic role of *HLA-DRB1*01* in the susceptibility of MMF [100]. Other syndromes implicated in an adjuvant effect are the Gulf war syndrome (GWS) and siliconosis. GWS, suggested to be caused by multiple vaccinations over a short period of time, is portrayed by chronic fatigue and other manifestations similar to MMF. Siliconosis is related to exposure to silicone implants, previously considered inert material. These comparable conditions syndromes, together with post vaccination events, are suggested to be part of a common syndrome denominated ASIA (Autoimmune Autoinflammatory Syndrome Induced by Adjuvants) [101] characterized by the presence of one or more of the following clinical findings: myalgia, myositis, or muscle weakness, arthralgia and/or arthritis, chronic fatigue, non-refreshing sleep, or sleep disturbances; neurological manifestations (especially associated with demyelination), cognitive impairment, memory loss, pyrexia and/or dry mouth. A noteworthy common denominator is that the exposure to a component that comprises an adjuvant effect can be documented in each of those medical conditions. ASIA may present as no classical clinical and laboratory manifestations characterizing a new syndrome and not necessarily a well-defined AD. ASIA can occur weeks and even years following exposure to a culprit agent [101].

The incidence of narcolepsy, a sleep disorder characterized by loss of hypothalamic hypocretin (orexin) neurons, is proposed to have increased after the pandemic AS03 adjuvanted H1N1 vaccination in Swedish and Finish while in Chinese, infection was suggested to trigger the disease, potentially supporting an immune-mediated pathogenesis [102]. Although the disease has been suggested to feature some autoimmune characteristics, as of now there is not enough evidence to support it as an autoimmune condition.

5. PERSPECTIVES AND CONCLUSIONS

The immune response network theory in its simplest form is based on the premise "the response to a vaccine is the cumulative result of interactions driven by a host of genes and their interactions, and is theoretically predictable…" [8]. Scientists are fostering this definition by recognizing and including the impact of epigenetics, metagenomics and other factors that might influence or play a role in defining the onset of a vaccine response [8]. The main obstacles impairing our ability to predict a response and to develop effective vaccines or treatments are the increased genetic variability in the human population and the constant evolution of pathogens, which produce a wide spectrum of possible host–pathogen interactions and compel the use of a systemic approach.

These are exciting times to be doing research given the rapid pace of development of high-throughput technologies for clinical and basic research. Methodological approaches are maturing towards a systems view to identify and characterize immune responses by inspecting different omic layers of information (e.g., proteomics, transcriptomics, metabolomics and genomics) [11, 14]. The ultimate goal for applying these new technologies would be to identify biomarker signatures, which will nurture how innate and adaptive responses could be measured to be integrated into a unified network. Moreover, comprehensive approaches will be required to ensure new vaccine candidates will not induce autoimmune-related phenomena. Thus, a systemic approach would allow not only designing but also potentially unraveling action mechanisms and perhaps enable prediction of the immunogenicity and efficacy of the vaccine [20, 103].

Personal and family history of autoimmunity and other non-communicable diseases, together with a genetic scan could be simple and useful tools for evaluating new vaccines as well as for translational strategies to implement personalized medicine. New and promising genome-wide approaches are starting to take this further in terms of accessibility to the public and their commercialization; nowa days getting screened for the risk to disease, your ancestry and/or even to have inventoried your complete T- and B-cell receptors is available and relatively not expensive. All these applications stem from applications being developed with the aim of personalizing your risk and help in your health decisions. For example, mapping of the T and B-cell receptor promises to transform our understanding of adaptive immune dynamics [104]. Nevertheless, the experimental design of any application is challenged by main drawbacks such as genetic heterogeneity, population epidemiology, phenotype and subphenotype definition, host-pathogen interactions and the vast gap between getting from a systems view to a translation and even further to a personalized setting [12]. This does not mean we should forget or close our minds to a systems view. On the contrary, every day we get to see more and more approaches tackling this set backs and pushing the envelope further to make what might seem as a unsolvable puzzle and to embrace these approaches massively in order to lower costs and to make them routine.

By performing a simple pubmed search, using a search term such as "vaccine AND genetics AND association AND human" as per december 2014, about 1052 reports are filtered of which 435 have been reported within the last five years. From these 435 only about 50 (~5%) report a genetic effect for a variant. This gives the impression of a slow pace in the field that is in its infancy. Closing the gap between clinical research, a systems approach, translation and personalized medicine is not unique to the field of vaccinology. Systems biology applications promise to narrow the gap between clinical trials and discovery science, which will require robust approaches to test novel concepts. Also, a complete multidisciplinary structure is needed to conceive the most appropriate measurements pre- and post-data acquisition. Translational and personalized medicine still need better attention not only from the scientific viewpoint but also from the political and economical one. No matter how the scientific and political bearings, and economical monopolies are defined it should be clear that the human protection from any viewpoint should be safeguarded and prioritized.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by the Universidad del Rosario, Bogota, Colombia.

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Received on: September 08, 2014 **Revised on: December 22, 2014** **Accepted on: December 23, 2014**