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REVIEW

Impact of host genetic polymorphisms on vaccine induced antibody response

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ABSTRACT

Many host- and vaccine-specific factors modulate an antibody response. Host genetic polymorphisms, in particular, modulate the immune response in multiple ways on different scales. This review article describes how information on host genetic polymorphisms and corresponding immune cascades may be used to generate personalized vaccine strategies to optimize the antibody response.

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Introduction

In the last century, vaccines have become the primary prevention strategy of many infectious diseases and have saved millions of lives.[1] On the other hand, the development of effective vaccines against global killers such as human immunodeficiency virus, *Mycobacterium tuberculosis*, and malaria parasites (*Plasmodium spp.*) remains a major challenge: Just recently, the European Medicines Agency gave a positive scientific opinion on the first malaria vaccine Mosquirix (RTS,S), although the vaccine's efficacy is limited.[2] Existing vaccines for *Mycobacterium tuberculosis* are only partially effective.[3] Also, vaccines against influenza or measles may fail in some cases. In particular, patients at the extremes of age,[4] pregnant women,[5] as well as patients with chronic diseases such as diabetes,[6] autoimmune diseases,[7,8] or after transplantation[9-11] show lower vaccine response rates. A better understanding of the host-pathogen interaction and new insights into vaccine immune response modulating factors will help to improve current vaccination strategies and to develop novel types of vaccines.[12,13]

Vaccination effectiveness is influenced by various vaccine-, pathogen-, and host-related factors (see Fig. 1).[4,14-16] Several studies have demonstrated that the host genetic background (genotype) has a strong influence on the immune response, e.g. to influenza, Hepatitis B or measles vaccination.[17-19] Over the last few years, it has been proposed frequently that genetic information might be used to predict vaccine effectiveness and might help to develop more effective, individualized vaccination strategies.[15,20,21] In this review, we summarize general concepts of how the genetic variations of the host can contribute to variability of vaccine-induced humoral immunity. Further, we discuss important clinical studies and how mathematical, mechanistic models help uncover therapeutic targets for personalized vaccination strategies.

The Vaccine Induced Immune Response: A Network of Networks

In general, vaccines aim to induce a significant level of neutralizing antibodies against specific viruses or bacteria, leading to protective immunity. In clinical studies seroprotection is normally defined as a specific antibody titer or antibody titer increase (seroconversion).[22] However, vaccine-induced immunity is far more complex and can be understood as a dynamic network of molecular, cell-to-cell and tissue interactions that are organized in a hierarchical structure. Molecular interactions form networks and are themselves organized in networks on a higher cellular level: Dendritic cells detect the vaccine antigen and other components through pattern-recognition receptors, in particular Toll-like receptors (TLRs).[23] Activated TLRs in turn initiate various signaling pathways through Toll/interleukin-1 receptor(TIR)-domain containing adaptor proteins such as myeloid differentiation primary response protein 88 (MyD88) and TIR domain containing adapter molecule 1 (TICAM1). This results in the expression of inflammatory genes, which are mainly regulated by a specific interferon regulatory factor or nuclear factor-κB (NF-κB), leading to a production of various cell surface receptors, cytokines, and chemokines.[24] Activated dendritic cells mature to antigen-presenting cells and migrate to lymph nodes, where they present vaccine epitopes to T-cell receptors through human leukocyte

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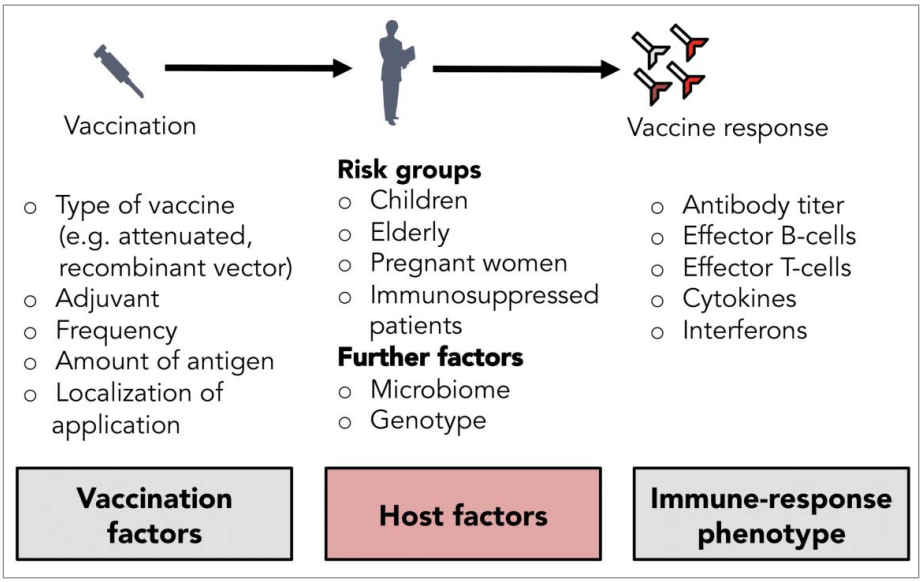

Figure 1. Selected factors for a successful vaccination.

antigen (HLA) molecules on their cell surface.[25] This in turn initiates the maturation of naïve $CD4^+$ T-cells to effector T-cells. The additional secretion of cytokines such as interleukin (IL) 12 and interferon (IFN) γ leads to proliferation of type 1 T helper cells (Th1), while the secretion of cytokines such as IL-4, IL-6, and IL-10 leads to proliferation of type 2 T helper cells (Th2). Th2 cells in turn support the proliferation of B-cells and their differentiation to antibody-secreting plasma cells and are thus an important factor for a successful vaccination.[26-28] Due to its complexity, the vaccine-induced immune response is a focus of on-going research and further processes involved in the humoral immune response have been reported.[29,30]

Immunological network structure and robustness

Basically, intercellular signaling processes of immune cells are orchestrated by cytokines, chemokines, and cell surface receptors, while intracellular signaling processes are conducted by various signaling pathways (e.g., TLR or Janus Kinase (JAK)/Signal transducer and activator of transcription (STAT) signaling pathway). Gene regulatory networks control both intra- and intercellular processes. As often described for biological interaction networks,[31-33] one can also assume that in an immune response only few components such as NF-κB regulate many processes (so-called key regulators) while most components regulate only a few processes. An advantage of such a network topology is that a single mutation in a random gene hardly affects the global immune response, because the failure does not propagate.[34] In addition, gene redundancy, overlapping functions of genes as well as regulatory feedback mechanisms are able to compensate for gene perturbations. The concept underlying these phenomena is known as biological robustness and is a key property of living systems.[35,36] The immune system shows features of robust systems such as functional redundancy of genes and proteins.[37-39] For example, a mutation in IFN-α1 (IFNA1) may affect its binding affinity to a receptor, but it has many paralogues, which are themselves potent alpha interferons (IFN-α2-14).[37] On the other hand, mutations in the NF-κB signaling pathway or several mutations in HLA molecules has been linked to diseases such as Crohn's disease and other autoimmune disorders.[40-42] We assume that in immunosuppressed patients, e.g. transplant recipients, the level of robustness is reduced due to immunosuppressive drugs, which decreases the compensatory mechanisms. Immunosuppressive drugs used in transplant patients mainly affect different signals of T-cell activation, e.g., Calcineurin inhibitors, as well as proliferation capacities of T- and B-cells such as mycophenolic acid, rapamycin or methotrexate.[43] Other immunosuppressive drugs affect signaling pathways such as JAK/STAT or TNF-α inhibitors.[44] Therefore in such risk groups, genetic polymorphisms affecting the vaccine outcome may be easier to unmask.

Genetic polymorphisms in vaccine response

Evolution acts on many levels

The immune response is continuously shaped by evolutionary adaptations on the genome level of both host and pathogen, although with different rates. The development of vaccines against pathogens with dynamic antigen variation (e.g., human immunodeficiency virus (HIV) and other RNA viruses) remains a major challenge.[45] Knowledge of genetically stable regions in the pathogen genome helps to develop new vaccination strategies.[46] Similarly, the knowledge of genetic variations in the host, which lead to an increased antibody response, may help to predict vaccine efficiency and uncover important factors of the immune response. For instance, HLA molecules show high genetic variation among individuals (more than 13,000 alleles in the IMGT/HLA database, release 3.21.0) and HLA polymorphisms have been used to reconstruct human migration events.[47] Due to the key role of HLA in the self/non-self immune recognition, it is not surprising that vaccine response shows variability between individuals.

Single nucleotide polymorphisms (SNPs)

SNPs are single nucleotide variations of the genome sequence, which occur frequently within a population (by definition at least 1%).[48] In genetic studies, particular SNPs, so-called tag SNPs, are used as markers for haplotypes. Haplotypes are regions with high linkage disequilibrium and are represented by a set of SNPs.[49] To create a haplotype map of the considered genome, genotyping studies usually only need to examine a set of characteristic SNPs instead of sequencing the whole genome.[50]

Due to technical advances in genotyping techniques,[51] the number of submitted SNPs in the NCBI dbSNP database has grown exponentially over the last 10 y. The human genome has about 3 billion base pairs.[52] Early studies estimated an average SNP frequency within the human genome of about one SNP per 1000 base pairs (corresponds to 3 million SNPs).[53,54] Today, there are almost 98 million SNPs listed in dbSNP (release build 144). However, the majority of SNPs must be regarded as candidate SNPs as the results of the studies that originally discovered them have not been reproduced. Some studies highlighted that a significant amount of SNPs in the dbSNP database is not reliable.[55,56] In comparison, the SNP map provided by the international HapMap project reported about 10 million SNPs with a minor allele frequency (MAF) of at least 5%.[57] Most SNPs, however, probably do not impact the phenotype due to biological robustness (as mentioned above).

In general, SNPs can be located within coding or non-coding sequences[58]: Within the coding region, a SNP may change the amino acid sequence of the respective protein (missense SNP), result in a stop-codon (nonsense SNP) or just have no effect on the protein sequence (synonymous SNP). SNPs within the non-coding region can affect the produced protein amount on the DNA or RNA level: At the DNA level, SNPs in the 5′ untranslated region (UTR) may affect the transcription factor binding, which leads to an up or down regulation of gene expression. SNPs in the 3′-UTR may affect microRNA binding and, as a result, gene silencing. At the RNA level, SNPs may affect mRNA degradation, RNA splicing, or the RNA sequence of non-coding RNA.

Impact of SNPs on the humoral immune response

Presuming an evolutionary pressure exerted by host-pathogen interaction, one can hypothesize that SNPs either have none, a positive or a negative, but never a fatal effect on the host. In fact, several independent studies identified a couple of SNPs to influence treatment outcome of infectious disease such as influenza, Hepatitis C virus (HCV), and cytomegalovirus (CMV) as well as the antibody response after vaccination (e.g., influenza, measles).[19,59-62]

A very prominent example concerns IFN-λ.[63,64] Since 2009, SNPs in *IFNL3/4 g*enes are associated with the HCV treatment outcome.[60,61,65-70] In particular, SNPs in *IFNL3* (rs8099917) and *IFNL4* (rs368234815) have been proposed as predictors for spontaneous viral clearance and treatment success to pegylated interferon α/ribavirin (PEG-IFN-α/RBV) treatment.[60,61] The *IFNL4* SNP (rs368234815) has also been associated with CMV retinitis in HIV-infected risk patients (n=1134, p-value=7E-3),[71] as well as with CMV replication in solid-organ transplant recipients at risk (n=455, p-value=4E-02).[72] Moreover, an *IFNL3* SNP (rs8099917) may modulate the humoral immune response after vaccination.[62] Individuals carrying the minor allele in one or both alleles showed an increased seroconversion rate after influenza vaccination.[62] Quantitative real-time PCR investigations have shown, that *IFNL3* expression in individuals carrying the minor allele in one or both alleles was lower in PBMCs.[70] *In vitro* studies showed that *IFNL3* suppressesTh2-cytokines[74-77] and modulates B-cell function.[62,78] Although the impact of IFN-λ on immune cells is not yet understood, these studies indicate that *IFNL3* is an important regulator of the Th1/Th2 balance and modulates viral clearance/antibody response.

Further SNPs that influence the humoral immune response to influenza vaccination have been reported (see Table 1): Gelder et al. investigated associations between HLA class II alleles and H1N1/H3N2 hemagglutination-inhibition (HAI) titers in an influenza risk group. They identified 4 alleles (n = 73, p-value range of 2.3E-03 to 1.6E-02, significance level p-value < 5.0E-2).[79] Poland et al. were not able to reproduce the HLA class II associations to H1N1/H3N2 antibody titer (likely due to insufficient statistical power). Instead, they found association of HLA class I alleles and H1N1 antibody titer, as well as several SNPs in coding and non-coding regions of cytokines and cytokine receptors (n = 184, p-value range of 2.3E-03 to 9.0E-02, significance level p-value < 5.0E-2).[80] Franco et al. combined genotype, gene expression and antibody titer information in order to identify genes whose genotype influences the antibody response through an alteration of gene expression. They identified 20 genes (n = 199, p-value < 5.0E-08, significance level p-value < 5.0E-2).[17] Most of the identified genes are not specifically linked to the immune system, but to intracellular transport and membrane trafficking. Seven genes encode proteins involved in antigen transport and antigen processing, but these findings have to be confirmed through further studies with larger sample size.[20]

Several genome wide association studies (GWAS) investigated the antibody response to various other vaccines, e.g. hepatitis B,[81] smallpox,[82] measles[19,73,83,84] and rubella.[85] These studies mainly identified SNPs in cytokines, cytokine receptors and co-receptors, but these findings are hard to interpret, because there are no replication studies by other research groups and none of the SNPs has been investigated on the RNA or protein level, which is required though for a biological interpretation.[86] Similarly to influenza vaccination, variations in HLA molecules have been associated to hepatitis B vaccine response: Png et al. identified three independent variants in HLA class II and class III regions in an Indonesian population.[87] Interestingly, polymorphisms associated to antibody response in cytokines and cytokine receptors have been found in genotyping studies of cytokine coding genes but not in genome-wide genotyping studies. Common caveats of GWAS are summarized in the next section.

Toward personalized vaccination strategies: identification and investigation of SNP impacts

Gene-association studies propose the first hypothesis

In summary, the impact of genetic polymorphisms on the vaccine induced humoral immune response has been studied

Table 1. Genes with polymorphisms that influence the vaccine induced antibody level (selected studies).

Vaccine	Gene(s)	Function	Study	n	Remarks	Reference
HBV	*CD11a (ITGAL)*	part of LFA-1	43 candidate SNPs across 133 genes[1]	662	reproduced in second group (n=393)	Hennig et al. 2008
	HLA-DR, HLA-DP	HLA class II molecules	GWAS[2]	1683	reproduced in second group (n=1931)	Png et al. 2011
	HLA Class III		GWAS[2]	1683	reproduced in second group (n=1931)	Png et al. 2011
Measles	*CD46*	co-receptor	66 candidate SNPs across 3 genes[3]	744	replication study, prev. identified	Ovsyannikova et al. 2011
Influenza	*HLA-DRB1, HLA-DQB1*	HLA class II molecules	HLA class II alleles[4]	73		Gelder et al. 2002
	HLA-A	HLA class I molecule	HLA class I and class II alleles[5]	184		Poland et al. 2008
	IL6, IL12B, IFNB1	cytokine	candidate SNPs in cytokines[5]	184	SNPs in coding or regulatory region only	Poland et al. 2008
	IL1R1,IL2RA, IL10RA, IL12RB2, IL1RN	cytokine receptor	candidate SNPs in cytokine receptors[5]	184	SNPs in coding or regulatory region only	Poland et al. 2008
	NAPSA, GLMP, GM2A, DYNL1, SNX29, TAP2,FGD2	antigen transport and processing	GWAS and gene expression[6]	199	reproduced in second group (n=125)	Franco et al. 2013
	JUP, FBLN5	cell junction and adhesion	genotype and gene expression[6]	199	reproduced in second group (n=125)	Franco et al. 2013
	OAS1	antiviral response	genotype and gene expression[6]	199	reproduced in second group (n=125)	Franco et al. 2013
	LST1	lymphocyte proliferation inhibition	genotype and gene expression[6]	199	reproduced in second group (n=125)	Franco et al. 2013
	CHST13, PAM	metabolism	genotype and gene expression[6]	199	reproduced in second group (n=125)	Franco et al. 2013
	RPL14, NAPSB, DIP2A, LRRC37A4, NSG1, HRC2	various or unknown	genotype and gene expression[6]	199	reproduced in second group (n=125)	Franco et al. 2013
	IFNL3	cytokine	2 candidate SNPs in *IFNL3* gene[7]	196	reproduced in healthy volunteers (n=28)	Egli et al. 2014

[1] infants
[2] Indonesian population over 5 y of age
[3] schoolchildren
[4] influenza risk group according to ACIP
[5] 18–40 y old male Caucasians
[6] 18–40 y old males, ethnically homogeneous
[7] immunosuppressed patients

mostly in GWAS despite two main caveats: First, the replication of GWAS results proves to be difficult, and second, GWAS show at best statistical but not causal associations. In order to infer causal associations and to understand mechanistic details, the impact of SNPs has to be studied on several levels such as on the RNA or protein level as well as on the immune cell response and on the host antibody response[12] (see Fig. 2). However, it is reasonable to infer the first hypothesis from a genetic association with the host antibody response, because not every SNP that affects the RNA or protein level has a physiological effect.

Several factors complicate the replication of genetic association data: Many GWAS are insufficient for solid statistical analysis due to various reasons, e.g., an insufficient case/control ratio, an insufficient sample size or different case/control population groups. The linkage disequilibrium and thus the selected tag SNPs strongly influences the statistical power of a sample size and it is not clear to which extent tag and haplotype maps are transferable across population groups.[86,88] Furthermore, the required sample size increases with the number of tested SNPs (when investigating small effects) and decreases for high minor allele frequencies and high prevalence of the investigated phenotype (e.g., weak antibody response to vaccination).[86,89,90] This is the reason why GWAS that test few SNPs in risk groups need relatively low sample sizes. In contrast, a healthy group may show a very robust immune response such that a large group needs to be tested to find a particular geno-/phenotype association. In a less robust patient cohort, e.g., after transplantation, lower patient numbers may depict a particular phenotype. However, confounding effects such as differences in the level of immunosuppression must be ruled out thoroughly. A further caveat is that definitions of vaccine response phenotypes and tests are often not standardized. The surrogate marker "seroprotection" has an arbitrary titer for different pathogens, e.g. >1:40 for influenza. Conventional serological parameters can seriously over- or underestimate the clinical protection of an individual.[91]

However, if no prior knowledge of vaccination-related genes exists, a GWAS can be helpful to propose a first hypothesis[86]: A GWAS identifies a broad set of candidate genes and alleles associated to a vaccine induced antibody level, which then need to be replicated and associated to further vaccine response phenotypes, such as cytokine profiles. Several papers have highlighted that the careful design of a GWAS significantly improves its quality.[86,89,90] Subsequent case-control studies are required to confirm the first findings and, finally, the exploration of SNP impacts on RNA, protein and immune cell level will complement GWAS results and help to understand the underlying mechanism behind genotype-associated vaccine response (see Fig. 2).

Although various genetic associations with vaccine response already have been proposed, only few replication studies and subsequent research studies have been performed. In contrast to vaccine research, the research of genetic factors for cancer susceptibility and cancer therapy is more advanced.[92,93] A bibliometric analysis of recent

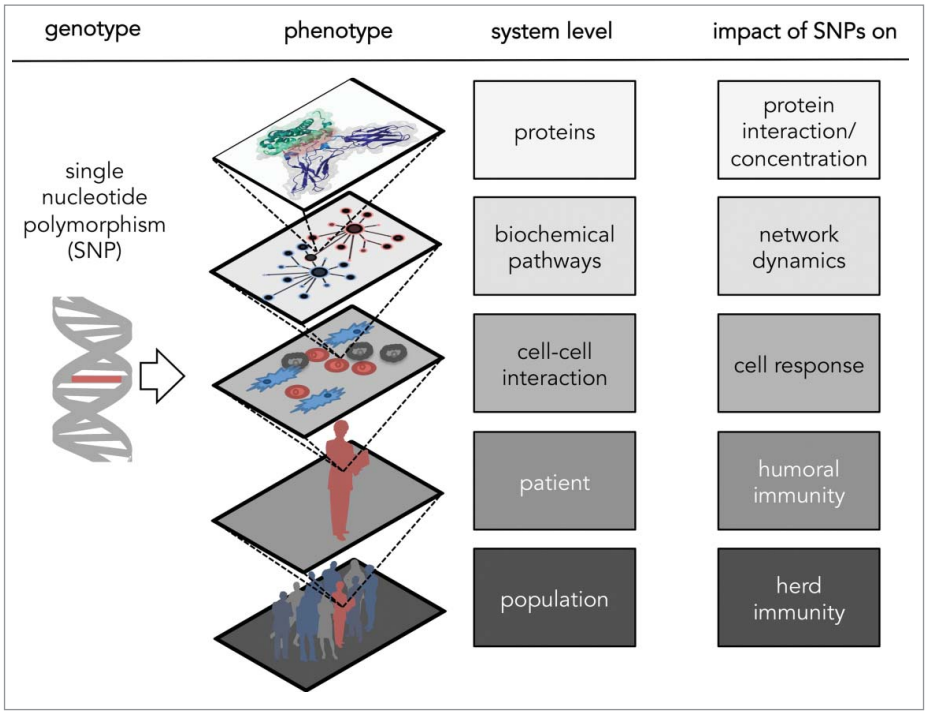

Figure 2. Multiscale impact of single nucleotide polymorphisms (SNPs).

publications in vaccine and/or SNP related research reflects the current scientific landscape (see Fig. 3; [94]): Although immunobiological research (green cluster) shows close proximity to genetic studies (blue cluster), vaccine research and clinical studies (red cluster) are almost separated from genetic studies. In contrast, cancer research (yellow cluster) highly overlaps with both genetic studies and immunobiological research.

Experimentally validated mathematical models unravel mechanistic details

Systems Biology applies mathematical models to test mechanistic hypotheses on biological processes: For instance, transport and recycling processes of cell surface recepors or signaling pathways are simulated and the simulation results are validated against experimental data.[95,96] Such mechanistic models can be

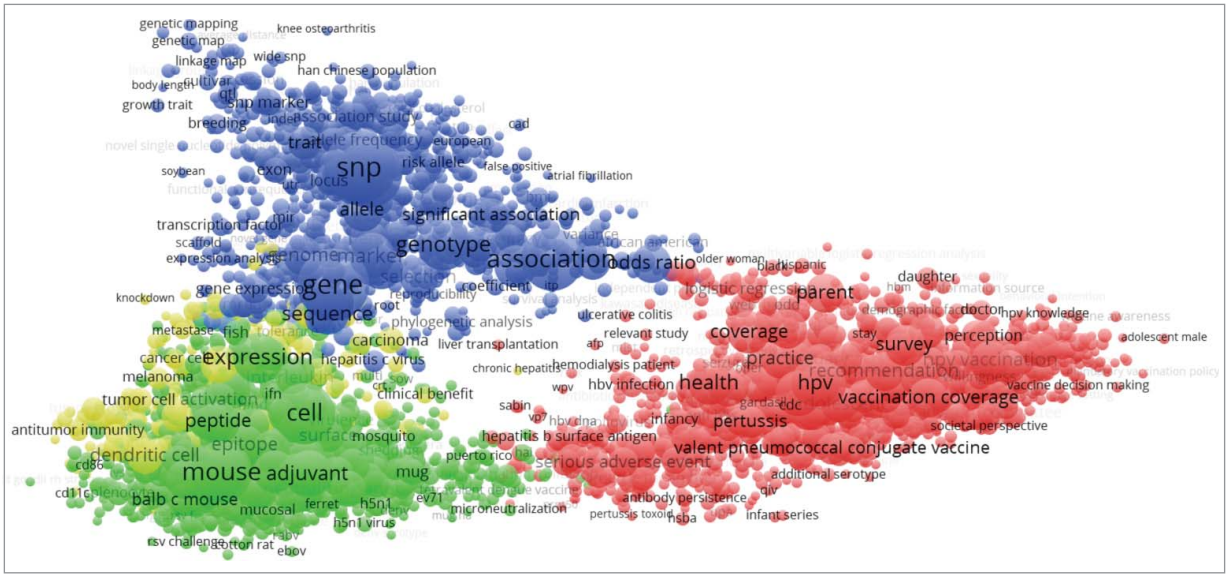

Figure 3. Bibliometric map automatically created with Visualization of Similarity (VOS) viewer. Scientific terms are clustered with respect to their co-occurrence in title and abstract of PubMed references, which are published over the last 3 y (2013/01/01 - 2015/08/14) with 'vaccination', 'vaccine', 'humoral immune response', 'single nucleotide polymorphism(s)' or 'SNP(s)' in title. Term proximity reflects co-occurrence and term size reflects occurrence frequency. Genetic terms (blue cluster) overlap with cancer terms (yellow cluster) and show close proximity to immunobiological terms (green cluster). In contrast, clinical and vaccination terms (red cluster) are almost separated from genetic terms. Bridging terms are for instance 'liver transplantation', 'chronic hepatitis' and 'ethnicity'. In total, 4,366 terms from 16,658 references are clustered.

also applied to test hypotheses on how SNPs modulate the immunological signaling network and cause the observed variability in vaccine response: Cell signaling and effector cell communication can be formalized in mathematical models and simulated.[97,98] The consequences of the investigated genetic polymorphism need to be implemented, for instance in the form of changes in protein concentration or changes in kinetic factors. If the simulation results do not match the observed vaccine response phenotype, further experiments are required to identify missing parts in the model such as crucial interactions. If simulation results match experimental results, perturbation experiments can be applied to test the predictive power of the model: for instance, antagonists can be used to block cytokine receptors. If the model is able to predict the impact of such perturbations, it can be further used to test modifications for improved antibody response. If the experimental tests do not show the same results as the model, the model has to be validated again. This iteration between experiments and mathematical modeling helps to unravel crucial interactions involved in vaccine response. Finally, such models can be used to predict the vaccine response based on patient data. Predictive models enable *in silico* experiments, for instance to determine potential adjuvant targets or to suggest personalized vaccination strategies (e.g., antigen amount and vaccination frequency).[13,99,100]

Conclusion

In summary, the association of SNPs and vaccine outcome has just begun. Important steps for a more profound understanding of these associations will be the mechanistic exploration of the impact of SNPs through an integrative analysis of gene expression, protein and immune cell data and their integration in mathematical models. In the near future we hope to use this knowledge to improve current vaccine strategies and develop new types of vaccines.

Abbreviations

CD	Cluster of differentiation
CMV	Cytomegalovirus
GWAS	Genome-wide association study
HAI	Hemagglutination inhibition assay
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IFN	Interferon
IL	Interleukin
JAK	Janus kinase
MAF	Minor allele frequency
MyD88	Myeloid differentiation primary response protein 88
NF-κB	Nuclear factor-κB
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PEG-IFN	Pegylated interferon
PRR	Pattern recognition receptor
RBV	Ribavirin;
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism
spp	Species pluralis
STAT	Signal transducer and activator of transcription
Th1	T helper cells type I
Th2	T helper cells type II
TICAM1	TIR domain containing adapter molecule 1
TIR	Toll/interleukin-1 receptor
TLR	Toll-like receptor
UTR	Untranslated region

Disclosure of potential conflicts of interest

The authors have no conflict of interest and nothing to disclose.

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