

Vaccination in autoimmune diseases: a blessing in disguise?

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Infections and vaccinations are often associated with the development of autoimmune diseases (AID). Infections may trigger AID via antigen-specific (molecular mimicry) or antigen-nonspecific mechanisms (bystander activation). By contrast, a protective role of infections has also been proposed. The hygiene hypothesis proposes that infections are responsible for educating our immune system, thereby maintaining the balance between activation and suppression. Among others, important factors in maintaining this balance are regulatory T cells and heat-shock proteins. Several studies have focused on disease activity and antibody formation after influenza vaccination in rheumatoid arthritis or systemic lupus erythematosus. In general, disease activity was not affected by this vaccine and antibody responses were adequate. Of interest, some studies included patients using methotrexate and/or tumor necrosis factor- α receptor blockade. Although the reported influenza antibody responses were often reduced, there appears to be no published evidence that the clinical course of influenza is more severe in these cases. The alleged relation between vaccination and AID has resulted in avoiding vaccination in patients with established AID, such as juvenile idiopathic arthritis (JIA). However, this strategy is not supported by a large volume of clinical evidence. The effects of influenza vaccine in JIA were the most studied, and no increased disease activity or serious side effects were reported. There are no large-scale studies on the use of the measles, mumps and rubella (MMR) booster in children with AID. Several studies reported side effects of a variety of vaccines in children and adults. These data were obtained from health authority registries. From these data, thrombocytopenia (idiopathic thrombocytopenic purpura-like) was accepted as an adverse effect of MMR vaccination and arthritis has been associated with rubella vaccination in young women. As microbial exposure decreases, the role of vaccinations in educating our immune system increases. Besides achieving protective immunity, vaccines should educate our immune system. In this way, vaccines might prevent infections as well as AID.

Pathogenesis of autoimmune disease

The incidence of autoimmune diseases (AID) has increased over the last few decades and the pathogenesis of these diseases remains a matter of research. It is generally assumed that AID arise in genetically predisposed patients after environmental triggers. Many factors are recognized as possible triggers, among others, infections and vaccinations [1–3].

It appears logical that factors directly involving the immune system, such as infections and vaccinations, are also capable of disrupting the existing homeostasis in this system. This may lead to abnormal immune responses directed against host tissue. These autoimmune responses do not necessarily result in AID [3]. Clinical manifestations occur only if additional disease-favoring factors are present, such as local inflammation [4]. A distinction should be made between the effect of infections and vaccinations on the onset of AID (etiology) and the effect on exacerbation of ongoing AID. Understanding the pathogenesis of AID and the role of

infections in this process could enable us to balance the risks and advantages of vaccinations in relation to AID.

First, the effect of infections on the development of AID is described in this article. Several mechanisms of inducing AID, homeostatic mechanisms to prevent AID and the danger theory are described. Next, the protective role of infections and possible mechanisms are discussed, with emphasis on the possible relation of the hygiene hypothesis with regulatory T cells and heat-shock proteins (Hsps). Subsequently, the role of vaccinations on the development of AID and also its influence on established disease, mainly chronic arthritis, is described. To conclude, the liaison between the various hypotheses and mechanisms is outlined and united in future perspectives.

AID & infections

Induction of AID by infections

There is little doubt that certain infections may trigger the onset or enhance the activity of AID [5]. Various viral, bacterial and parasitic infections

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have been linked to several AID [1]. For example, Epstein–Barr virus, parvovirus B19 and rubella virus have been reported to be linked with chronic arthritis and juvenile idiopathic arthritis (JIA) [1,6]. Several bacterial infections can cause AID. For example, rheumatic fever can develop after group A β -hemolytic streptococcal infection [7], *Mycobacterium tuberculosis* and *Proteus mirabilis* have been associated with rheumatoid arthritis (RA) [1] and *Shigella*, *Salmonella*, *Yersinia* and *Campylobacter* spp. may cause reactive arthritis and possibly also RA [8]. The mechanisms involved are not fully elucidated, but extensive research has provided a better understanding of the role of infections.

Mechanisms of AID induction by infections

In a genetically predisposed individual, an infection can trigger AID via antigen-specific or antigen-nonspecific mechanisms [3]. Viral persistence causing epitope spreading might also be of importance [9].

The antigen-specific mechanism involves adaptive immunity and depends on molecular mimicry [9]. Mimicry occurs when antigens of the microorganism and the host have similar epitopes. These similarities cause the host immune system to recognize itself. Mimicry involves B and T lymphocytes. B lymphocytes are activated through direct recognition of antigens of the microorganism. The activated B cells can subsequently cross-react with antigens expressed by host tissue, leading to autoimmune

reactions and the formation of autoantibodies. Microbe-reactive T lymphocytes recognize their antigen when it is degraded to small immunogenic peptides and presented by major histocompatibility complex (MHC) molecules. The activated T cells subsequently cross-react with self-antigens expressed by host tissue or presented by antigen-presenting cells (APCs).

The antigen-nonspecific mechanism involves the innate immune response and depends on bystander activation. Innate immunity influences subsequent development of the adaptive immune response to an antigen. In the absence of this nonspecific stimulus, the antigen-specific stimulus leads to anergy or apoptosis of the immune cell. Bystander activation results in additional immunopathology in the infected organ, thereby enabling AID to develop. Both humoral (co-stimulatory molecules, cytokines and complement) and cellular (macrophages, natural killer cells and APCs) components are involved [5].

During infection, microbial antigens activate APCs via Toll-like receptors (TLRs), resulting in upregulation of MHC molecules, expression of co-stimulatory molecules and secretion of cytokines. The inflammation leads to tissue damage and release of self-antigen. Presentation of host antigen by activated APCs can then, with the appropriate co-stimulatory molecules and TLRs on the APCs, stimulate preprimed autoreactive T cells. Additionally, naive T cells are more likely to cross-react when an antigen is

Table 1. Relation between microbial exposure and autoimmune disease.	
Microbial exposure	Microbial deprivation (hygiene hypothesis)
Protection against autoimmune disease	Induction of autoimmune disease
Direct immunosuppression and antigen competition	Imbalanced activation of autoreactive cells
Deletion of autoreactive T cells and elimination of autoreactive T cells from target sites via chemokine gradients	Maintenance of autoreactive T cells and accumulation of autoreactive T cells at target site
Clonal expansion of microbe-specific T cells	Relative lymphopenia, leading to homeostatic lymphocyte proliferation with expansion of autoreactive T cells
Selective pressure to choose genetic polymorphisms in MHC genes that secure survival for the population as a whole	Change in make-up of MHC; genes due to lack of selective pressure caused by infections
Active T-cell regulation and induction of Tregs	No induction of Tregs, which causes a dysbalance in the immune system
Induction of autoimmune disease	Protection against autoimmune disease
Molecular mimicry between pathogens and host tissue	No risk of cross-reactivity
Bystander activation, with release of self-antigen and attraction of autoreactive cells	No risk of local tissue inflammation and priming of the adaptive immune response
Epitope spreading, with continuous activation of autoimmune reactions	No risk of continuous autoimmunity leading to autoimmune disease

MHC: Major histocompatibility complex; Tregs: Regulatory T cells.

presented in response to an infection [10]. Antigen-processing pathways are major features of autoimmunity. Antigens can be processed via either MHC class I or class II. In the former, the effector cells are CD8⁺ T cells. CD8⁺ T cells kill target cells directly after cross-reaction with an autoantigen, or initiate bystander activation. When antigens are processed via MHC class II, they are recognized by CD4⁺ T cells. The cytokines (e.g., tumor necrosis factor [TNF] and transforming growth factor [TGF]- β) released by activated CD4⁺ T cells attract additional autoreactive T cells and macrophages. The macrophages, in turn, cause bystander killing of the uninfected neighboring cells.

Finally, persistent (viral) infections with continuous antigen spreading may perpetuate these local inflammatory reactions, resulting in the development of overt AID [9].

Homeostatic mechanisms of the immune system

Autoimmunity should not be confused with AID. Autoimmunity is a feature of a normal immune system. This was stated for the first time in the danger theory [11]. This theory implies that the immune system does not care about self and nonself, but that its primary function is to differentiate between danger and nondanger. In order to activate antigen-specific cells, an additional second signal is required. These signals are provided by molecules or molecular structures released or produced by cells undergoing stress or abnormal cell death. Resting APCs are then activated to present the second signal and thereby initiate immune responses. Danger signals, such as TNF- α , interleukin (IL)-1 β and Hsps, enable the immune system to distinguish between harmful and harmless antigens [12]. Without a danger signal, autoreactive cells become tolerized. Autoimmune reactions only become pathogenic when the immune response is persistent and uncontrolled and autoreactive effector cells penetrate the target organ [4]. Numerous homeostatic mechanisms exist to prevent the development of AID, at the level of innate and adaptive immunity [3].

Defects in the innate immune system can lead to autoimmunity, since defects in apoptosis of antigen-bearing dendritic cells and defective clearance of apoptotic cells by complement factors can result in autoimmune syndromes [4]. Moreover, APCs have been shown to be required to induce T-cell tolerance to self-antigens [13].

Adaptive immunity, especially its lymphocytes, is also tightly regulated. T-cell responses to antigens are controlled by activation-induced cell death. Second, competition for antigen and growth factors by lymphocytes prevents excessive immune responses to autoantigens. Moreover, the T-cell repertoire is fine-tuned based on the receptor affinity for antigens. The activation of cells with high-affinity receptors is prevented through clonal exhaustion or deletion [14].

Finally, the immune response is controlled by regulatory T cells (discussed later). These cells are capable of suppressing the response to self-antigens [15].

Protection against AID by infections

In contrast to initiation or acceleration of autoimmunity, a protective role for infections against the development of AID has also been proposed [16]. Decreased exposure to infections may explain the increase in frequency of AID and allergic diseases in developed countries. As is reported for multiple sclerosis (MS) and Type I diabetes, a dramatic increase in the incidence of AID has been documented in the Western world [17,18]. The distribution shows a North–South gradient in Europe and North America, with a higher incidence in the northern countries [18]. Genetic factors could explain these variations, but since immigrants have an equally high incidence of AID as the native-born, environmental factors will play a major role [19]. Various environmental factors have been mentioned, among others, the absence of infection, as argued in the hygiene hypothesis [20]. It states that the relative deprivation of infections and microbial antigens in Western countries causes an imbalance in the immune system. This leads to the opportunity to develop AID or allergies/asthma, also termed ‘input deprivation syndromes’ [21].

Infections may protect against AID via various mechanisms [16], for example, via nonspecific suppression of immune responses. A well-known cause of infection-induced immunosuppression is the depletion of CD4⁺ T cells caused by HIV [22]. Second, antigenic competition between microbial and host antigens may lead to diminished or ineffective triggering of phagocytes and autoreactive T cells. Third, strong inflammation at sites other than the target site of autoimmune destruction may attract autoaggressive lymphocytes away from their site of action owing to chemokine gradients. In addition, ongoing autoimmune reactions with over-expression of cytokines could induce apoptosis of autoreactive lymphocytes.

Table 2. Vaccination studies in patients with autoimmune diseases.

Vaccine	Disease	Medication used	Effects on disease activity	Reported side effects	Antibody response	Ref.
Influenza	RA (n = 10) SLE (n = 14)	NSAIDS, MTX?	Unaltered	None	Normal	[55]
Influenza	RA (n = 149) RA (n = 82)	NSAIDS, MTX, TNF	Unaltered	None	Normal to decreased	[56,57]
Influenza	SLE (n = 56)	CS, HC, AZA	Unaltered	None	Normal to decreased	[65]
Influenza	JIA (n = 34)	NSAID, MTX	Unaltered		Normal	[52]
Influenza	JIA (n = 49) SLE (n = 11)	NSAID, MTX, CS	Unaltered		Normal	[50]
Hepatitis B	JIA (n = 31)	MTX, CS	Unaltered	None	Normal	[51]
MMR	JIA (n = 207)	MTX, CS	Unaltered	None	Not tested	[62]
Meningococcal C	JIA (n = 234)	NSAID, MTX, CS	Unaltered	Same as controls	Normal to decreased	[53]

AZA: Azathioprine; CS: Corticosteroids; HC: Hydroxychloroquine; JIA: Juvenile idiopathic arthritis; MMR: Measles, mumps and rubella; MTX: Methotrexate; NSAID: Nonsteroidal anti-inflammatory drugs; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; TNF: Agents blocking TNF- α receptor.

According to the hygiene hypothesis, infections might be responsible for maintaining the delicate balance between activation and regulation of our immune system [20]. This hypothesis states that the maturation of our immune system is influenced by infections. In order to function correctly, the immune system must learn from the environment. Control mechanisms of the immune system can be activated by appropriate exposure to pathogens. Factors that play a key role in the hygiene hypothesis include regulatory T cells (Tregs) and Hsps. Tregs are specialized subsets of T cells that are of major importance in keeping the balance via immune suppression. There are two different types of Tregs. Naturally occurring Tregs are positively selected in the thymus and express CD25 and FoxP3 (a transcription factor) [23]. They can prevent the activation of autoreactive T cells and therefore maintain the tolerance to self-antigens [24]. Their mechanism of action remains uncertain. However, direct cell–cell contact and expression of surface molecules appears to be required [25]. Adaptive Tregs include type 1 Tregs and T-helper type 3 cells, and are induced in the periphery after pathogen exposure [26]. Their induction is dependent on the type of presentation by APC, cytokine profiles and the presence of low-dose antigen. Adaptive Tregs may also be induced via linked suppression. In this process, an alloreactive T cell is re-educated by a Treg when both cells recognize an antigen presented by the same APC. In order for Tregs to become activated,

they require antigen recognition. Other requirements for *in vivo* suppression are the capacity to home to and proliferate in draining lymph nodes and to migrate into inflamed tissue [25]. Adaptive Tregs can produce high amounts of inhibitory cytokines (IL-10 and TGF β) and have suppressive capacity.

How do these Tregs exert their regulatory function? Our group focuses on the role of Hsps in relation to Tregs and AID. Hsps are present in all eukaryotic and prokaryotic cellular organisms. They are upregulated when a cell is under stress, for example, during inflammation [27]. With reference to the danger theory, Hsps can serve as danger signals via stimulation of APCs [12]. Different families of Hsps mediate this stimulation. For example, Hsp60 and -70 activate APCs via the TLR family.

Hsps are highly conserved during evolution, resulting in substantial overlap in amino acid sequence between microbial and mammalian Hsps. Therefore, it was initially expected that recognition of self-Hsp by T cells would induce autoimmunity. However, Tregs that recognize self-Hsp60 are capable of down-regulating inflammation, as was shown by an experimental model of adjuvant arthritis [28]. In this model, mycobacterial Hsp60 is a relevant antigen for T cells [29]. Surprisingly, in contrast to inducing disease, preimmunization with mycobacterial Hsp60 protected against the induction of arthritis when administered nasally or mucosally [30]. This was mediated by the cross-recognition of

self-Hsp60 by Tregs [31]. Since Hsps are upregulated under stress, Tregs recognize their antigen primarily at the site of inflammation and cause local downregulation of the immune response. Indeed, increased expression of self-Hsp60 can be found in inflamed synovial tissue from patients with RA and JIA [32]. In children with JIA, Treg frequency and T-cell reactivity to self-Hsp60 were associated with disease remission and a favorable prognosis [33]. Furthermore, specific epitopes of Hsp60 were discovered to which JIA patients had tolerogenic immune responses [34].

Thus, self-Hsp60-reactive T cells are present in the adult immune repertoire and are capable of downregulating inflammation. Hsps can induce immune regulation by several mechanisms [20].

One mechanism is mucosal tolerance. Tolerance for bacterial Hsp is induced in the gut-associated lymphoid tissues. The environment of the gut is tolerogenic, since it would be highly inconvenient to elicit an immune response against every antigen that is presented in the gut. In this environment, T cells are continuously exposed to conserved bacterial Hsps, causing the T cells to adopt a regulatory phenotype, reflected by the production of regulatory cytokines (IL-10 and TGF β). The upregulation of Hsp at sites of stress (e.g., inflammation), will attract these Tregs, which can subsequently balance the inflammatory response [35].

A second mechanism involves the induction of anergic peripheral T cells. Nonprofessional or nonactivated APCs present self-Hsp constitutively without co-stimulatory molecules. This will force the T cells into an anergic state. These anergic T cells can suppress T cells reactive to self-Hsp presented by professional or activated APCs in inflamed tissues.

Another mechanism is altered peptide ligand regulation, where peptides that trigger T cells with high affinity promote a pro-inflammatory response. By contrast, slightly altered peptide ligands that trigger T cells with low affinity promote an anti-inflammatory response. After positive thymic selection, T cells with intermediate affinity receptors for self-Hsp60 are part of our immune repertoire. T cells that are reactive to microbial-Hsp in the gut perceive self-Hsp as partial agonists or altered peptide ligands with a low affinity and develop a regulatory phenotype [36].

Apart from the protective role of Tregs in AID, other groups have demonstrated the importance of Tregs in infectious diseases [37]. A

delicate balance exists between protection and pathology. Tregs may limit effector responses, resulting in failure to control infections. On the contrary, Tregs may help to modulate excessive immune responses, thereby limiting tissue damage [37].

In conclusion, Hsps and Tregs might explain why increased hygiene can cause an imbalance in our immune system, resulting in AID and allergies/asthma. Continuous exposure to bacterial Hsp60 will skew the immune response to self-Hsp60 into a regulatory type. Without the exposure to microbial antigens, there will be a lack of regulatory T-cell responses to self-Hsp.

In this context, it is interesting what microbial antigens we are discussing. Are the childhood infections that we vaccinate for also the infections necessary to elicit regulation of our immune response? In our view, it is highly unlikely that vaccinations will play a detrimental role, since they prevent only a limited number of all possible infections. By contrast, much attention is being paid to ordinary constituents of the commensal microflora and parasites. In Western countries, these so-called old friends disappear, and are harmless and capable of triggering immune regulation in the host [38]. For example, the incidence and severity of adjuvant arthritis can be modified by changing the commensal bowel flora [39].

AID & vaccinations

Theoretically, if infections can trigger AID, modified forms of infections (i.e., vaccinations) might also do the trick. However, the homeostatic mechanisms active during infections are also applicable to the host response to vaccination. When discussing the role of vaccinations in AID pathogenesis, it is important to make a distinction between the role of vaccination in initiating AID (etiology) and its role in exacerbating established AID [40].

Vaccinations & initiation of AID

Over the years, many vaccinations have been associated with the development of AID. Based on current available evidence, autoimmune adverse effects after vaccination have been confirmed in some cases. The Institute of Medicine of the National Academy of Science in the USA has accepted thrombocytopenia (idiopathic thrombocytopenic purpura-like) as an adverse event of measles, mumps and rubella (MMR) vaccination [41,42]. Additionally, chronic arthritis in women was accepted as an adverse effect of

rubella vaccination [43]. Interestingly, the risk of thrombocytopenia and chronic arthritis after MMR vaccination was lower than after wild infection [41].

Several case reports exist of subjects that developed AID after various vaccinations and evidence has been extensively reviewed [1–3,41,44–47]; although, interesting questions remain unanswered. Would these subjects also have developed AID without vaccination? Would they have developed AID had they been exposed to the wild infection? Several arguments against a causal relation between vaccination and AID exist. As described above, well-controlled epidemiological studies do not support the hypothesis that vaccines cause autoimmunity [2,47]. It is, however, uncertain whether available epidemiologic tools are sensitive enough to detect a link between vaccination and AID.

Second, since the incidence of AID has increased and these diseases develop in individuals in age groups that are selected for vaccination, one can question whether the alleged association is not merely a coincidence, rather than a consequence. Additionally, wild-type viruses and bacteria are much better adapted to growth in

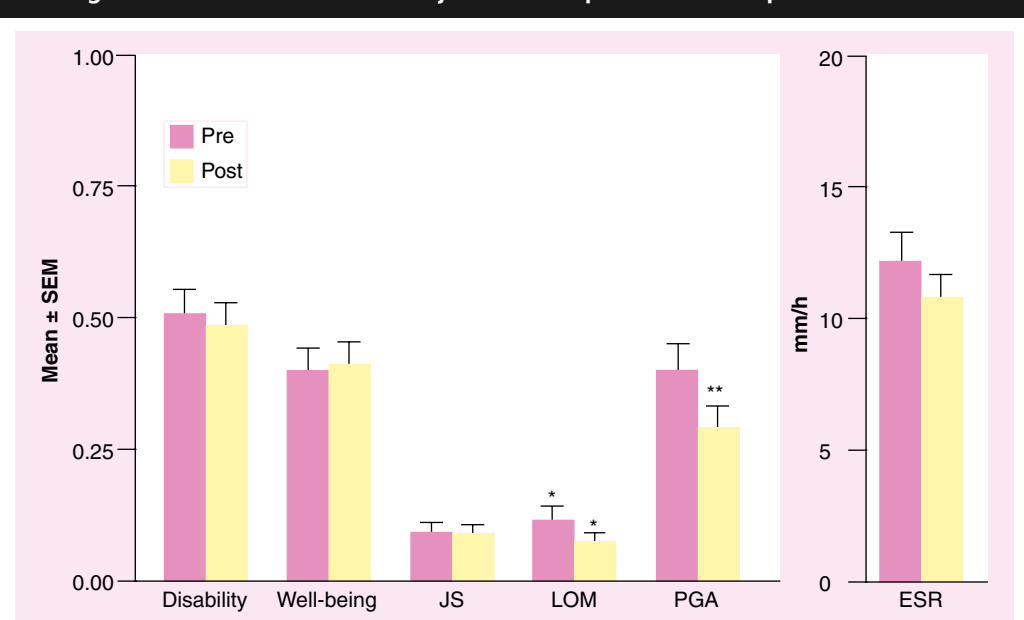
humans than vaccines and much more likely to stimulate self-reactive lymphocytes [2]. Therefore, the risk of autoimmune reactions after vaccination should always be compared with these risks after natural infection.

Mechanisms that are responsible for AID development after vaccination are the same that apply for infections, as described above. Again, molecular mimicry between vaccine and host epitopes and bystander activation appear to play a role. In addition, formation of immune complexes and the induction of autoimmune responses by adjuvant material in vaccines can be of importance [45]. At any rate, in order to develop an AID after vaccination, self-reactive T or B cells, self-antigen and additional signals, such as cytokines, must be present. Furthermore, regulatory T cells and other homeostatic mechanisms must fail to control destructive autoimmune responses.

Vaccination & the exacerbation of AID: vaccination versus chronic arthritis

The alleged relation between vaccination and arthritis has resulted in concerns about vaccinating patients with established AID, such as JIA.

Figure 1. Mean \pm SEM of core set criteria 3 months before and 3 months after meningococcal C vaccination in 234 juvenile idiopathic arthritis patients.



Pre: 6-month period before vaccination, Post: 6-month period after vaccination. Disability: childhood health assessment questionnaire, domain Disability; Well-being: childhood health assessment questionnaire, domain Well-Being; JS: active joints; LOM: joints with limitation of movement; PGA: physicians' global assessment of disease activity. Statistically significant differences between pre- and post-vaccination means are indicated as follows: * $p < 0.05$; ** $p < 0.005$.

ESR: Erythrocyte sedimentation rate; SEM: Standard error of measurement.

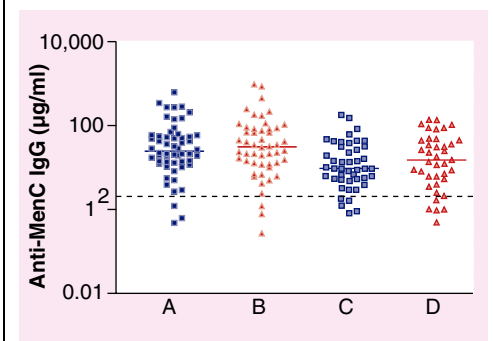
Adapted from [53].

In these patients, additional local danger signals are already present due to ongoing inflammation and tissue damage. It can also be possible that patients with established AID already have a failing immune homeostasis, for example, resulting from insufficient or nonfunctional Tregs [48,49]. Vaccinations may aggravate these ongoing autoimmune responses. However, with-holding vaccination puts patients at increased risk of infection. Studies considering vaccination of JIA and RA patients with dead vaccines failed to demonstrate a flare or clinical deterioration [50–56]. In a recent prospective study in a Dutch cohort of JIA patients, no changes in disease activity were seen in the 6 months before and after vaccination with meningococcal C vaccine, as shown in Figure 1 [53]. The number of disease flares in these intervals was also unchanged. Children using higher dosages of immunosuppressive drugs or combinations of such drugs had somewhat lower anti-MenC titers after vaccination using an enzyme-linked immunosorbent assay (Figure 2) [53]. In a serum bactericidal assay against the serogroup meningococcal C strain, all tested patients, including the four JIA patients with a low anti-meningococcal C IgG response, were, nevertheless, able to mount serum bactericidal assay titers of at least 8 [57]. These studies indicate that vaccination of JIA patients, with inactive dead vaccines, is safe.

The MMR vaccine, a live attenuated vaccine, and its relation to the development of chronic arthritis, has been extensively studied. It is known that wild rubella infection can cause acute arthritis, particularly in young females [58]. Chronic arthritis has been associated with persistence of rubella virus after vaccination in early, uncontrolled, observational studies [58]. By contrast, well-controlled, epidemiological studies failed to show this association [59]. Mostly, the connection between MMR and autoimmune reactions was temporal, not causal. However, although a causal relation between rubella vaccination and arthritis may exist, the risk of developing (chronic recurrent) arthritis after rubella vaccination is smaller than the risk of arthritis after a natural rubella infection [58,60].

We recently studied the effects of MMR vaccination on disease activity of JIA. We reported no increase in disease activity and medication use after MMR vaccination. This was also true for patients using methotrexate [61]. It is reassuring that vaccinations do not exacerbate JIA. This also accounts for vaccination of patients with other AID, for example, systemic lupus erythematosus [40] and MS [62].

Figure 2. Anti-MenC IgG levels and antirheumatic medication.



(A) No medication. (B) Nonsteroidal anti-inflammatory drug (NSAID) only. (C) NSAID and low dose methotrexate (MTX). (D) High dose MTX or combinations of disease-modifying anti-rheumatic drugs. A group of 157 juvenile idiopathic arthritis patients tested showed a significant rise in anti-MenC IgG geometric mean concentration (GMC) from 0.4 µg/ml before vaccination to 28.9 µg/ml after vaccination (range 1.0–1820.5 µg/ml; $p < 0.0005$). Anti-MenC IgG GMC were significantly lower in patients of medication groups C and D compared with GMC in patients of group A and B. For details, see [53]. Ig: Immunoglobulin; MenC: Meningococcal C.

Conclusion

The pathogenesis of AID and the role of infections and vaccinations is an exciting field of research. Infections might not only induce disease, but can also protect against autoimmunity. At any rate, infections are important in educating our immune system.

As yet, evidence does not indicate an increased risk of AID after vaccination. Additionally, vaccination appears not to aggravate established AID. Since decreasing herd immunity places patients with chronic AID at increased risks of infections, we recommend vaccinating patients.

It is reassuring that our immune system has sufficient homeostatic mechanisms to prevent development of AID. This does not imply that vaccinations have no influence on our immune system at all. Infections have a dual role in the etiology of AID, either initiating or protecting (as stated in the hygiene hypothesis). The same duality may account for vaccinations. At this point, the influences of hygiene and vaccines on AID intertwine. Both hygiene and vaccination cause a decrease in infections. With regard to the development of AID, this might either be positive (less induction) or detrimental (less education and therefore, less regulation). Since

our exposure to (harmless) pathogens decreases, owing to better hygiene, the role of vaccinations in educating our immune system increases. However, current vaccinations might not be able to educate our immune system, since most vaccinations replace infections with a different type of immunological stimulus. In contrast to naturally occurring infections, this stimulus might fail to induce Tregs, thereby indirectly

leading to AID in due course. In our view, it is unlikely that vaccinations will play a direct detrimental role in this context. Vaccinations prevent only a limited number of all possible infections. However, the role of vaccinations in educating our immune system increases. This should be considered when developing new vaccines; future vaccines could and should compensate for this.

Executive summary

Pathogenesis of autoimmune disease

- Infections and vaccinations have been associated with triggering autoimmune diseases.

Induction of autoimmune diseases by infections

- Antigen-specific mechanisms include molecular mimicry.
- Antigen-nonspecific mechanisms include bystander activation.

Homeostatic mechanisms of the immune system

- Autoimmunity is a feature of a normal immune system and numerous homeostatic mechanisms exist to prevent the development of autoimmune diseases.
- Apoptosis of antigen-presenting cells and clearance of apoptotic cells by complement factors regulate autoreactive immune responses at the level of the innate immune system.
- T cell responses to autoantigens are controlled by activation-induced cell death, antigen and growth factor competition, clonal exhaustion or deletion, and fine-tuning of the T-cell repertoire based on the receptor affinity for antigens.
- Regulatory T cells (Tregs) are capable of suppressing the response to self-antigens.

Protection against autoimmune diseases by infections

- Infections might protect the host by nonspecific suppression of the immune response, antigenic competition, confiscation of autoaggressive lymphocytes from their site of action and apoptosis of autoreactive lymphocytes due to over-expression of cytokines.
- The hygiene hypothesis states that insufficient exposure to infections and microbial antigens in Western countries causes an imbalance in the immune system. This leads to the opportunity to develop autoimmune diseases.

Mechanisms underlying the hygiene hypothesis: Tregs & heat-shock proteins

- Tregs play a dominant role in maintenance of self-tolerance.
- Heat-shock proteins (Hsps) are upregulated when a cell is under stress and Tregs that recognize self-Hsp60 are capable of downregulating inflammation.
- Hsps can induce immune regulation by mucosal tolerance, by induction of anergic peripheral T cells and via altered peptide ligand regulation.
- Repetitive exposure to bacterial Hsp60 will skew the immune response to self-Hsp60 to a regulatory type. Ordinary constituents of the commensal microflora and parasites appear to play a role in triggering this immune regulation in the host.

Role of vaccinations in the induction of autoimmune disease

- Some autoimmune adverse effects after vaccination have been confirmed.
- Idiopathic thrombopenia is an accepted adverse effect of measles, mumps and rubella (MMR) vaccination.
- Vaccinations replace infections with a different type of immunological stimulus, which might fail to induce Tregs.

Vaccination versus juvenile idiopathic arthritis

- The alleged association between vaccination and arthritis resulted in concerns about vaccinating patients with established autoimmune diseases.
- Studies considering vaccination of juvenile idiopathic arthritis (JIA) patients with dead vaccines failed to demonstrate a flare or clinical deterioration.
- The MMR vaccine, a live attenuated vaccine, did not increase disease activity or medication use in children with JIA.

Future perspective: generation of new, safe & effective vaccines

- A good vaccine produces protective immunity, educates the immune system and induces the formation of Tregs. Molecular mimicry and bystander activation must be prevented.
- Hsps might serve as excellent adjuvants in future vaccines, because of their strong immunogenicity and their capacity to activate Tregs.
- Future vaccines might prevent infectious diseases as well as autoimmune diseases.

Future perspective: vaccination against AID

Theoretically, a good vaccine has several requirements. Nowadays, its main goal is to achieve protective immunity. However, ideally it should also educate the immune system and induce the formation of Tregs [20]. In the mean time, molecular mimicry and bystander activation must be reduced to a minimum [3]. Hsps are capable of inducing immune responses that closely resemble natural infection. As adjuvants in future vaccines, Hsps might be able to elicit a

regulatory immune response in conjunction with the intended effect of forming protective antibodies to the pathogen. It is imaginable that vaccinations will be required for immunoregulatory mechanisms or even for therapeutic goals [62]. For example, Hsp peptides have already been used in clinical trials for treatment of RA [63]. New insight in infections, vaccinations and the pathogenesis of AID enables us to create new safe and effective vaccines. By using these vaccines in the future, we might be able to prevent infectious diseases and AID.

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