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Autoimmune Diseases of the Innate and Adaptive Immune System including Atopic Dermatitis, Psoriasis, Chronic Arthritis, Lyme Disease, and Alzheimer's Disease

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Abstract

In atopic dermatitis, we have recently shown the innate immune system is activated by biofilm-forming staphylococci that occlude sweat ducts. Toll-like receptor 2 (TLR 2) is activated and moves from its epidermal control location in the basal zone to the proximal stratum corneum (surrounding the occluded duct). There it likely initiates the MyD88 and the PAR 2 pathways in an effort to inactivate the staphylococci; these efforts are fruitless because of the biofilms and lead to the prime pathological finding of spongiosis and to the prime symptom of pruritus which leads to the disease. If the pruritus is intense enough to cause excoriations severe enough to disrupt the epidermis, the involvement of the dermis likely causes the activation of the adaptive immune system leading to the documented appearance of IL 31, another even more potent pruritogen.

We have also shown that the innate system is involved in psoriasis, again with TLR 2. This time it was present in the dilated upper dermal capillaries; TLR 2 has been shown to lead to TNFa, IL 12/23, and IL 17 which have all been shown to be involved in the production of psoriatic lesions. In this instance, the streptococcus is most likely the organism involved; it is not recoverable because it internalizes or makes biofilms, so TLR 2 instead of combating the bacterium attacks host cells. Anti-streptococcal IgG is markedly elevated in plaque psoriasis in one half the patients; it is of interest to postulate these patients were those who would develop the systemic findings of arthritis, uveitis, and the metabolic syndrome which develop in 40% of patients.

In chronic arthritis, Lyme disease, and Alzheimer's disease where the disease has been shown to be caused by Borrelia and dental spirochetes, TLR 2 is activated because of the presence of the microbes and their biofilms and leads to the chronic course noted in osteoarthritis, Lyme neuroborreliosis and Alzheimer's disease. When the adaptive immune system is involved, as in rheumatoid arthritis and after a stroke, it is curious that the disease occurs more rapidly and is much more destructive.

Keywords: Immunity; Adaptive immunity; Innate immunity; Atopic dermatitis; Psoriasis; Chronic arthritis; Lyme disease; Alzheimer's disease

Atopic Dermatitis

Atopic dermatitis, psoriasis, and chronic arthritis have long been considered autoimmune diseases. Alzheimer's disease and Lyme disease, however, have not been thought of in that light. In this work, we hope to elucidate how the innate and the adaptive immune systems interact with each disease to produce the familiar symptoms and signs of that disorder. Hopefully, this will provide a framework to approach other autoimmune diseases in similar fashion. Atopic dermatitis was an autoimmune disease with no known initial stimulus. It has been termed the "itch that rashes" with no known event preceding the itch [1]. Recently, the events leading to the disease have been shown to be as follows [2]: normal flora staphylococci make biofilms, occlude eccrine ducts, activate the innate immune system (Toll-like receptor 2 [TLR 2]), and set in motion known pathways that lead to pruritus, the primary symptom, and spongiosis, the primary pathological sign of the disease.

In the first instance, proteinase activated receptor 2 (PAR 2) is the pruritogen that is generated by TLR 2. In the second, TLR 2 activates the MyD88 pathway which leads to NFkB and TNFa which is the most important molecule in creating spongiosis [2]. This forms the environmental hit in the double hit phenomenon that is this disease. The genetic hit arises from the filaggrin gene that causes malformation of the stratum corneum or anything that causes disruption of that important outer layer of the skin. Examples of this are Malassezia yeasts in seborrheic dermatitis and dermatophytes in tinea pedis [3]. Once the epidermis is breached (by scratching), the adaptive immune system, IL 31 for example, is activated allowing for continued (and worse) pruritus and tissue destruction [4].

The treatment of atopic dermatitis has been covered in depth recently, but it is of interest to note the importance of helping restore the stratum corneum (as well as reducing the inflammation) with attention to factors related to bathing. This is accomplished by less bathing, the use of less soap, less scrubbing, and more moisturization [5]. In this regard, treating the skin in this manner is one of the only times in medicine where it is possible to treat the genetic abnormality of the disease.

Psoriasis

Psoriasis is also an autoimmune disease with no known initial trigger. This has recently been shown to be streptococcus, which has long been known to be active in guttate psoriasis, but its importance

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in plaque psoriasis was inapparent [6]. The most likely reason for this is due to the behavior of this organism: it "hides" from view and is undetectable by culture. This "hiding" is accomplished either by internalization or by biofilm formation [7,8]; with internalization, bacteria would move intracellularly, remain there up to a year, and move out and recolonize. With the biofilm, bacteria would occasionally leave the biofilm and become apparent to the immune system as "exporter" cells before such time as they were able to attach and to establish new biofilms. Recently, soluble TLR 2 was noted in the upper dermal blood vessels in the pathology of the plaque psoriasis [9]. This correlates with the observation in psoriatic arthritis on blood monocytes [10]. This accumulation of TLR 2, similar to atopic dermatitis, also upregulates the MyD88 pathway which leads to TNFa that is so prominently noted in this disease. TLR 2 also leads to IL12/23, and IL 17 as well as TNFa [11-13]. Consequently the innate immune system has a role in this autoimmune disease.

The role of the adaptive immune system is not so clearly delineated. It is known that serum immunoglobulin G (IgG) is markedly elevated in plaque psoriasis [14]. It seems reasonable to postulate this elevation derives from the internalization of the organism: as microbes re-emerge from the cells, they would be exposed to the immune system, and an anamnestic response would ensue. It would further be interesting to postulate this IgG would be involved in the more severe signs and symptoms—arthritis, uveitis, and the chronic metabolic syndrome. This would correspond with activated immune system causing greater pathology than the innate in the other autoimmune diseases. As in atopic dermatitis, the microbe represents the environmental hit in the double hit phenomenon where the genetic hit is one of the family of PSORS genes [15].

There is even more evidence to show that the streptococcus is the etiologic agent in psoriasis: first, there are epidemiologic observations where it has been shown if there is no streptococcus in the environment, there is no psoriasis [16]. Moreover, if the streptococcus is treated for a considerable time with penicillin (as a sequela similar to rheumatic fever) it leads to total disappearance of the disease [17]. Tonsillectomy also leads to amelioration of the disease [18].

Chronic Arthritis

There are many missing links in the evaluation of arthritis as an autoimmune disease, but many of the components are in place. In osteoarthritis, for example, biofilms have been found in aseptic joints in those joints needing "re"-replacement as well as in joints needing replacement for the first time [19]. This type of arthritis has been very strongly linked to oral spirochetes as a source for the microbes responsible for the biofilms [20]. In the oral cavity, the spirochetes are well known for causing dental plaque, which itself is a biofilm [21]. If caught early enough, treatment with penicillin and a biofilm-dispersing agent will give resolution of the joint discomfort [22]. The 30% of patients who were not helped by this regimen required joint replacement within 3 months after completion. Thus, it is ineffective in the late stages of the disease because the disease destruction is too far advanced. Also, this indicates that osteoarthritis is a chronic infection. Also, because of the very chronicity, it indicates osteoarthritis is more likely to be an innate immune system disease as opposed to an adaptive response.

Rheumatoid arthritis where an antibody is present is much more rapid in onset and much more destructive [23]. This adaptive arm of the immune system is far more capable of devastation because of the many ways of killing it has in its arsenal, such as complement, alternate pathway, killer T cells, TNFa and many others [22].

Alzheimer's Disease

Alzheimer's disease has not previously been considered an autoimmune disease, but with microbes, biofilms, and both the innate and adaptive immune systems at work, it has all the elements necessary. First came the recognition that organisms were in the brain on polymerase chain reaction (PCR) [24]; this confirmed earlier reports of their presence [25,26]. The microbes were identified as 75% dental spirochetes and 25% Lyme (Borrelia) spirochetes. Next, Alzheimer's disease was shown to have the very same pathology of plaques, neurofibrillary tangles, etc. as neurosyphilis (general paresis of the insane) which meant they were the same disease with the only difference being they were they were caused by different spirochetes - *Treponema pallidum* vs *Treponema denticola*, for instance [27].

The organisms have been shown to make biofilms (in the same areas of the hallmark plaques) and elicit an immune response [28]. TLR 2 has been shown to be upregulated adjacent to the plaques; this follows observations that TLR 2 is upregulated in neural microglial cells in Alzheimer's disease [29]. This whole process that occurs in tertiary neurosyphilis and in Alzheimer's disease takes many years to develop (up to 50 years). This points to the slow destruction that is part of the innate immune system.

The adaptive immune system causes much more destruction, much more rapidly than its counterpart. In traumatic brain injury and specifically in stroke (cerebrovascular accident), patients are at risk of getting Alzheimer's disease much more rapidly - 2 years vs 30-50 years. It has been shown that lymphocytes, after a stroke, enter the brain at the site of the trauma; moreover, IgG from the lymphocytes permeates a wide area of the brain [30]. Normally, the blood brain barrier prevents the lymphocytes from entering the brain. The IgG influx creates the destruction of the tissue because it cannot penetrate the biofilms coating the spirochetes and destroys the surrounding tissue (as an innocent bystander) [22]. Thus it is similar to the other disease with the innate system leading to chronic disease and the adaptive system leading to rapid widespread destruction.

Lyme Disease

Lyme disease is similar to arthritis both with regard to having many missing links in autoimmunity; however, it has microbes, biofilms and clinical findings that make it a likely autoimmune candidate. With the Borrelia spirochetes being found in the brains in Alzheimer's disease, [24-26] and with Montauk knee being a representation of Lyme arthritis, and with biofilms present in both joints and brains, all that is missing is proof of the innate immune system activity. However, increased activity of the adaptive immune system with IgG has been noted [31].

Random Thoughts

Keeping in mind the foregoing, some thoughts on autoimmunity are presented. In 1985, the incidence of leprosy worldwide was 6 million and in 2013 with the population of the world increasing, it was less than 1 million [32]. What happened? The only apparent change was the addition of rifampin to the ordinary treatment with Dapsone. Rifampin is a biofilm dispersing agent and would allow access to the mycobacteria by the Dapsone [33]. Are biofilms present in leprosy? Presently, it is undetermined, but amyloid is present in leprosy and inasmuch as amyloid is the infrastructure of biofilms, the possibility exists [4].

Similarly, rifampin added to 3 antimycobacterial drugs (levofloxacin, ethambutol, and azithromycin) resulted in remarkable clearing of cutaneous sarcoidosis [34]. This was a truly remarkable achievement, and may carry over to other forms of the disease.

Ten percent of patients with systemic lupus erythematosus have a false positive RPR, a non treponemal serologic test for syphilis based on phospholipids. It is of considerable interest that 10% of Borrelia spirochetes have a phospholipid in their walls [35]. What if the false positives were really not false? This seems not to be coincidental.

Thirty five percent of patients with Lyme disease, treated supposedly appropriately with doxycycline, have tertiary disease (arthritis or neuroborreliosis, for instance). 35% of patients with untreated syphilis have tertiary findings. The apparent similarity can easily lead to the conclusion that treatment with doxycycline is similar to no treatment at all [36].

Tertiary syphilis has been eradicated over the past three decades, with the exception of the AIDS epidemic where it resurfaced briefly [37]. Where the pathology of neurosyphilis and the pathology of Alzheimer's disease are the same (except for different spirochetes), penicillin administered before the onset of tertiary symptoms and signs would very likely eliminate this scourge just as it did syphilis. Timing of penicillin administration is yet to be determined, but patients with the APOe4 gene and those with traumatic brain injury should probably receive it immediately and at least biannually because of the ongoing nature of the disease [38]. Lyme disease is generally a one-time disorder, just as syphilis, except for the patients with repeated exposure to Ixodes tick bites; thus, a one-time treatment with Bicillin as in syphilis might logically be considered.

Pretreatment of dental work also would seem to be most reasonable (similar to pretreatment of joint or valve implants). The brain is seemingly more important to protect than implants. Otherwise, treatment incorporating penicillin and a biofilm-dispersing agent (such as citalopram or rifampin) would potentially stop or slow progression of Alzheimer's disease [22]. The damaged neural tissue is unable to regenerate unfortunately.

Summary

We have shown the essential ingredients in the autoimmune diseases we have presented to be microbes, biofilms or internalization, and the innate and the adaptive immune systems. Most microbes are capable of forming biofilms, but we have shown that certain ones have a predilection for the skin, the pharynx, the joints, and the brain. Once the biofilms are formed, the slime coats the microbes and does not allow penetration either by antibiotics or by the immune system. We have demonstrated how TLR 2 of the innate immune system is activated and is responsible for the chronic findings of atopic dermatitis, psoriasis, and Alzheimer's disease. It is very likely to be involved with osteoarthritis and Lyme neuroborreliosis as well.

The adaptive immune system, on the other hand is much more rapidly destructive in rheumatoid arthritis, and Alzheimer's disease occurring after a stroke. We have postulated how the upregulated adaptive immune system causes much more destruction in atopic dermatitis and psoriasis.

Treatment was alluded to, and the earlier it is begun in all diseases, but especially Alzheimer's disease is most highly recommended. The later it is begun, it is likely to require a biofilm-dispersing agent along with the antibiotic. The damage that had been caused is not reversible, especially as refers to neural tissue.

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