

Infectious Trigger of ANCA-Associated Vasculitides and Other Autoimmune Diseases

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Autoimmune reaction occurring subsequently to bacterial infection is a well known phenomenon. Reactive arthritis proceeding after bowel infection with pathogenic bacteria (e.g. *Campylobacter spp.*, *Salmonella enterica*) and rheumatic fever caused by infections of Group A streptococci are two familiar entities.

Nevertheless, the cause of many autoimmune diseases remains unsolved. Associations of various autoimmune diseases to certain HLA and non-HLA alleles are of concern and even genetic links between certain autoimmune disorders have been described [1]. Genetic associations partially explain why certain autoimmune diseases are more common in a designated population. Examples of ethnic predispositions are a high prevalence of Kawasaki disease in asian people while granulomatosis with polyangiitis (GPA), formerly termed Wegener's granulomatosis, is more common in caucasians.

Beside ethnic background female gender is associated to the formation of definite autoimmune diseases (rheumatoid arthritis, Sjögren's syndrome, poly- and dermatomyositis, and lupus erythematoses (SLE) [2]. In SLE the ratio of males : females is 1 : 9 [3] and early age at menarche (age ≤ 10 years), oral contraceptive use, and use of postmenopausal hormones increases the risk of SLE [4]. Consequently, it was suspected that action of estrogen promotes development of autoimmune diseases associated with female gender. In lupus-prone mice knock out of estrogen receptor alpha resulted in reduced SLE severity and was associated with prolonged survival. Interestingly, bone marrow derived dendritic cells and splenic B cells from estrogen receptor alpha knock out mice showed reduced inflammatory response after stimulation with TLR agonists [5] rising the question of infectious triggering of SLE.

Principally, infectious trigger might be achieved by at least two mechanisms, the formation of an inflammatory environment facilitating the formation of auto-immune processes and the generation of cross-reacting auto-antibodies as a consequence of an infection [6].

When attacking an infectious agent the immune reaction itself emerges an inflammatory environment lowering the threshold of auto-immune process formation. An example of tolerance breaking is applying tetramethylpenadecane (TMPD or pristane) to mice subsequently resulting in the formation of various anti-autobodies and TMPD-lupus. Pristane is an isoprenoid alkane found in various plants including marine ones and in high concentration in crude oil. It has to be emphasized that no further immuno-stimulation than the application of this substance was essential to break immune tolerance and to induce pristane-lupus [7]. A similar effect might be present when "auto-immune syndrome induced by adjuvants" (ASIA) occurs in human. In contrast to TMPD-lupus in mice only a minority of vaccinated individuals develop ASIA indicating that additional factors (genetic predisposition, other co-existing environmental factors) must be added to the application of adjuvants [7].

A related reason might also be causative when autoimmune disorders occur after treatment with various drugs. Hydralazine, procainamide, diphenylhydantoin were shown to induce lupus erythematoses in susceptible individuals. Moreover, disrupted silicone breast implants

induced a variety of autoimmune symptoms [8]. However, when immunogenic substance had been removed autoimmune symptoms disappeared [9]. On the other hand, it is also possible that molecular mimicry of foreign substances and "self" structures of the host organism resulted in the formation of cross-reacting antibodies thereby initiating autoimmune processes. The formation of cross-reacting antibodies may also happen as a consequence of the infection by a micro-organism. However, only for few cellular targets of auto-antibodies the microbial counterpart is known.

Nevertheless, Marshall and co-workers state that most auto-antibodies in real are cross-reacting antibodies targeting not cultivatable micro-organisms causing chronic infections of phagocytic cells. A key reaction to maintain chronic infection is interference with vitamin D receptor function which in turn eases other micro-organisms to cause infections resulting in a plethora of infecting micro-organisms accompanied by a polyclonal (auto-) antibody response. Instead of inhibiting the immune system with immunosuppressive drugs, Marshall and collaborators treat their patients with olmesartan in combination with antibiotics, e.g. minocycline, clindamycin and/or macrolide antibiotics, to clear occult infection of phagocytic cells. Olmesartan is an angiotensin II receptor antagonist ultimately used to treat high blood pressure. Marshall et al. assume that this drug normalizes function of the vitamin D receptor allowing the host organism the production of missing cathelicidin, beta-defensins and other endogenous anti-microbial substances. Instead lowering symptoms of auto-immune disease this treatment initially causes aggravation of symptoms when shifting the stalemate between immune system and micro-organisms toward an overbalance of the immune-response. The immune system might become stimulated even more when components of destroyed micro-organisms are released resulting in a deterioration of symptoms [10]. Therefore, patients treated in accordance to Marshall's protocol have to accept a long period of suffering (up to several years) before mitigation from autoimmune disease will be concrete. However, to date there are only few case reports about patients treated by this procedure available while studies are still lacking. According to the information given on the homepage describing this method (<http://mpkb.org/home/mp>) Marshall's protocol is restricted to Th1 driven auto-immune diseases.

SLE and GPA are examples of Th1 driven diseases characterized

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by predominance of T helper cells secreting IFN-gamma and IL 2. In contrast, Churg-Strauss-Syndrome (CSS) is a Th2 driven autoimmune disease predominated by IL 4 and IL 5 secretion [11]. GPA, CSS and microscopic polyangiitis (MPA) are diseases characterized by necrotizing vasculitides of the small vessels. These diseases are often accompanied by the formation of auto-antibodies targeting components of azurophilic granula of polymorphic mononuclear cells (PMN) called “anti-neutrophil cytoplasmic antibodies” (ANCA). Two major antigens of ANCA have been described: Proteinase 3 (PR 3) and myeloperoxidase (MPO). In indirect immune-fluorescence analysis with ethanol fixed PMN PR 3-ANCA lead to a cytoplasmic staining pattern (c-ANCA) while MPO-ANCA cause perinuclear fluorescence (p-ANCA). Patients suffering from MPA and CSS mostly exhibit p-ANCA while GPA patients most often have c-ANCA.

CSS patients initially exhibit allergic symptoms including asthma and eosinophilia. Subsequently a systemic necrotizing vasculitis develops. Commonly, GPA patients suffer from affections of upper respiratory tract before necrotizing systemic vasculitis causes damages of various organs. Most often kidneys and lung are affected. MPA is a systemic necrotizing vasculitis also resulting in damage of various organs. Again, vasculitis of kidneys and lung commonly hampers most of the problems. In clinical practice often it is not possible to differentiate disease entities GPA and MPA because in both diseases pauci-immune necrotizing glomerulonephritis most often is the key symptom to treat. Moreover, immuno-suppressive treatment of both diseases does not differ.

Therefore, it has been questioned whether both diseases are part of a single disease spectrum. Within the past 15 years many studies showed that both diseases probably have different genetic association. Nevertheless, the genetic impact on disease formation seemed to be small [12]. However, a recent genome wide association study using chip technology showed that patients with p-ANCA exhibit other HLA and non-HLA associations than c-ANCA patients. The associations of both patient groups also differed from those of healthy controls. Interestingly, associations of ANCA subgroups were stronger than association of disease entities [13] indicating different pathogenicity of c-ANCA and p-ANCA associated vasculitides. Recently, the epidemiology of GPA and MPA has been examined over a period of 22 years. While GPA exhibited a periodicity showing maximum incidence every 7.6 years no periodicity has been observed for MPA indicating infectious triggering of GPA but not of MPA [14]. Beside annual cycles increased numbers of incidence have been observed in winter declining in summer suggesting respiratory infections as a trigger of ANCA-associated vasculitides [15].

Beside epidemiological data there is more evidence of infectious triggering of ANCA-associated vasculitied, especially for GPA. In comparison to healthy individuals GPA patients are more often colonized with *Staphylococcus aureus* and colonized patients more often suffer from relapses than non-colonized patients [16,17]. Mostly, co-trimoxazole is an effective antibiotic to treat infections caused by *S. aureus* and MRSA. Treatment of GPA patients with co-trimoxazole induced stable disease remission [18] and reduced frequencies of disease relapses [19].

A staggering observation of molecular mimicry has been described to be involved in pathogenesis of GPA [20]. In order to generate high amounts of PR 3 the authors inserted DNA of the PR 3 gene into bacteria. Randomly the gene was integrated into bacterial DNA either in direction of the reading frame or back to front against the reading frame resulting in bacterial production of PR3 or a protein called

complementary PR 3 (cPR 3). Interestingly, GPA patients exhibited PR 3-ANCA as well as antibodies targeting cPR 3. In a mouse model the authors were able to induce formation of PR 3-ANCA by applying cPR 3-antibodies. In contrast to PR 3 protein lacking homology to microbial components amino acid sequence of cPR 3 protein exhibited similarities to a variety of microbial components. Therefore the authors concluded that an infection initially resulted in the generation of antibodies to a microbial component and subsequently in the generation of anti-idiotypic antibodies targeting the binding sites of the initially generated antibodies. Since the structure of these binding sites were homologous to that of cPR, anti-idiotypic antibodies were equivalent to PR 3-ANCA. Because of the variety of micro-organisms showing homologies to cPR 3 infection by a large number of micro-organisms may induce or aggravate GPA. Consequently, infections with various micro-organisms were described to be involved in GPA pathogenesis: *Blastomyosis dermatidis*, hepatitis C virus, cytomegalovirus, *Helicobacter pylori*. Moreover, a case of a patient suffering from severe cat scratch disease has been published. The patient developed retinal vein occlusion and a macular exudate resulting in residual macular degeneration and optic atrophy. Interestingly, the patient developed c-ANCA and titres of c-ANCA paralleled ocular inflammatory activity [21]. Cat scratch disease is caused by infections of *Bartonella henselae*. The major immunogenic antigen of *Bartonella henselae* is Bad A exhibiting similarities in the amino-acid sequence to cPR 3 in the range of 36–56% (unpublished data).

However, it has to be mentioned that in healthy controls and GPA patients the prevalence of cPR 3-antibodies did not differ challenging the theory of autoantigen complementarity in vasculitis associated with PR 3-ANCA [22].

Nevertheless, another spectacular finding gives clues on infectious triggering of ANCA-associated vasculitides. PR 3- and MPO-ANCA patients often also show antibodies to lysosomal membrane protein-2 (LAMP-2). In PMN LAMP-2 is located in azurophilic granules together with PR 3 and MPO. Interestingly, LAMP-2 epitope P41–49 is homologous to bacterial FimH present in various Gram-negative bacteria species, e.g. *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* [23,24].

Although this short report is far from being complete concerning the impact of infections to the formation of ANCA-associated vasculitides and other auto-immune diseases it is obvious that this relation merits attention not only from rheumatologists but also from medical microbiologists and infectious disease consultants. Therefore, you are invited to extent our knowledge of this topic by submitting articles to the Journal of Bacteriology and Parasitology. At this, you will have the opportunity to learn about the exceptional tools of the OMICS group: digital books, audio listening, language translation, and social networking.

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