A trigger database of autoimmune diseases to assess complex trigger-disease-relationships

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Abstract: - Studies on the development of immune diseases, such as rheumatoid arthritis RA, need to assess the potential environmental triggers that are active before the disease becomes obvious, and the genetic susceptibility of the patients in which these triggers act. Additionally, it is necessary to assess if the presence of such triggers in an arthritis prone patient will give rise to the immune reactions associated with RA or even triggering the development of RA. This knowledge would help not only to address much better the issue of causality of these potential triggers and the immune system, but also to design studies and methods for influencing the disease triggering immune events before the development of clinical symptoms of the disease. In this work here a database is suggested and a connected ontology of these triggers to show the various influences and feedbacks that are possible. Those have been observed so far only in single cases, which are difficult to reproduce scientifically due to the complexity of the immune system and the variety of triggers. In the context here, rheumatoid arthritis is the show case for all autoimmune diseases. The trigger database can also bridge the gap between systems biology and the medical immunology.

Key-Words: - trigger, immune system, rheumatoid arthritis, autoimmune disease, environment, database, ontology

1 Introduction

Rheumatoid arthritis RA is classically described as an autoimmune disease of unknown etiology, where genes and environment contribute to the development of the disease. Rheumatoid arthritis is only one of around 400 to 550 rheumatic diseases, and unfortunately, for most them the causes are not known. Rheumatic diseases altogether form one of the largest groups of human diseases.

Increasing evidence suggests that many rheumatic diseases result from interactions of predisposing genetic and environmental factors [1,2]. The complex nature of this heterogeneous group of diseases, and far more the complexity of the immune response, however, makes an understanding of their development difficult.

For many reasons, progress has been considerably slow in finding the infectious and non-infectious environmental agents that may trigger these diseases in genetically susceptible individuals. The investigation of environmental risk factors for the development of a human disease has traditionally relied on comparisons of disease incidence or prevalence in exposed and unexposed cohorts, and where possible in case-control studies. That approach, however, has not been able to track the influence of environmental triggers on development and process of these multifactorial immune diseases.

Knowledge about the complex interaction between one or several triggers and the immune system for these autoimmune diseases is essential for finding a solution or progress in finding the causes for the various autoimmune diseases.

2 Development of RA and the concept of triggers

RA is a disease defined by clinical criteria. The American College of Rheumatology ACR [3] lists a number of symptoms which have to be fulfilled, they are then linearly summed up and giving a number for the disease incidence as a measure for severity. A threshold is also defined by the sum of the symptoms: a sum less than the threshold can still show the symptoms but in a less severe way or in a fewer number of joints, while only a sum higher than the threshold is clinically defined as rheumatoid arthritis. Thus, we can expect different pathogenetic pathways to result in clinical conditions with enough similarities to be classified into the entity we currently call RA.

Rheumatoid arthritis is a chronic disease, and the known clinical symptoms of RA are representing already the chronic stage of the disease. Little is known about the early symptoms and the development of RA, since the doctoral visits are usually in the chronic stage.

Studies on early RA have just started in the last couple of years.

Often suggested in the epidemiology of RA is a role for infection as a susceptibility factor, although many other explanations are possible. Historically, it has been suggested that in European countries RA is a disease of recent onset, also named "new-world disease" [4]. Prehistoric skeletal remains from North American human populations show that the disease was present over 4000 years ago [5]. The hypothesis was posed that onset of RA is related to transmission of a relevant infection from the native population of the Old World to the colonizers [5]. RA was declining in incidence [6], with recent decreases of disease occurrence in populations thought to be genetically predisposed, such as the North Americans of European origin [7]. But other autoimmune diseases such as multiple sclerosis and Type 1 diabetes mellitus show increases. Although this may reflect changes in many environmental factors, changing rates of infection are as well a plausible explanation. Consistent with this are data suggesting a shift towards an old age at peak onset [8]. Such an effect would be consistent with a decline in infection in early life, which reduces the risk in such a group as they age.

Large parts of our understanding of disease development and progress is obtained from animal models, correlations of laboratory parameters with disease incidence, and clinical studies. Observing and reporting environmental factors including infections before the chronic stage of the disease are less in the centre of attention due to the difficulty in relating present infections with the immune disease. But the triggering of the disease might be many years in the past and is most probably less recognizable than the later chronic stage, otherwise there would be many more cases of early immune disease or early RA.

Disease progression in RA often is intermittent so the disease and its severity can be stabile over a long time till there is another deterioration of the disease. This batch wise deterioration supports the influence of several triggers over time, which not necessarily have to be the same triggers. Figure 1 gives a longitudinal view of the disease development in RA. It shows trigger events occurring before and during the onset of the first symptoms of undifferentiated arthritis towards the eventual fulfillment of the ACR criteria for RA, and the shifts in disease severity.

It can be hypothesized that there are specific symptoms in the early stages of these autoimmune diseases although they are most probable limited in time as well as limited in the severity of symptoms and the number of simultaneously impacted organs. Thus, the patients are not visiting a doctor if a joint only hurts a little or just for a few hours, but when the swelling or the hurting of the joints is getting increasingly permanent. There are no hints so far how long the onset of the disease might be before it becomes chronic. Looking at the chronic stages which can progress for decades it can be hypothesized, that the early stage could be equally long.

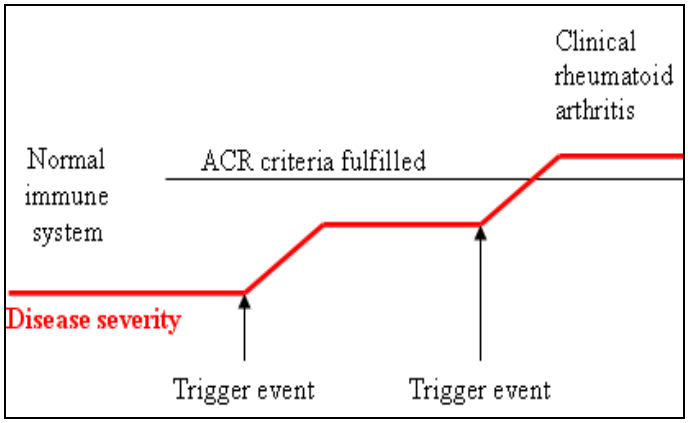

Figure 1: Triggered development of disease severity.

3 Potential triggers suggested for auto-immune diseases

There are several groups of triggers which are thought to have an impact on the course and severity of the symptoms of the autoimmune disease. Among the most mentioned are infection, smoking, sex, age, trauma, apoptosis, animal pets namely cats, family size, area of residence.

Viruses and bacteria have been mostly in the focus when looking for infections, but fungi are also mentioned. A special issue of infection might not be the infection itself but side effects like molecular mimicry, bystander effects, heat-shock proteins and protein-protein-interactions, as well as remnants and debris of the infecting organisms.

Studies have shown increased levels of antibodies to mycobacterial heat shock proteins in sera [9] of patients with RA, suggesting the possibility of a cross-reactive epitope. But experimental studies have failed to show any evidence of mycobacterial infection by culture or molecular techniques, and studies of anti-mycobacterial chemotherapy have failed to produce consistent improvement in disease [10–12]. Mycoplasma is known to cause arthritis in some animal species, and can last for at least a year. Most recent studies report an increased frequency of Mycoplasma infection in RA compared to controls, and a similar prevalence for infection is also reported in other chronic inflammatory rheumatic diseases [13–16].

Several studies have used PCR based techniques to look for heavily conserved sequences of bacterial DNA in synovial samples from a variety of rheumatic diseases. DNA from a number of bacterial species has been detected in synovial fluid [17,18], although no

consistent relationship between organism and disease is apparent from these studies except in cases of septic arthritis or post-chlamydial reactive arthritis. DNA from a wide variety of organisms, including Hemophilus, Bordetella, and Acinetobacter, were isolated from synovial fluid from patients with RA.

Parvovirus B19 infection is associated with short-lived arthropathy, with clinical similarities to RA, and with the possibility to develop a chronic rheumatoid pattern arthritis. But serological evidence of human parvovirus infection was very infrequent in a cohort study [19]. Epstein-Barr virus is often seen as a potential trigger. Serological and molecular evidence has been produced revealing coexistence of EBV infection and RA [20–22]. Epstein-Barr virus, however, has been frequently detected in the synovial tissues of RA patients [23].

4 Tracking the triggers

Although the concept of triggers is a rather old one, no progress has been made in this field due to the complexity of triggers and immune system, and additionally, due to the long time processes are developing in such diseases. An overview of the triggers exits only for a few selected agents. Most triggers are only named in single case reports of patients. The possible interaction of several triggers in a longer onset of the disease and their temporality is not possible yet. Several questions to be addressed in this context are:

- What triggers are involved?
- Was it a single trigger event or a multiple trigger event?
- In which order do all these events take place?
- How are these trigger events dependent on time?
- Are there thresholds for triggers to be effective?
- Are there delays in the disease progress and how long is the latency?
- Which immune reactions are associated with the triggers, and which immune reactions may actually cause the disease?
- In which genetic context are potential triggers of the disease associated with later emergence of the disease?

The solution for tracking these triggers is a database approach for all triggers possibly involved in the development of autoimmune diseases in their temporal and spatial heterogeneity. The database can facilitate the identification of these triggers, their impact on immune processes, the complex interaction between several triggers as well as between triggers and immune response. This database should store all observed possible triggers, description of anamneses, and other disease information as well as environmental information.

A possible further goal is to build a trigger ontology, revealing the relationships between triggers and the immune reaction. Furthermore, groups of similar functional relationships can be clustered as it was invented for the gene ontology.

5 Conclusion

During the past 50 years much has been accomplished in the definition and understanding of autoimmune diseases in terms of genetics, mechanisms of disease, and the role of environmental factors. But the origin of these diseases still remains in the dark.

A registry of all of the potential triggers and the search in patient's anamneses for these triggers at the earliest possible symptoms could be effective to find pathways and feedback loops in the complexity of single or multiple trigger events. Eventually hints on the long-lasting latency from infection to disease onset could be found in this way.

The database approach would enable researchers to get an overview of all the triggers that are at present investigated only on a single case basis.

It also opens up the possibility of future early assessment of the disease before it becomes chronic.

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