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Immunogenetic and immunological aspects of rheumatoid arthritis : DERAA and anti-citrulline reactivity can make the difference

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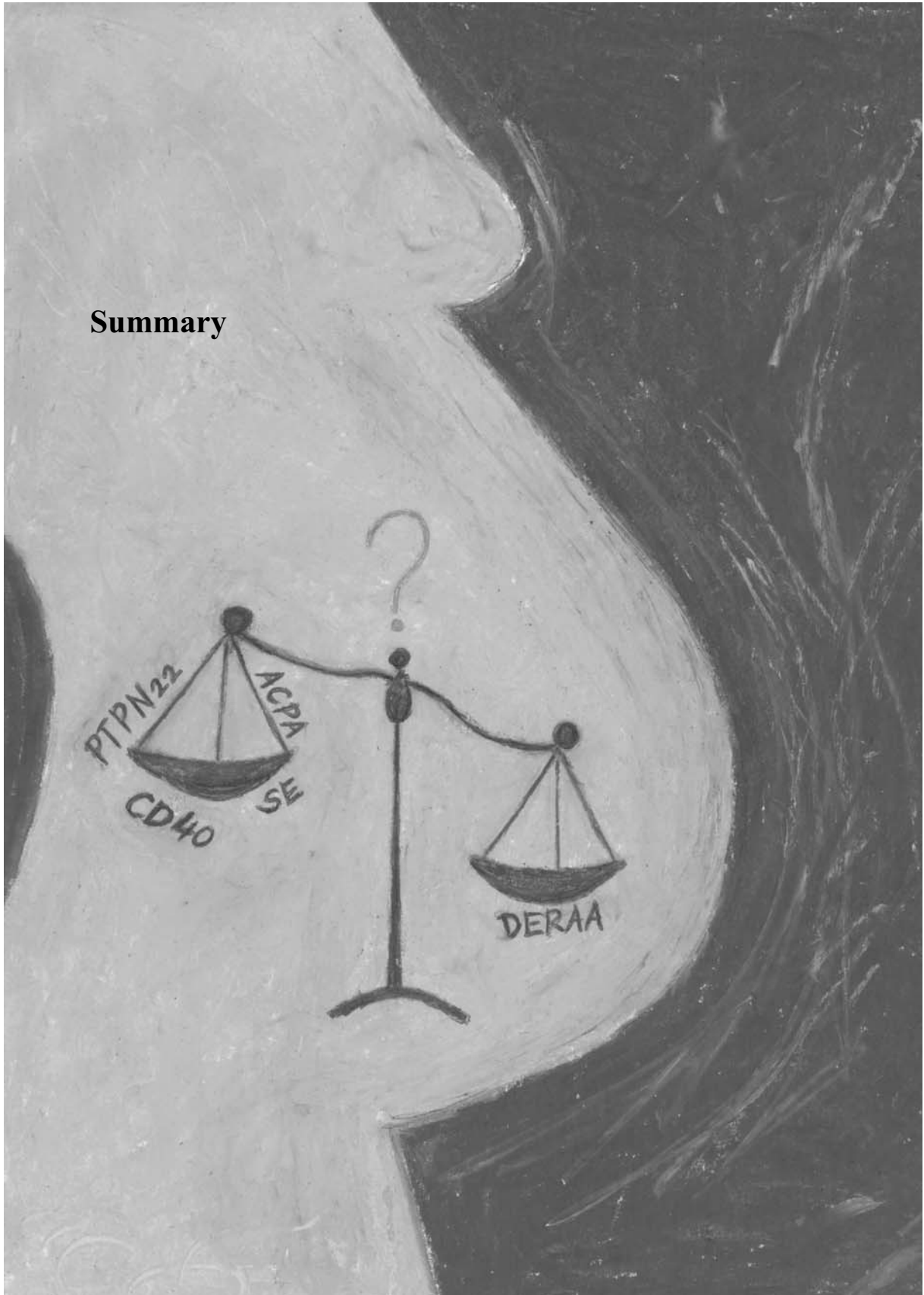
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Summary



Rheumatoid arthritis

Arthritis is a group of conditions characterized by joint inflammation. This inflammation can be caused by different mechanisms (e.g. autoimmunity, fractures, wearing, or infection) and can lead to breakdown of the cartilage in the joints. Rheumatoid arthritis (RA) is a chronic inflammation of several joints caused by autoimmunity. The diagnosis of RA is based on a list of seven criteria: morning stiffness, arthritis of 3 or more joint areas, arthritis of hand joints, symmetric arthritis, rheumatoid nodules, serum rheumatoid factor and radiographic changes. Since only four of these seven ACR criteria have to be fulfilled for the diagnosis of RA, the RA patient population is clinically heterogeneous. The occurrence of RA varies among countries and areas over the world; in Europe it has a prevalence of approximately 1% within the Caucasian population. In the Dutch population, women are affected by RA approximately two times more frequently than men. The progression of the disease is often measured by making x-rays of the joints (e.g. each year) in addition to assessments of physical function and questionnaires. The mechanism of RA development is complex and largely unknown, but it is generally accepted that both genetic and environmental factors play a role. In this thesis, on the one hand, factors involved in the protection against RA are studied. On the other hand, processes and genetic factors involved in the severity of RA and an increased risk of RA development have been investigated. In this summary several basic immunological aspects will be discussed and all chapters will be discussed briefly.

The immune system

The immune system is comprised of cells involved in adaptive and innate immune responses, each cell exerting his own function. Adaptive immune responses are characterized by the fact that they are antigen-specific immune responses of cells having a receptor specific for the antigen it responds to, which are the T cell receptor and B cell receptor in this case. When a B cell recognizes the antigen with its B cell receptor, this can result in the production of antibodies. An antibody is a protein that binds specifically to its corresponding antigen and thereby pathogens are neutralized or prepared for uptake and destruction by phagocytes. Adaptive immune responses occur during lifetime and involve specific antigen recognition and expansion of B and T cells. This distinguishes such responses from innate immunity, which includes the engulfment and digestion of pathogens by phagocytic cells that are immediately available. The innate immune response is directed against common components of



pathogens and not against an individual pathogen. Innate and adaptive immune responses are interdependent, and are exerted mainly by white blood cells (leukocytes). The different cells from the immune system all exert their own function. Antigen presenting cells (APC), e.g. dendritic and B cells, scan the whole body for its content, both self-proteins and infectious agents. They can take up these proteins, cut them in pieces (called peptides) and present these peptides via what is called a HLA molecule to a T cell (**Figure 1**). These HLA molecules are the most important genetic risk factor involved in RA development. Regarding the risk of RA development, three variants can be discriminated; either by a variant that increases the risk of RA development (called shared epitope (SE)), or by a variant that gives a lower chance of RA development (called DERAA), or by a neutral variant that does not have an influence on the development of RA.

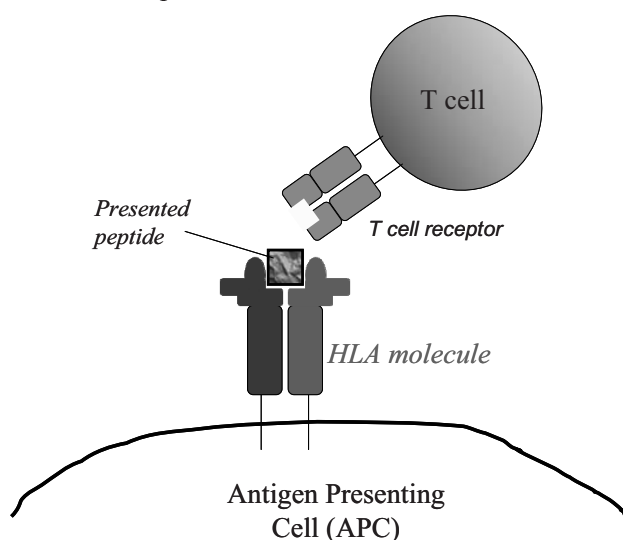


Figure 1. Presentation of a peptide to a T cell by an antigen presenting cell (APC). The peptide is presented bound in a HLA molecule to the T cell via its specific receptor.

Protection by “DERAA”

Different individuals can have different HLA molecules. Each variant has a slightly different composition of the building blocks, called amino acids, it consists of. There are 20 different amino acids which can be indicated with a one letter code. The variants containing at a specific position the amino acids that are coded by the letters “DERAA”, give an individual a lower chance to develop RA. This effect had been described already, but we describe in **Chapter 2** and **Chapter 3** of this thesis that a mother with a HLA molecule containing this DERAA-motif confers a life-long

protection to her child against the development of RA both with and without passing the gene responsible for this HLA molecule to the child. This in contrast to a father that has a DERAAs-containing HLA molecule. The father can only confer protection to the child when his DERAAs-containing HLA molecule is inherited by the child.

Vimentin-specific T cells

RA patients can develop different kinds of antibodies, from which some can react against proteins from the body which have a little difference compared to the regular protein. This change is called citrullination and therefore these antibodies are called anti-citrullinated protein antibodies (ACPA). Citrullination is a common natural process present in all individuals, but only RA patients can develop these antibodies. One of the proteins these antibodies can react to is vimentin. This is a self-protein that is present in every cell of an individual. B cells can receive signals from activated T cells to produce antibodies. In **Chapter 4** of this thesis it was studied whether we could identify the peptides from the vimentin protein which an APC presents to a T cell to activate this T cell. We were especially interested in Citrulline-specific T cell responses. This identification was performed with the help of HLA-transgenic mice expressing a human HLA-molecule on their cells. Two peptides inducing a Citrulline-specific T cell response were identified. The cells from 10 RA patients and 5 healthy controls were tested for reactivity against these two peptides. Several RA patients showed a Citrulline-specific response, which was absent in the 5 healthy controls. Since the amount of tested individuals was small, more extensive studies have to be performed to identify the presence/absence of T cell responses in different groups of individuals.

PTPN22 and CD40

Next to HLA molecules there are several other genetic factors involved in the risk of RA development. In this thesis, two of these genes are studied. They are called PTPN22 and CD40.

The sequence of building blocks of a gene, called nucleotides, can differ between different individuals in a population. When the frequency of a single nucleotide change is equal or higher than 1%, this is called a single nucleotide polymorphism (SNP). The most studied SNP of the PTPN22 gene is associated with RA and several other autoimmune diseases. There were indications that there is also a relation between this SNP of the PTPN22 gene and the development of ACPA antibodies. We investigated in **Chapter 5** whether this SNP can give additive value to the prediction of the



development of RA when information about the PTPN22 gene is combined with presence/absence of ACPA antibodies. The analyses showed that both information on the PTPN22 SNP and the presence/absence of ACPA can help to predict the development of RA, but both factors combined do not result in additive value for prediction.

Because nowadays, RA patients are seen in an earlier phase of the disease, before the appearance of well established indicators of poor prognosis such as erosions and nodules, markers which have a good predictive value on radiographic damage in an early phase of the disease will become more important. Therefore, we investigated in **Chapter 6** whether different SNPs, including one in the CD40 gene, are involved in the progression and severity of RA once patients are diagnosed. It was shown that the SNP of the CD40 gene was indeed associated with the severity and progression of RA. The CD40 gene encodes a molecule, CD40, that is involved in the interactive signaling between B and T cells to activate them. Further studies have to show the functional effects of the SNP in the CD40 protein.

The studies included in this thesis are quite diverse but all deal with different aspects playing a role in RA development or progression of the disease. Several questions have been answered, but all result in a range of new questions that need to be answered in future studies. I hope this summary will explain a little bit the struggles I have been trying to answer in the last 5 years. Of course everybody is invited to read the detailed versions of each article in the indicated chapters!