Immune system explained

The immune system is of great importance for protection of the organism against foreign substances, and consists of molecules, cells and tissues that work collectively to provide this protection. One of the key members of the immune system is the MHC (Major Histocompatibility Complex), a molecule expressed on antigen presenting cells, such as macrophages, dendritic cells and B cells, and required for the proper antigen presentation. The MHC is responsible for binding peptides originated from foreign proteins and displaying them on the surface of antigen presenting cells, allowing their recognition by T cells, which will initiate an immune response. MHC molecules are highly polygenic, which means that there are multiple different MHC genes, and consequently different sets of MHC molecules with different specificities in each person. Besides that, MHC genes are also very polymorphic, with many different variants in the population. [1-3]

The human MHC genomic region, on chromosome 6, encodes HLA (Human Leukocyte Antigen) genes, and the great diversity previously cited is responsible for the differences seen in immune responses within a population. [1, 4] There are two main classes of HLA (I and II), both responsible to present peptides to T cells and trigger an appropriate immune response. The main difference between these classes is that HLA I molecules present endogenous antigens derived from viruses and phagocytosed or internalized pathogens to CD8+ T cells, triggering a citolytic response on recognized cells, while HLA II molecules present exogenous antigens generated intracellularly in antigen presenting cells to CD4+ T cells, that will trigger the production of antibodies by B cells. 1, 3, 5 Besides that, HLA I and II are differently expressed on cells: HLA class I is expressed in almost all cells of

the body, in high frequency on cells of the immune system and in low frequencies in non-nucleated cells, while HLA class II is exclusively expressed on cells involved in immune responses, such as antigen presenting cells. 1, 2 Both HLA classes I and II are divided into subtypes, being A, B and C the three more important of HLA class I, and DR, DP and DQ the three more important in the case of HLA II. 2, 3 Besides that, in the region in between HLA I and II regions it is possible to find HLA class III genes, that encodes some complement proteins such as C4A, C4B, C2, and factor B, some cytokines, such as TNF alpha and beta, and some other non-HLA proteins. 2, 4, 6

The adaptive immune system should ensure that the organism do not respond to its own proteins, otherwise it will result in injury to itself. This feature is called self-tolerance, which means that in a normal individual, the immune system has tolerance to self-proteins, being able to do not trigger an immune response against them. 1, 4, 7 This self-tolerance is maintained by two main steps: a) Thymic selection is a process that consists in presentation of self-proteins to T cells precursors in the thymus and elimination of the ones that present reactivity to them. During this step, approximately 95% of the T cells precursors are eliminated by apoptosis because of their reactivity. The surviving ones go out of the thymus as mature T cells, after passing through a process called positive selection. 4, 8 b) Since not all of the self-reactive T cells are eliminated in this first selection, mature T cells undergo a peripheral secondary selection in lymphoid and nonlymphoid organs, so the remaining self-reactive T cells can be eliminate. Besides that, there is a production of regulatory T cells during

thymic selection and in the periphery, that are important to help in the peripheral control self-reactive T cells that were able to escape of elimination. 4, 7, 8

When a breakdown in this self-tolerance occurs and the adaptive immune system reacts to self-proteins, a sustained immune response follows, because it is not possible to promote the clearance of this antigen from the organism. This process, which will lead to inflammatory tissue injury, is also known as Autoimmune Disease, and can have very different manifestations depending on its location. 1, 4, 9, 10 According to the review conducted by Gregersen and Behrens (2006)4, around 3% of the population have a known Autoimmune Disease, even though not recognized autoimmune mechanisms can influence other common disorders.

Some authors consider this breakdown or absence of tolerance questionable, as stated by Möller (1998). 11 Among other things, even in a normal and healthy organism there are some possible autoreactive T cells circulating peripherally, and this disruption of self-tolerance was never proved in experiments. Still, thinking about self-tolerance as something limited only to the self-antigens that were presented on thymic selection, it remains uncertain if autoimmune responses arises from a self-tolerance disruption or from the potential threat of these normally existing autoreactive T cells. 11

Although the exact aetiology of Autoimmune Diseases is not completely certain, there are some known factors related to them, such as environmental triggers (e. g. chemical agents and pathogens), hormonal influences (e. g. estrogen), and region and ethnic differences, but the most

important determinant of Autoimmune Diseases is the genetic susceptibility, mainly associated with certain HLA alleles, because of their central action in immune responses. 1, 4, 9, 10

Any disturb on HLA expression can lead to development of an Autoimmune Disease because T cell precursors also require HLA to present self-antigens, and if HLA molecules cannot present self-antigens to autoreactive T cells, they will not be eliminated during thymic selection and will circulate in the organism. 1, 4, 8 Besides that, another possible explanation to the influence of HLA on predisposition to Autoimmune Diseases is that self-antigens attached to certain HLA molecules are responsible for driving the positive selection of T cell precursors specific for them, depending on their level of expression: if they are present at small amounts or if they cannot bind properly to HLA molecules, they will conduct the negative selection, and if they are present at the degree needed or if they bind effectively they will conduct the positive selection. Then, insufficient expression of self-proteins during the thymic selection could increase the susceptibility for the development of an Autoimmune Disease. 1, 4 There are some theories to explain the separate mechanisms by which HLA class I and II can influence the predisposition to Autoimmune Diseases, cited by Gough and Simmonds (2007). 3 Concerning to HLA II mechanisms, in addition to this possibility of low affinity self-antigens leading to impaired elimination of self-reactive T cells, changes in the binding region of HLA II molecules could predispose mature T cells to recognize only a specific group of self-antigens, as a result of ineffective and incomplete thymic selection. Another discussed idea is that polymorphic regions of the receptor of HLA II molecules could lead to

selection of ineffective regulatory T cells or self-reactive T cells, predisposing to Autoimmune Diseases. 3 On the other hand, concerning to HLA I mechanisms, it is possible that the endogenous antigens presented, such as viruses and phagocytosed bacteria, predispose to an autoimmune response by mimicking self-antigens and activating autoreactive T cells. 3, 11 Besides this hypothesis, it is believed that some of these peptides can alter HLA I inhibitory activity on NK cells, which would act by lysing the cell and triggering a potential autoimmunity. 3, 13

Most of the known and described Autoimmune Diseases are related to an alteration of HLA II molecules, and some of the main examples include Rheumatoid Arthritis, Type 1 Diabetes and Hashimoto’s Thyroiditis. Ankylosing Spondylitis is another well-studied and important Autoimmune Disease, although it is associated with HLA I molecules. 3, 12

Rheumatoid Arthritis is one important example of cell mediated Autoimmune Disease, caused indirectly by T-lymphocytes and associated mainly with environmental factors and genetic susceptibility, among other potential influences. It is a chronic inflammatory disease that affects multiple synovial joints, such as fingers, knees, elbows, shoulders and ankles, with systemic psychological and systemic repercussions, affecting cardiovascular, respiratory, and skeletal systems. 14 According to the review conducted by Ghodke et al (2005)10, it occurs worldwide in a prevalence that varies from 0. 3 to 1. 5% in almost all populations, being women more susceptible than men. In summation, the mechanism of the disease begins when a self-antigen, still uncertain, but probably a peptide derived from the connective tissue (e. g. collagen) is recognized by T cell receptors of CD4+ T cells, which

release cytokines (e. g. IFN-ï ¥ §). These cytokines promotes phagocyte activation and release of other cytokines, including TNF-É‘, interleukins and other substances that along with IFN-ï ¥ § will activate resident synovial cells to produce proteolytic enzymes (e. g. collagenase). As a result, there is inflammation on the synovial tissue (also known as synovitis), destruction of synovial cells and synovial hyperplasia, followed by cartilage damage and bone erosion and consequent destruction of the joints. 1, 14

Several genetic loci are associated with susceptibility to Rheumatoid Arthritis, but the most studied and well-known of them is the HLA class II DRB1, 4, 9, 11, 12, 14 contributing to a third to half of the general genetic predisposition risk. 15 The hypothesis first presented by Gregersen (1987)16, suggests that some HLA-DRB1 alleles express a “ shared epitope”, that is a five amino acid sequence (QKRAA) responsible for the increased susceptibility to Rheumatoid Arthritis by influencing peptide binding and interaction between HLA and T cell receptor. 15, 17 These HLA-DBR1 alleles include DRB1*0101, DRB1*0102, DRB1*0401, DRB1*0404, DRB1*0405, DRB1*0408, DRB1*1001 and DRB1*1402. 3, 16 As summarized by McInnes and Schett (2011), the function of HLA-DRB1 in the pathogenesis of this disease is related to MHC molecule-based antigen presentation, self-antigen selection and T cell repertoire. However, they also present multiple other ideas as possibilities of influence of HLA-DRB1 on Rheumatoid Arthritis, including senescence induction on T cells and a potential proinflammatory function. 14 The study carried out by de-Vries (2002) suggested another association between HLA-DRB1 and Rheumatoid Arthritis, but in a distinct way: differences in the regular shared epitope may have a protective effect,

rather than a predisposing effect. These HLA-DRB1 alleles include DRB1*07, DRB1*1201, DRB1*1301 and DRB1*1501, among others. 18 Besides HLA-DRB1, many other non-HLA genes were described as having a potential link with Rheumatoid Arthritis, such as PTPN22, AFF3, CD28, CD40 and CTLA4, among other ones.

The symptoms of Rheumatoid Arthritis include pain and stiffness of the affected joints, both usually in the morning or after resting, as well as warmth, redness and long-term deformities. The treatment may be performed in a multidisciplinary way, with physiotherapy, occupational therapy, diet, pharmacological treatment and complementary therapies. The pharmacological management may include symptom control with analgesics and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), glucocorticoids, DMARDs (Disease Modifying Anti-Rheumatoid Drugs) and biological drugs, depending on each case. 19

Type 1 Diabetes, also known as Insulin Dependent Diabetes Mellitus (IDDM), is a multi-systemic metabolic disease, originated as a result of impaired insulin production and/or function and associated with genetic predisposition and environmental factors. It is another important example of a cell mediated Autoimmune Disease where a self-antigen, such as insulin or other Islet of Langerhans proteins, activate CD4+ T cells triggering the release of cytokines by activated phagocytes and activation of in situ CD8+ T cells, leading to inflammation and injury of insulin-producing pancreatic β-cells. 1, 15, 20 Because of reduction of insulin production, there is a disturbance in blood glucose control, leading to clinical symptoms caused by hyperglycaemia and ketoacidosis.

Several genetic loci were also described as being related to Type 1 Diabetes, but it is known that this disease has a particular link with HLA-DR3, DR4, DQ2 e DQ8, especially when combined DR4-DQ8 or DR3-DQ2. 9, 20 According to Devendra and Eisenbarth (2003), these two combination of HLA alleles are found in 9 out of 10 people with Type I Diabetes. As well as in Rheumatoid Arthritis, some protective HLA molecules were described, being DQA1*0102-DQB1*0602 the most common and effective of them, and several other non-HLA genetic loci have been described as potential influences on Type 1 Diabetes, but only one was proved to be associated: IDDM 2 on chromosome 11p5. 5. 21

As suggested by one of the names of the disease, injection of insulin is essential for regulation of blood glucose levels and for the effective treatment of Type 1 Diabetes. However, hypoglycaemia (low blood glucose levels) can occurs with treatment using insulin, mainly when used in excess, and because of this, another important part of the treatment is the monitoring of blood glucose levels.

References

1. Janeway CA Jr, Travers P, Walport M, et al. Immunobiology: The Immune System in Health and Disease. 5th edition. New York: Garland Science2001. www. ncbi. nlm. nih. gov. ezproxy. liv. ac. uk/books/NBK10757/(accessed 27 Mar 2014)

2. Robinson J, Halliwell JA, McWilliam H, Lopez R, Parham P, Marsh SGE. The IMGT/HLA Database Nucleic Acids Research; 2013; 41: D1222-7. www. ebi. ac. uk/ipd/imgt/hla/(accessed 27 Mar 2014)

3. Gough SCL, Simmonds MJ. The HLA Region and Autoimmune Disease: Associations and Mechanisms of Action. Paris: Curr Genomics 2007; 8(7): 453–465. www. ncbi. nlm. nih. gov/pmc/articles/PMC2647156/(accessed 27 Mar 2014)
4. Gregersen PK, Behrens TW. Genetics of autoimmune diseases – disorders of immune homeostasis. Nature Reviews Genetics 2006; 7: 917-928. www. nature. com/nrg/journal/v7/n12/full/nrg1944. html(accessed 27 Mar 2014)
5. Mantegazza AR, Magalhaes JG, Amigorena S, Marks MS. Presentation of phagocytosed antigens by MHC class I and II. *Traffic* 2013; 14(2): 135-52. www. onlinelibrary. wiley. com/doi/10. 1111/tra. 12026/full(accessed 28 Mar 2014)
6. Deakin JE, Papenfuss AT, Belov K, Cross JGR, Coggill P, Palmer S, Sims S, Speed TP, Beck S, Graves JAM. Evolution and comparative analysis of the MHC Class III inflammatory region. BMC Genomics2006; 7: 281. www. biomedcentral. com/1471-2164/7/281(accessed 28 Mar 2014)
7. Sakaguchi S. Naturally arising CD4+ regulatory T cells for immunologic self-tolerance and negative control of immune responses. *Annual review of immunology* , 2004; 22: 531-562. http://www. annualreviews. org/doi/full/10. 1146/annurev. immunol. 21. 120601. 141122? url_ver= Z39. 88-2003&rfr_id= ori: rid: crossref. org&rfr_dat= cr_pub= pubmed(accessed 28 Mar 2014)
8. Kyewski B, Klein L. A central role for central tolerance. *Annual Review of Immunology* 2006; 24: 571-606. www. annualreviews. org/doi/full/10. 1146/annurev. immunol. 23. 021704. 115601? url_ver=

Z39. 88-2003&rfr_id= ori: rid: crossref. org&rfr_dat= cr_pub= pubmed(accessed 28 Mar 2014)

9. Ray S, Sonthalia N, Kundu S, Ray SG et al. Autoimmune Disorders: An Overview of Molecular and Cellular Basis in Today's Perspective. *J Clin Cell Immunol* 2012; S10. www. omicsonline. org/autoimmune-disorders-an-overview-of-molecular-and-cellular-basis-in-todays-perspective-2155-9899. S10-003. pdf(accessed 29 Mar 2014)

10. Ghodke Y, Joshi K, Chopra A, Patwardhan B. HLA and disease. European Journal of Epidemiology2005; 20(6): 475-488. www. link. springer. com/article/10. 1007%2Fs10654-005-5081-x (accessed 29 Mar 2014)

11. Möller E. Mechanisms for induction of autoimmunity in humans. *Acta Paediatrica* 1998; 87: 16-20. www. onlinelibrary. wiley. com/doi/10. 1111/j. 1651-2227. 1998. tb01228. x/abstract(accessed 29 Mar 2014)

12. Nepom GT. Class II antigens and disease susceptibility. *Annual Review of Medicine* 1995; 46: 17-25. www. annualreviews. org/doi/full/10. 1146/annurev. med. 46. 1. 17? url_ver= Z39. 88-2003&rfr_id= ori: rid: crossref. org&rfr_dat= cr_pub= pubmed(accessed 31 Mar 2014)

13. Mandelboim O, Wilsons SB, Valés-Gómez M, Reyburn HT, Strominger JL. Self and viral peptides can initiate lysis by autologous natural killer cells. Proc Natl Acad Sci 1997; 94(9): 4604–4609.

http://www. ncbi. nlm. nih. gov/pmc/articles/PMC20770/(accessed 31 Mar 2014)

14. McInnes IB, Schett G. The Pathogenesis of Rheumatoid Arthritis. *N Engl J Med* 2011; 365: 2205-19. http://www. nedai. org/items/nejmra1004965iainmcinnes. pdf(accessed 1 Apr 2014)

15. Kallon D. Autoimmune Diseases and HLA. *HLA Disease Associations: The Autoimmune diseases site* [Internet]. www. hladiseaseassociations. com/autoimmune-diseases-and-hla/(accessed 02 Apr 2014)

16. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987; 30: 1205-1213. [PubMed: 2446635]

17. Holoshitz J. The rheumatoid arthritis HLA-DBR1 shared epitope. *Curr Opin Rheumatol* 2010; 22(3): 293-298. www. ncbi. nlm. nih. gov/pmc/articles/PMC2921962/(accessed 02 Apr 2014)

18. de Vries N, Tijssen H, van Riel PLCM, van de Putte LBA. Reshaping the shared epitope hypothesis: HLA-associated risk for rheumatoid arthritis is encoded by amino acid substitutions at positions 67–74 of the HLA–DRB1 molecule. *Arthritis & Rheumatism* 2002; 46: 921–928. www. onlinelibrary. wiley. com/doi/10. 1002/art. 10210/abstract(accessed 03 Apr 2014)

19. National Collaborating Centre for Chronic Conditions (UK). Rheumatoid Arthritis: National Clinical Guideline for Management and Treatment in Adults. London: Royal College of Physicians (UK); 2009.

(NICE Clinical Guidelines, No. 79)www. ncbi. nlm. nih. gov/books/NBK51812/(accessed 04 Apr 2014)

20. Gillespie KM. Type 1 diabetes: pathogenesis and prevention. CMAJ2006; 175(2): 165-170. www. ncbi. nlm. nih. gov/pmc/articles/PMC1489998/(accessed 02 Apr 2014)

21. Devendra D, Eisenbarth GS. Immunologic endocrine disorders. *J Allergy Clin Immunol* 2003; 111(2): S624-S636. www. sciencedirect. com/science/article/pii/S0091674902913436#(accessed 03 Apr 2014)