Facultade de Ciencias
Departamento de Biología
Área de Microbiología

Literature review: Autoimmune diseases induced by viruses

Revisión bibliográfica: Enfermedades autoinmunes inducidas por virus

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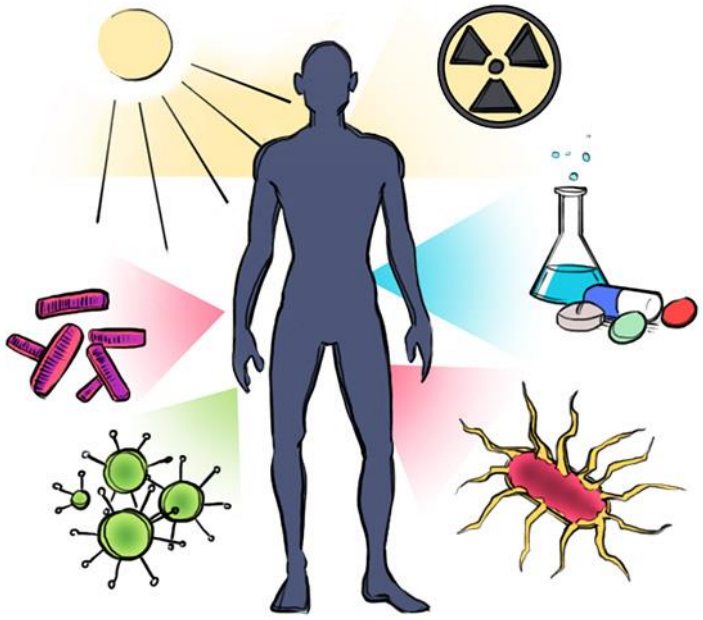

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Traballo de fin de grao

Data de defensa: 28 de xuño de 2017

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Abstract

Autoimmune diseases are disorders caused by a malfunction in the immune system. Genetic background, environmental factors and lifestyle habits have been considered as the factors triggering the development of these diseases. Among the environmental factors, viruses are one of the most important and studied causes of autoimmune diseases. However, even if the relationship may be clear, the mechanisms behind the viral infections contributing to the illness progress are not well known. Some theories have been suggested but more experimentation is needed to their acceptance. Type 1 diabetes and multiple sclerosis are two examples of this type of disorders. Viral infections have been related to the development of multiple sclerosis and type 1 diabetes, but other causes may also be partially responsible. In fact, interactions and different contribution of these factors might finally trigger these diseases. In conclusion, evidences showed the association between viral infection and autoimmune diseases, but more investigation is needed.

Key words

Autoimmune diseases, environmental factor, viral infection, viruses, multiple sclerosis, type 1 diabetes

Resumen

Las enfermedades autoinmunes son trastornos causados por un mal funcionamiento del sistema inmunológico. Predisposición genética, factores ambientales y hábitos de vida se consideran como los factores que desencadenan el desarrollo de estas enfermedades. Entre los factores ambientales, los virus son una de las causas más importantes y estudiadas de las enfermedades autoinmunes. Sin embargo, incluso si la relación pueda ser clara, los mecanismos detrás de las infecciones víricas que contribuyen al progreso de la enfermedad aún se desconocen. Se han sugerido algunas teorías, pero se necesita más experimentación para que puedan ser aceptadas por la comunidad científica. La diabetes tipo 1 y la esclerosis múltiple son dos ejemplos de este tipo de enfermedad. Las infecciones víricas se han relacionado con el desarrollo de la esclerosis múltiple y la diabetes tipo 1, pero otros factores también pueden ser parcialmente responsables. De hecho, las interacciones y la diferente contribución de estos factores pueden finalmente provocar estas enfermedades. En conclusión, las evidencias han mostrado la asociación entre infección viral y enfermedades autoinmunes, pero es necesaria más investigación.

Palabras clave

Enfermedades autoinmunes, factor ambiental, infección vírica, virus, diabetes tipo 1, esclerosis múltiple

Resumo

As enfermidades autoinmunes son desordes causados por erros na función do sistema inmunitario. A predisposición xenética, os factores ambientais e o estilo de vida consideránse como os factores que poden desencadear o desenvolvemento destas enfermidades. Entre os factores ambientais, os virus son unha das causas máis importantes e estudadas que poden levar ás enfermidades autoinmunes. Con todo, aínda que a relación pode ser clara, os mecanismos subxacentes ás infeccións víricas que contribúen á progresión da enfermidade aínda non se comprenden ben. Algunhas teorías suxeríronse, pero máis experimentación é necesaria para que poidan ser aceptadas pola comunidade científica. A diabetes tipo 1 e a esclerose múltiple son dous exemplos deste tipo de enfermidade. As infeccións víricas poden estar asociadas ao desenvolvemento de esclerose múltiple e diabetes tipo 1, pero outros factores tamén son parcialmente responsables. De feito, as interaccións e os distintos grados de contribución destes factores poden, finalmente, provocar a enfermidade. En conclusión, as evidencias amosan a existente asociación entre infección viral e enfermidades autoinmunes, pero é necesaria máis investigación.

Palabras clave

Enfermidades autoinmunes, factor ambiental, infección vírica, virus, diabetes tipo 1, esclerose múltiple

1. Introduction

Autoimmune diseases are disorders caused by a malfunction of the immune system since the organism does not recognise and attacks its own cells (Jose *et al.,* 2014; Page *et al.*, 2011; Smith and Germolec, 1999). The causes beyond these diseases are still unknown in multiple cases, although some general mechanisms can be involved to trigger autoimmunity such as genetics, environment or even previous viral or bacterial infections (Delogu *et al*., 2011). It is also known that the pathogenesis is not only due to one factor but to different combining factors.

These diseases can have different symptoms and may affect any organ, therefore the amount of this type of conditions is very high, existing more than eighty types of autoimmune diseases (Ercolini and Miller, 2009; Jose *et al*., 2014; Page *et al*., 2011). Some examples are multiple sclerosis, autoimmune hepatitis, diabetes mellitus type I, rheumatoid arthritis and autoimmune pancreatitis.

The presence of some genes may increase the probability of having an autoimmune disease, triggered by the environment. These genes may control different processes affecting the roles of T and B lymphocytes, important cells in immunity (Jose *et al*., 2014). Moreover, molecular mimicry and microbial agents are also mechanisms leading autoimmunity.

Concerning infections in autoimmune diseases, microbial agents may lead to autoimmunity in different situations. It may happen that the pathogen has similar elements of a self-antigen, it is the called molecular mimicry. The immune cells do not distinguish the antigen from the pathogen damaging the organism. Epitope spreading (epitope is the part of an antigen recognised by the immune system), bystander activation and cryptic antigens are also involved in microbial autoimmunity. One reason or another, these different mechanisms activate parts of the immune system, therefore ultimately activating the self-immune response (Ercolini and Miller, 2009).

Scientists discovered the existence of autoimmune diseases during mid-20th century. At first, they were not understood due to the unknow process of how immune system can distinguish self-antigen from foreign elements (Margo and Harman, 2016). With the medicine advances, researchers could answer this question and investigate better autoimmune diseases (Rose, 2016). However, these discoveries occurred quite late in the 20th century (Wong, 2015).

Nowadays, autoimmune diseases are becoming to be more important as the incidence and prevalence are increasing in industrialized countries (Rose, 2016). However, the experimental studies and investigation remains low as the costs are elevated and the results are not always positive (Moccia *et al.*, 2017).

Physical exercises and physiotherapy may be some medical actions to help patients in some diseases (Page *et al*., 2011). However, it is not enough. Ideal medicines or prevention techniques have not been discovered yet, or even, palliative medicines are still in experimental processes leading to unsafe and ineffective trials. Anyway, finding proper treatments is hard due to the high quantity of autoimmune diseases, the distinct

symptoms that may occur and the late apparent diagnosis (Rose, 2016). The unknown precise cause of autoimmunity makes even more difficult reducing these cases. So, repair or decrease damage is the objective of researchers to improve patient's lives (Rose, 2016).

The aim of this review is to recap and illustrate the main aspects of the viral infections which lead to autoimmune diseases. On the other hand, highlighting the impact of these diseases and the importance of the role of some pathogens, such as viruses, is also desired. Therefore, the latest objective is to encourage investigating these disorders since people have becoming more affected by this kind of illness. In order to summarize different reviews and articles, searching in PubMed and Scopus has been carried out with the search terms, alone or combined: "autoimmune diseases", "viral", "virus", "autoimmunity".

First, the mechanisms of viral infection and molecular mimicry would be explained, as it is fundamental to study them to better understand the resulting autoimmune diseases. Its study is also helpful to find different methods against viral autoimmune diseases. Moreover, some important examples of autoimmune diseases are going to be discussed, as well as the importance of several viruses that will trigger autoimmunity.

2. Current Perspectives

We are surrounded for lots of diseases that affect our lives directly or indirectly. Some of them are autoimmune diseases whose rising effects and incidence are deteriorating population wellness and health, becoming a significant issue for society. As the causes of these diseases are not well known, it is required to increase the number of studies and investigations (Rose, 2016). In addition, viral infections would trigger more cases of autoimmune diseases.

Viral infections arise commonly among all populations, and some evidences indicate that viruses may be responsible of different autoimmune diseases (Correale and Gaitán, 2015; Libbey *et al.*, 2014). Sometimes these infections may trigger altered immune responses causing attacks against viral and self-elements, and finally autoimmunity (Getts *et al.*, 2013). It has been proved that cases of autoimmune diseases have higher presence of infections than in normal population (Libbey *et al*., 2014).

The impact of autoimmune diseases is increasing as the incidence and prevalence are becoming higher. It is thought that this kind of diseases are not common, but the effects are quite important (Wang *et al.*, 2015). The incidence is rising quickly, resulting in new cases, more in women than in men (Page *et al*., 2011). The global prevalence of autoimmunity is around 5 % (Wang *et al*., 2015).

As autoimmune diseases include high burden of mortality, it can be a major concern among people (Wang *et al*., 2015). In a study, the relevance of a famous actor death by an autoimmune disease has been recorded; this fact increased the searches at web browsers and some social networks, with high results of autoimmune disorders and vasculitis searches and trends. Therefore, autoimmune diseases news affected

population and increased their curiosity, leading to look for more information. This explains that when there are famous examples of an autoimmune disease, society is more aware about it (Bragazzi *et al*., 2016).

For instance, it has been tested that patients with HIV may present more probabilities of suffer an autoimmune disease (Yen *et al*., 2017).

Furthermore, it has been shown that incidence of autoimmune hepatitis is higher than thought, affecting all races and ages, being more present in women (Primo *et al*., 2009), and it is related to other diseases (Aizawa and Hokari, 2017). But, antiviral drugs might eliminate autoimmune hepatitis (Aizawa and Hokari, 2017).

Diabetes mellitus type 1 prevalence is high in South Spain, that may lead to a concerning morbidity and mortality. Comparing with previous data, diabetes prevalence is greater than in other parts of Europe and it can be linked to obesity prevalence (Soriguer-Escofet *et al*., 2002).

Regarding multiple sclerosis, the global prevalence is 33 per 100,000 people, but it depends on the geography (Vidal-Jordana and Montalban, 2017). In Western countries, it has a relevant impact and costs that may decrease with knowledge. So, investigation has been done even the costs are quite elevated. However, the evolution of new techniques and new materials can decrease the costs, leading to more investigation and more treatments (Moccia *et al*., 2016). Canada is the country with the highest rate of multiple sclerosis, with 291 cases per 100,000 people, almost 10 times more than the global mean (Brown, 2016).

Therefore, the incidence and prevalence varies depending on the disease. Age, gender, ethinicity, geography… also have a role in the epidemiology (Wang *et al*., 2015).

3. Virus and autoimmune diseases

It has been confirmed that different pathogens may lead to autoimmune disease, activating or spreading self-immune responses (Ercolini and Miller, 2009; Steed and Stappenbeck, 2014). They induce this kind of illness mainly by molecular mimicry. Moreover, the activation of the immune response can be triggered by epitope spreading or bystander activation (Delogu *et al*., 2011; Molina and Shoenfeld, 2005). Some significant microorganisms behind autoimmunity, being a primary factor, are viruses, some of them well studied and known (Steed and Stappenbeck, 2014). However, the clear interactions vary depending on the disease and more information is still needed (Ercolini and Miller, 2009; Steed and Stappenbeck, 2014).

3.1 Role of viruses

Viruses can break tolerance to self and trigger autodestruction events of tissue or a complete organ (von Herrath *et al.*, 1998). Immune tolerance is the process of unresponsiveness to elements that may induce immune responses. So, the immune system can distinguish non-pathogenic microbes or self-antigens from pathogens. This may lead to a good self-defence (Steed and Stappenbeck, 2014). Therefore, the breakdown of the immune tolerance will result in attacks to viral and self-antigens and their elimination (Getts *et al*., 2013).

The mechanisms leading to autoimmune diseases by virus are: molecular mimicry, bystander activation, epitope spreading and viral persistence (Delogu *et al*., 2011; Ercolini and Miller, 2009; Fujinami *et al.*, 2006; Getts *et al*., 2013). The interaction between the virus and the host should be considered since some viruses create persistent and latent infections. Therefore, it would be essential to find out when viral cycle leads to autoimmunity (Steed and Stappenbeck, 2014).

Molecular mimicry refers to an immunologic shared epitope between a host and a microbe. So, the microbe may have proteins with amino acid sequences or structure homologues in humans (Ercolini and Miller, 2009; Getts *et al*., 2013; Trela *et al.*, 2016). Since the microbe may carry similar elements, the activated T cells (cell that controls the immune responses) react against self-antigens causing damages and the activation of further immune responses, this process is called cross-reaction (Delogu *et al*., 2011; Fujinami *et al*., 2006).

Concerning viruses, these pathogens can have cross reactive epitopes with host self-proteins. Monoclonal antibodies have been shown cross-reactivity with host proteins in different studies and diseases. Moreover, viruses also activate epitopes, presented to antigen-presenting cells, contributing to the development of autoimmune diseases (Fujinami *et al*., 2006; Trela *et al*., 2016;). Some viral models have been studied and therefore needed to explain the mechanisms of acquired autoimmunity via molecular mimicry. It also has been determined that T cells with low affinity for a self-antigen may initiate molecular mimicry because of viral infections (Getts *et al*., 2013). However, not all similar peptides of humans and microbes will lead to autoimmunity, as they stay inert, not causing molecular mimicry (Trela *et al*., 2016).

Bystander killing has become more relevant thanks to animal models experiments confirming this mechanism. Viral infections contribute to trigger APC (antigen presenting cells), which can activate autoreactive T cells. Finally, this will lead to an autoimmune disease (Fujinami *et al*., 2006). Viruses may initiate bystander activation, too. So, bystander T-cell activation might be caused by the presentation of antigens to aberrant autoreactive T-cells. Even if those T-cells have low affinity for self-antigen, they are indeed activated by the viral infection (Getts *et al*., 2013).

In relation with this mechanism, epitope spreading contributes to the activation of an immune response due to viral infections leading to the delivery of self-antigens and *de novo* activation of autoreactive responses (Getts *et al*., 2013).

The immune response spreads and creates more responses against parts of the same protein or a different one. In animal models, it has been seen that dominant epitopes bring out the first responses (Delogu *et al*., 2011).

Other mechanism is the persistence of viral infections, as the latent constant of viral antigen may activate the immune response any time. Moreover, antiviral antibodies or presentation of cryptic antigens may have importance in the autoimmunity development, thus, initiating an autoimmune disease (Delogu *et al*., 2011; Fujinami *et al*., 2006).

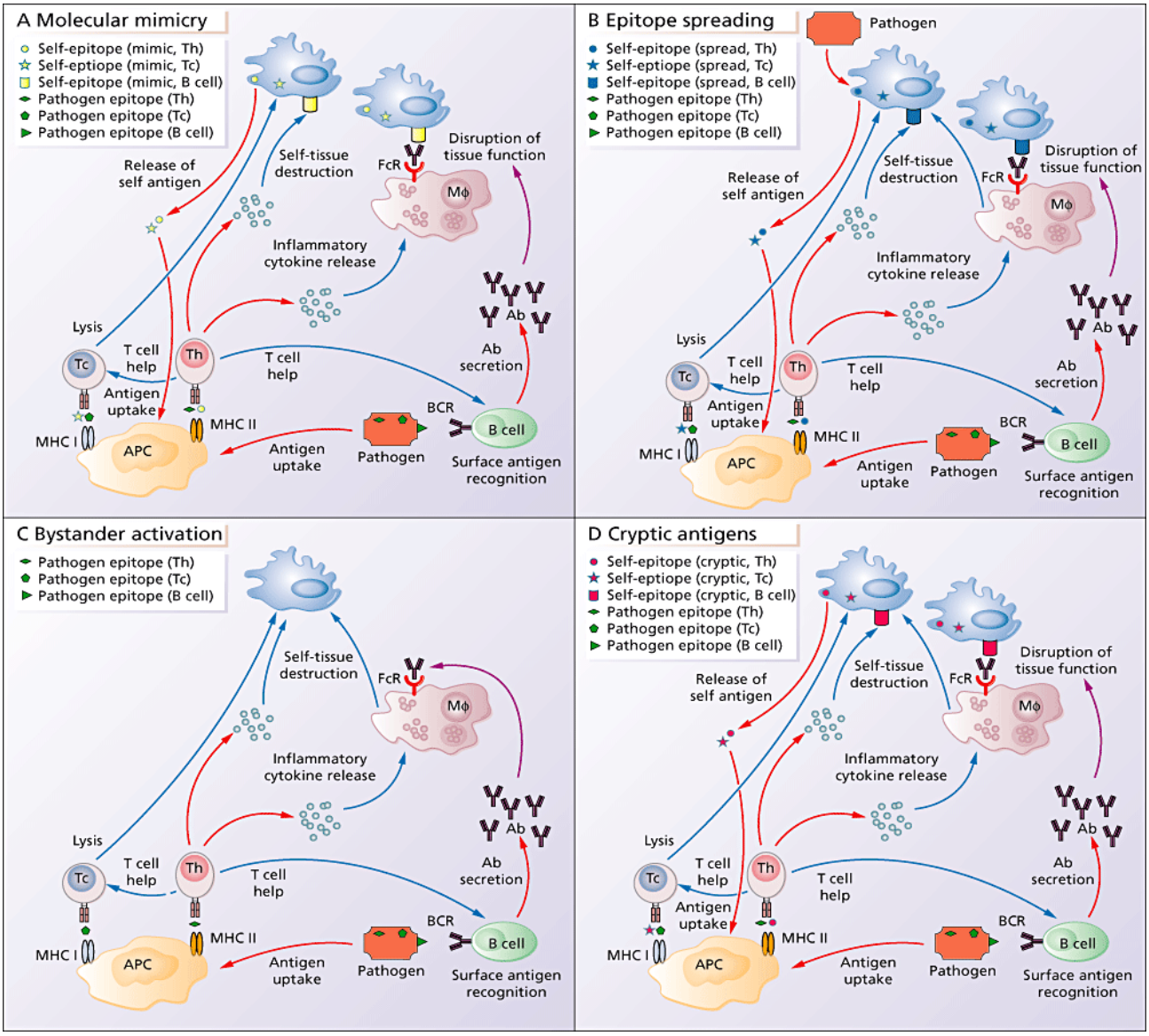

Figure 1: Mechanisms of induced autoimmunity by microbe infections (Ercolini and Miller, 2009)

Then, these mechanisms will contribute in many and different ways to the evolution of autoimmunity, but the process behind is still unknown. It is possible that variations are due to the different viral infections and type of viruses (Getts *et al*., 2013). In addition, microbe triggers of autoimmunity are hard to identify because the apparent clinical responses need time to be detected (Delogu *et al*., 2011).

Autoreactive T-cells and infections are required to initiate the progression of an autoimmune disease (Delogu *et al*., 2011).

3.2 Example: Epstein-Barr virus

Epstein-Barr virus (EBV) is a ubiquitous herpesvirus and a very well-studied virus. It can cause latent infections and it has a role in several autoimmune diseases as lupus, rheumatoid arthritis or multiple sclerosis. In patients with systemic autoimmune disorders, there are a presence of high loads of the virus, altered specific T-cells and antibodies against EBV (Fujiwara and Takei, 2015; Steed and Stappenbeck, 2014). EBV is a needed factor for the progress of multiple sclerosis. It has been shown that one mechanism that leads to autoimmune diseases, due to EBV infections, is molecular mimicry between EBV proteins and self-proteins (Tousirot and Roudier, 2008).

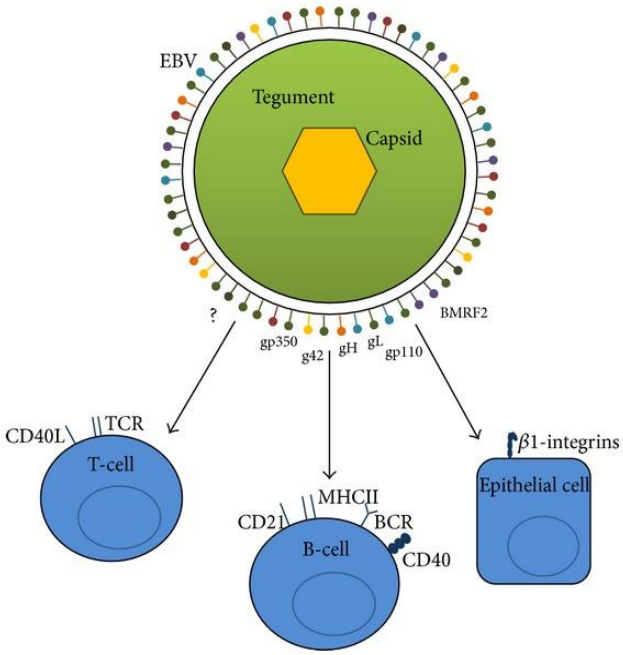

Figure 2: Drawing of EVB and its target cells (Draborg *et al.,*2013)

However, there are more mechanisms that explain the induction of autoimmunity by EBV infection. EBV infects several lymphocytes, and induces the immune response to evade and supress apoptosis of those infected lymphocytes. These processes may cause tolerance breakdown and, lately, autoimmunity (Draborg *et al.*, 2013).

4. Virus and multiple sclerosis

Multiple sclerosis (MS) is a human inflammatory disease of the central nervous system where demyelinating occurs (Croxford *et al.*, 2005; Libbey *et al*., 2014). MS is a rare disorder mediated by autoreactive T-cells (Croxford *et al*., 2005; Brown, 2016). However, the causes underlie MS are quite common and are being studied. The main factor leading to MS are genetic background and environmental factors as Epstein-Barr virus, low levels of vitamin D, smoking or even obesity (Brown, 2016; Correale and Gaitán, 2015; Libbey *et al*., 2014; Mostafa *et al*. 2017; Olsson *et al.*, 2017). The combination of these elements contributing to MS is clear, but the possible interactions between them to trigger MS remain unknown (Brown, 2016; Correale and Gaitán, 2015).

Genes only explain a small part of the propensity to develop MS. The main genetic risk factor consists of human leukocyte antigen complex (HLA). There are also other molecules and *loci* involved, like T-cell receptors or non-HLA genomic regions (Brown, 2016; Correale and Gaitán, 2015; Libbey *et al*., 2014; Olsson *et al*., 2017). However, the environmental factor o epigenetics may change gene expression altering some immune pathways that ultimately lead to MS. Thus, genes alone do not cause MS, in fact, their contribution is low (Brown, 2016; Correale and Gaitán, 2015; Jörg *et al*., 2016).

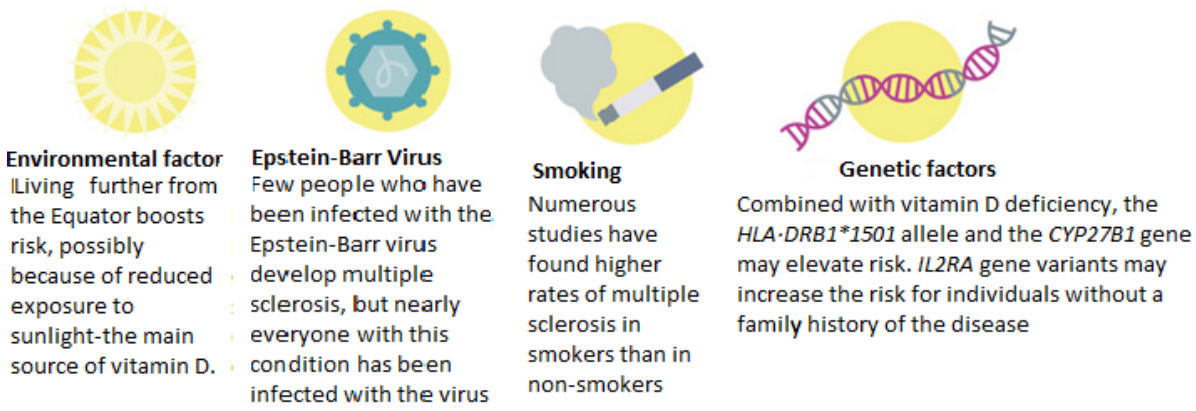

Figure 3: Causes that trigger autoimmune diseases (Schmidt, 2016)

During MS development, oligodendrocytes from the central nervous system are considered the main target cells, as autoimmune T cells (helpers) destroy them stopping myelin production. Other types of T cells are also important for demyelination (Mentis *et al.*, 2017).

Clinically, MS has become a major concern as the prevalence has increased around 10 times in the last years. Incidence is growing as well as the patients' survival explaining the increased levels. Because of that, health care has also improved to treat this disease. However, inequity has been seen so, more investigation and funding is needed (Browne *et al*., 2013; Mentis *et al*., 2017).

4.1 Environmental factors

Several studies have concluded that the main factors initiating MS development are pathogen infections, low vitamin D or lifestyle habits (smoking, diet). MS has a clear geographical distribution due to the probable effect of lower quantity of vitamin D on people. However, this link and how vitamin D influences continue being unknown (Brown, 2016; Correale and Gaitán, 2015).

Vitamin D has a major role in calcium homeostasis regulation and it is important for immune and inflammation regulation. Vitamin D may influence in several autoimmune diseases (Correale and Gaitán, 2015). So, vitamin D is an immunoregulator of some cells as T cells, being able to activate these cells but also inhibiting different transcription factors (Correale and Gaitán, 2015). Other immune cells influenced by vitamin D are the B cells (lymphocytes whose function is the antibodies production), decreasing antibody production with lower vitamin D levels.

Researchers have been trying to demonstrate the impact of vitamin D in the development of MS, discovering that low levels of vitamin D may be a risk as well as genetic background (Brown, 2016). Thus, the MS risk is less when there is more sunlight exposure or vitamin D supplements ingestion (Correale and Gaitán, 2015). In some experiments, vitamin D and a derivative have been used as protective elements for immunity.

However, other studies showed that risk genes can also be affected by vitamin D levels causing mutations and vitamin D may interact with HLA loci increasing MS risk. Vitamin D interacts with the vitamin D receptor present in immune cells, these effects combining allelic variations determine MS risk (Correale and Gaitán, 2015).

In addition, infections also may influence the development of MS. Pathogenic agents like bacteria, viruses or parasites may have an important role, not only as risk factor but also as protective agents (Libbey *et al*., 2014). This idea is supported by the hygiene hypothesis, which explains that exposure at early age to harmless, infectious agents protect against MS (Correale and Gaitán, 2015; Jörg *et al*., 2016; Libbey *et al*., 2014). But, an exposure at later life may increase the MS risk (Libbey *et al*., 2014). Therefore, there is a correlation between high risk of MS and a high sanitation during early life (Correale and Gaitán, 2015).

For example, the nematode parasite *Trichuris trichiura* appearance seems to decrease MS global prevalence. In some way, this parasite induces some protection against MS. In fact, in poor countries limited sanitary conditions and high parasites predominance contribute to low levels of allergic and autoimmune diseases (Correale and Gaitán, 2015). On the other hand, some recent studies have been carried out in developing countries. They found an increase of MS prevalence due to the lower cases of infections. Animal model experiments also demonstrate these hypotheses (Correale and Gaitán, 2015; Libbey *et al*., 2014).

Thus, considering these ideas and discoveries, the risky group to develop Ms is mainly predisposed young adults affected by multiple infections, living in good sanitary conditions (Correale and Gaitán, 2015, Libbey *et al*., 2014).

Despite the evidences that pathogens may have a role in MS process, their acceptance as main factors have not been accomplished yet (Libbey *et al*., 2014). There are so many potential influences (genetic make-up, environment, nutrition and lifestyle habits) that is not possible to identify one pathogen as MS cause. Smoking, obesity, UV exposure and pathogen infections interact affecting adaptive or innate immunity, leading to MS (Libbey *et al*., 2014; Olsson *et al*., 2017).

4.2 Viral agents

Viruses are a type of pathogens also responsible of MS aetiology. Two hypothesis may explain why a virus might cause MS development. One, only an agent leads to MS with a rare expression of a frequent virus or a common expression of a rare virus. The second one is called competing hypothesis where several agents disturb different pathways contributing MS (Mentis *et al*., 2017).

There are several mechanisms through virus may origin demyelination, elimination of myelin and axonal deterioration (Libbey *et al*., 2014; Mentis *et al*., 2017). In these mechanisms lysis of oligodendrocytes (infected or unaffected) takes place, but it can be done by the virus, by the host immune system, by nonspecific bystander immune response or by self-reactive immune response. The immune responses are triggered by the viral infection (Libbey *et al*., 2014; Mentis *et al*., 2017). Several researches have explained the possible link between viruses and MS, being rabies virus the first one discovered. Now, the best considered as causal factor are herpes viruses and human endogenous retroviruses (Libbey *et al*., 2014).

Some viral mechanisms can be responsible of the immunology of MS: molecular mimicry, bystander activation, epitope spreading, fertile field, and viral “déjà vu” (Mentis *et al*., 2017).

Some studies showed that molecular mimicry epitopes activate immune responses and trigger different autoimmune diseases. So, the similarity of viral proteins and human proteins stimulate autoreactive T cells leading to autoimmunity (Olson *et al.*, 2001). This mechanism has also an important role in MS since molecular mimicry induces autoreactive T cells, so activation of an inflammatory response attacks central nervous system (CNS) myelin (Croxford *et al*., 2005; Mentis *et al*., 2017). Nevertheless, the direct association between mimicry activated autoimmunity and viral agents has not been proved. Some viral infections may increase the number of altered T cells by molecular mimicry, but the mimic epitopes from virus still need to be investigated. Thus, some evidences that virus molecular mimicry enhance MS have been recorded (Croxford *et al*., 2005).

In bystander activation, viral elements and receptors induce self-proteins presentation to dendritic cells to finally create autoreactive T cells. These T cells would trigger inflammation and cell death (Grigoriadis and Hadjigeorgiou, 2006; Mentis *et al*., 2017).

Epitope spreading may induce T and B cell-mediated responses. Viral peptides activate macrophages eliminating neuronal myelin (Grigoriadis and Hadjigeorgiou, 2006; Mentis *et al*. 2017).

In fertile field theory, a transient, short-lived state (fertile field) is due to a viral infection. An initial inflammatory response by a viral infection produces autoreactive T cells via other mechanisms previously activated leading to neuronal inflammation. This fertile field depends on the type of virus, location and response (Libbey *et al*., 2014; Mentis *et al*., 2017).

The last theory, viral “déjà vu”, explains that a viral infection would create T cell clones which are going to be reactivated by other viruses, so finally causing neuronal inflammation (Mentis *et al*., 2017).

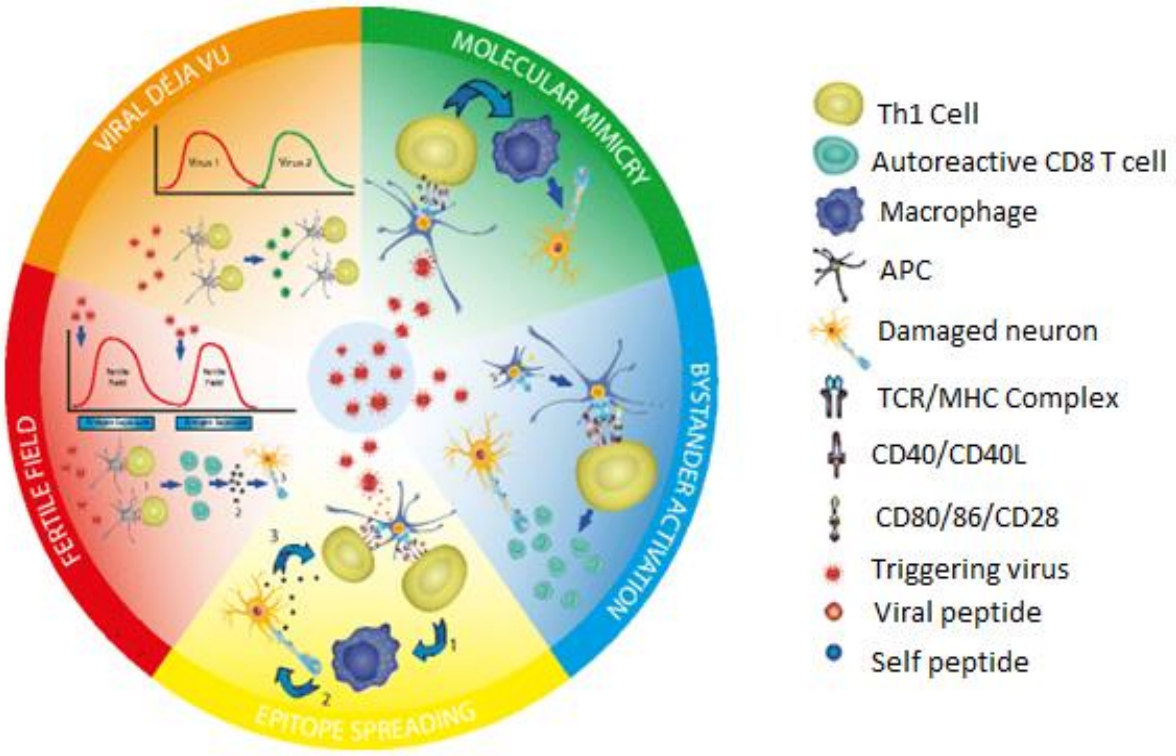

Figure 4: Mechanisms underlying viral aetiology to cause multiple sclerosis (Mentis *et al.*, 2017)

4.3 Epstein-Barr Virus

The strongest association of a virus and MS seems to be the influence of Epstein-Barr virus. This virus may not cause symptoms in so a big part of the population and therefore it is usually undiagnosed. However, this virus has a high persistence and a global high exposure (Brown, 2016; Correale and Gaitán, 2015). Some studies showed that several patients with MS are EBV seropositive. These MS patients have high number of anti-EBV

antibodies than healthy people. So, it demonstrates that EBV may be a factor inducing MS (Jörg *et al*., 2016).

There exist different theories to explain how EBV infection may culminate in MS, but more investigation is needed to better understand those possible mechanisms (Correale and Gaitán, 2015). One theory is based on the central nervous system infection by EBV. So, oligodendrocytes are killed and, therefore, there is no longer myelin production, damaging nerve function. Moreover, the virus also can induce an immune response that will kill the virus and it also will attack oligodendrocytes and neurons. Some studies showed viral presence in the CNS, but others did not have the same success (Brown, 2016).

The second hypothesis maintains that molecular mimicry may cause indistinguishable selection of myelin proteins and viral proteins, leading to disrupted myelination. Then, T cells are activated, because of the response against the virus, and start attacking viral and myelin proteins (Brown, 2016). There are evidences proving these theory as specific T-cell antigens have been found (Correale and Gaitán, 2015).

The third mechanism implicates another type of immune cells, the called B cells. When they are overactivated due to the viral infection the immune response continues spreading. As the immune cascades are not reversing, body cells are also injured. EBV induces B cells and T cells imbalance damaging their regulatory functions. Finally, these B cells trigger damages on the self-cells (Brown, 2016). In addition, after infection, B cells would be able to avoid apoptosis promoting CNS inflammation (Correale and Gaitán, 2015).

Moreover, since T cells have been altered by the viral infection, antibody production decreases. Therefore, virus may remain in the body forcing the immune system to continue working and still promoting loss of tolerance (Correale and Gaitán, 2015).

5. Virus and diabetes

Type 1 Diabetes mellitus (T1D) is an autoimmune disease where autoreactive T cells and inflammatory cytokines induce the pancreatic cells destruction. Therefore, this destruction leads to insulin loss (Jun and Yoon, 2001; Katsarou *et al*., 2017; Rodriguez-Calvo *et al.,* 2016). The aetiology of this disease needs more investigation since some aspects are not well known. However, researchers have concreted that genetic and environmental factors (viruses or other pathogens) may influence autoimmune diabetes development (Jun and Yoon, 2001; Katsarou *et al*., 2017; Kondrashova and Hyöti, 2014; Rodriguez-Calvo *et al*., 2016).

Nowadays, around 15 million of people suffers this disease whose development usually starts during childhood or teenage. Its prevalence and incidence have been increased and more cases in the future are being expected. These increases may be the result of environmental factors. Therefore, studying and understanding the causes underlie diabetes, it would be helpful to prevent and achieve early diagnosis (Kondrashova and Hyöti, 2014).

Type 1 diabetes may result from complex genetic make-up, but it seems not to be any obvious inheritance patterns. However, the risk of getting T1D is higher when relatives also have it. More than 60 risk genes have been found and one main *loci* involved is *HLA*, also partly responsible of other autoimmune diseases such as MS (Coppieters *et al.*, 2012; Regnell and Lenmark, 2017).

HLA play an important role as they are necessary to the adaptive immune system. Alterations in its heterodimers would trigger responses against proinsulin as well as against other essential proteins. So, these *loci* may influence the aetiology and pathogenesis of T1D (Regnell and Lenmark, 2017).

Some environmental factors may interact with the predispose genes, such as vitamin D, bacteria, or viral infections (Coppieters *et al*., 2012; Regnell and Lenmark, 2017).

5.1 Environmental factors

T1D may be resulted by environmental factors, as they can induce beta cell autoimmunity (cell in the pancreatic islets of the pancreas). It seems clear that high T1D prevalence may result from environmental impact since human genetics changes are not quick enough to reflect the rapid rises of the disease (Drescher *et al.*, 2015).

Pathogen infections are the most studied factors and many experiments have been done to prove its association with T1D (Regnell and Lenmark, 2017). These microbial infections have been suggested as a major regulator of TD1 risk. Two hypothesis may explain their importance: hygiene hypothesis considering that microbial exposure during early life may protect against T1D; the second theory, called triggering hypothesis, explains that a microbe produces beta cells damage (directly or via immune-controlled mechanisms) inducing T1D (Kondrashova and Hyöti, 2014).

Most microbial studies found that viral infections may be part of the risk factors, but also can have protective functions, whereas bacteria contribute to protection against T1D and other autoimmune diseases (Kondrashova and Hyöti, 2014). Some studies also suggest that gut microbiota may be associated with T1D. Intestinal microbiota play a crucial role in human health, so their possible importance in T1D relationship is not a surprise. Some studies confirmed that indeed there is an association between gut microbiota and T1D, but it is being investigated in animal and human models. Due to diet and environmental factors this microbiota may change resulting in normal or altered immune responses. Thus, microbiota modulation may trigger T1D. When this situation happens, T1D patients present different gut microbiota composition comparing to healthy individuals (Bibbò *et al.*, 2016).

Moreover, nutrition might regulate the T1D risk. For example, cow´s milk may contribute the progress of beta cell autoimmunity besides T1D development in children. Other studies suggest that diet in early life may also have an impact in the risk of this disease (Regnell and Lenmark, 2017).

More discoveries maintain that vitamin D may have a protection role against type 1 diabetes due to its ability of regulating the immune system. Also, fatty acids may influence the risk of autoimmunity. However, more clinical experiments are needed to prove these suggested associations. Sugar ingest, puberty, trauma or obesity have been also studied and linked to beta cell stress, thus finally leading to autoimmunity (Regnell and Lenmark, 2017).

In addition, some studies tested that psychosocial factors might be involved in T1D development. For example, stress can be a potential inducer but more investigation is needed to confirm this possible trigger (Teddy study group, 2008). Diet, stress or risk genes may interact contributing to the appearance of T1D.

5.2 Viral agents

Viral infections are well studied and seem to be one factor triggering type 1 diabetes (Kondrashova and Hyöti, 2014). A high number of viruses have been related with T1D, being enterovirus the main group suggested. For example, some studies showed that enterovirus more commonly infect diabetes patients. Moreover, a link between predisposed HLA genes and enterovirus infection has been discovered (Filippi and von Herrath, 2015).

Different arguments justify viral infections and T1D association: T1D can be classified as a seasonal disease and this type of diseases usually result from viral infections; most T1D patients produce specific viral antigens (Jun and Yoon, 2001).

These enteroviruses can induce T1D via different mechanisms, but more research is needed to prove them. The viral infection may enhance inflammation in the islets, due to T-cell cross reactivity, as well as the possible lysis of beta cells (Kondrashova and Hyöti, 2014; Filippi and von Herrath, 2015). However, the viral effects are different from expected. Enterovirus would be also able to create an autoimmune attack to the pancreatic islets. Anyway, as the mechanism are not totally understood and some discoveries are not enough clear, it is necessary more investigation (Filippi and von Herrath, 2015).

Other theories about the viral infection mechanisms suggest that viruses can interfere T-cell selection, interfering with T-cell maturation. Bystander activation, molecular mimicry or virus persistence are also some hypothesis to explain T1D and virus relationship (Coppieters *et al*., 2012).

To prevent from T1D triggered by enteroviruses infection, vaccination could be a strategy. Some reports support these ideas. Nevertheless, there are also contradictions as in poor countries T1D incidence is lower than in richer countries, but poor countries present higher levels of infections. In addition, the hygiene hypothesis explains that some pathogens may act as protective agents against T1D risk (Filippi and von Herrath, 2015).

Table 1: Viruses related to the development of Type 1 diabetes (adapted from Jun and Yoon, 2001)

Virus	Host	Evidence
Coxsackie B	Mice; primates; humans	Virus identified; possible destruction of beta cells
Cytomegalovirus	Humans	Association with T1D
Encephalomyocarditis	Mice; hamsters	Cytolytic destruction of beta cells
Epstein-Barr	Humans	Possible induction of T1D
Rubella	Hamsters; rabbits; humans	Possible association with T1D
Varicella zoster	Humans	Indirect association with T1D

5.3 Coxsackie B Virus

CVB (Coxsackie B virus) is a group of positive ssRNA viruses, belonging to enterovirus genus. These viruses can infect humans with low or none symptoms like cold-like manifestations. CVB has been well studied, and related to numerous human diseases (Tracy *et al*., 2002). As CVB has been detected in type 1 diabetes patients, it is considered as a viral factor which triggers this disease (Sané *et al.*, 2011). T1D patients' blood usually contain CVB RNA as well as high amounts of CVB antigens proving this hypothesis (Filippi and von Herrath, 2015). However, the aetiology role of CVB has not been demonstrated yet as this infection may only occur in a small population (Filippi and von Herrath, 2015; Tracy *et al*., 2002).

The mechanisms behind CVB and T1D relationship remain unclear, but some general theories have been suggested. To explain T1D underlying mechanisms several *in vitro* studies have been done as well as animal models usage. CVB may lead to T1D by beta cell lysis, bystander activation, viral persistence, molecular mimicry, antibody enhancement and thymus function disturbance and antibody enhancement (Sané *et al*., 2011).

Some studies revealed that CVB infection might accelerate T1D development. Nevertheless, in a specific experiment they could not prove CVB aetiology in T1D. However, they found that in early-life mice CVB infection play a protective role, decreasing T1D risk. The mechanism underlying these effects is still unknown (Tracy *et al*., 2002).

To conclude, the results of different experiments (*in vitro* and in animal models) may support the theories of the importance of CVB in T1D. Despite the success, more investigation is required to achieve a better understanding of the mechanisms and a future creation of treatments (Sané *et al*., 2011).

6. Conclusions/Conclusiones/Conclusións

Conclusions

Autoimmune diseases are due to a defect of the immune system as self-cells are being attacked by the organism. The symptoms are very variable that is why more than eighty different autoimmune diseases coexist.

These diseases have become a big concern due to their incidence and prevalence increase. Therefore, investigation has been realised to try to understand the mechanisms and causes behind these disorders.

Genetics, environmental factors and lifestyle habits may trigger the development of autoimmune diseases. Viral infections have been demonstrated to play a major role in the trigger of these diseases or at least increasing the development risk. The mechanisms underlying the diseases by viral infections go from molecular mimicry, bystander activation or epitope spreading, ultimately leading to autoimmunity. Therefore, viruses are, in fact, associated in one way or another to autoimmune diseases.

Multiple sclerosis and type 1 diabetes are two examples of autoimmune diseases. Viral infections have been suggested and proved to trigger MS and T1D via different mechanisms still being unclear. However, there are different hypothesis explaining the role of viral infections in the development of these diseases as well as the hypothesis that pathogens and viruses may also play a protective role. Other factors as genetic predisposition, diet, lifestyle habits or vitamin D levels may also trigger these diseases.

To sum up, there are evidences concluding virus and autoimmune diseases are associated. However, to explain this relationship and the mechanisms behind, more investigation is needed. For instance, experiments with virus and animal models can be done to prove the hygiene hypothesis and try to take advantage of their protective role using them as prevention treatments.

Conclusiones

Las enfermedades autoinmunes se deben a un mal funcionamiento del sistema inmunológico, ya que las propias células son atacadas por el organismo. Como existen más de ochenta enfermedades autoinmunes diferentes, los síntomas son muy variables y, por tanto, dependen de la enfermedad en cada caso.

Estas enfermedades se han convertido en una gran preocupación debido al aumento de su incidencia y de su prevalencia. Por lo tanto, se ha empezado a realizar múltiples investigaciones para intentar comprender los mecanismos y causas detrás de estos trastornos.

La genética, los factores ambientales y los hábitos de vida pueden desencadenar el desarrollo de enfermedades autoinmunes. Se ha demostrado que las infecciones víricas desempeñan un papel importante en el desarrollo de estas enfermedades o al menos

parecen aumentar el riesgo de su desarrollo. Los mecanismos que pueden desencadenar estas enfermedades por infecciones víricas van desde el mimetismo molecular, la activación inespecífica o la propagación de epítopos, que finalmente conduce a la autoinmunidad. Por lo tanto, los virus están, de hecho, asociados de una manera u otra a enfermedades autoinmunes.

La esclerosis múltiple y la diabetes tipo 1 son dos ejemplos de enfermedades autoinmunes. Se han sugerido y demostrado que las infecciones virales pueden ser desencadenantes de esclerosis múltiple y de diabetes tipo 1 a través de diferentes mecanismos aún no claros. Sin embargo, hay diferentes hipótesis que explican el papel de las infecciones virales en el desarrollo de estas enfermedades, así como la hipótesis de que los patógenos y los virus también pueden desempeñar un papel protector. Otros factores como predisposición genética, dieta, hábitos de vida o niveles de vitamina D pueden también causar estas enfermedades.

Hay evidencias que concluyen que virus y enfermedades autoinmunes están asociados. Sin embargo, es necesaria más investigación para explicar esta relación y los mecanismos subyacentes. Por ejemplo, se podrían realizar más experimentos con virus y animales para demostrar la hipótesis de la higiene y así, aprovechar sus propiedades protectoras usándolos como tratamientos preventivos.

Conclusións

As enfermidades autoinmunes son causadas por unha mal función do sistema inmune, porque as propias células son atacadas polo organismo. Ao existir máis de oitenta enfermidades autoinmunes diferentes, os síntomas varían amplamente dependendo da enfermidade.

Estas enfermidades tornáronse unha gran preocupación pola súa crecente incidencia e prevalencia crecente. Polo tanto, empezaron a realizarse múltiples investigacións para tratar de entender os mecanismos e causas detrás destes trastornos.

Xenética, factores ambientais e hábitos de vida poden desencadear o desenvolvemento de enfermidades autoinmunes. Suxeriuse que as infeccións virais poden actuar como factores con papeis importantes no desencadeamento de estas enfermidades ou polo menos aumentando o risco do seu desenvolvemento. Os mecanismos subxacentes á enfermidade por infeccións víricas varían dende mimetismo molecular, a activación non específica ou a extensión de epítopos, que finalmente conduce á autoinmunidade. Así, os virus están, de feito, asociados, dunha forma ou outra, ás enfermidades autoinmunes.

A esclerose múltiple e a diabetes tipo 1 son dous exemplos de enfermidades autoinmunes. Demostrouse que as infeccións virais son factores que poden provocar esclerose múltiple e diabetes tipo 1 a través de diferentes mecanismos aínda non claros. Sen embargo, hai diferentes hipóteses para explicar o papel das infeccións virais no desenvolvemento destas enfermidades, así como a suposición de que patóxenos e virus poden presentar un papel protector. Outros factores, tales como a predisposición xenética, alimentación, estilo de vida ou niveis de vitamina D poden inducir o desenvolvemento de estas enfermidades.

Hai evidencias que conclúen que virus e enfermidades autoinmunes están relacionadas. Sen embargo, máis investigación é necesaria para explicar esta relación e os mecanismos subxacentes. Por exemplo, deberían realizarse máis experimentos con virus e animais poderían para demostrar a hipótese da hixiene e así, aproveitar as súas propiedades protectoras usándoos como tratamentos preventivos

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