Consequences of errors in the functioning of the immune system Descriptive review

[Running title: Consequences of misstep of the immune system]

Majda Samih[1] and Ahmed Omar Touhami Ahami[2]

[1]Temporary teacher, Clinical and Cognitive Neurosciences Unit, Biology and Health Laboratory, Department of Biology, Faculty of Sciences, Ibn Tofail University, Kenitra, Morocco

[2]Head Professor, Clinical and Cognitive Neurosciences Unit, Biology and Health Laboratory, Department of Biology, Faculty of Sciences, Ibn Tofail University, Kenitra, Morocco

ABSTRACT: The immune system is a very complex network of cells, tissues and organs that work together to defend the body against pathogens. Its two main components are: the innate immune system and the adaptive immune system. However, when this system is compromised, the body's ability to defend itself is impaired, which can increase the risk of developing at least one of the more than 80 autoimmune diseases that affect a significant proportion of the world's population. These illnesses can cause a range of symptoms, including pain, fatigue, rashes, nausea, headaches and dizziness. They can also affect different parts of the body, such as the skin, muscles, joints, tendons, blood and blood vessels, and even other organs. Also, it is not uncommon to suffer from more than one type of autoimmune disease, as they share similarities in their basic immunological mechanisms. In this review, we aim to provide a more comprehensive understanding of the impact and severity of immune dysfunction. We will also describe the advantages and disadvantages of factors considered to promote immune function and summarize current knowledge about the mechanisms of certain autoimmune diseases. We hope to shed light on this complex subject and provide valuable insights into potential treatments and preventive measures for these diseases.

KEYWORDS: Immune system, autoimmune diseases, symptoms, immune dysfunction, preventive measures.

INTRODUCTION

The immune system is a highly effective defense mechanism that plays a crucial role in protecting the body against a variety of harmful pathogens, including viruses, bacteria, fungi and parasites. Its main function is to identify and eliminate these potential threats in order to preserve the body as a whole. However, it is equally important for the immune system to maintain a delicate balance between effectively eliminating pathogens and avoiding excessive immune responses. This balance is achieved through a process called immune tolerance, which ensures that the immune system does not attack the body's own cells and tissues. Although this system is designed to function optimally, in some cases it can be compromised or immune tolerance can be disrupted, resulting in a series of conditions known as autoimmune diseases, of which there are over 80 types [1]. These disorders occur when the immune system mistakenly recognizes the body's own cells or tissues as foreign and launches an immune attack against them. These disorders are classified according to whether the autoimmune attack is systemic or organ-specific [2]. They also share common features, including loss of tolerance [3], pathological pain [4], production of auto-antibodies, a strong genetic component, environmental triggers and overlap between different diseases [5]. Approximately 5% of the world's population is affected by these diseases, with women accounting for 80% of cases [6]. It is essential to maintain a healthy and robust immune system to prevent infection and disease. To do this, it is important to understand the pros and cons of the factors that influence immune health, in order to adopt a balanced approach aimed at optimizing the functioning of this mechanism.

FACTORS THAT CAN PROMOTE THE IMMUNE SYSTEM

ADVANTAGES AND DISADVANTAGES

A) NUTRITION

The immune system constantly protects the human body against external aggression and internal threats. Maintaining this performance requires an appropriate diet that provides the essential nutrients needed to function properly [7]. A balanced, nutritious diet helps to strengthen the immune system and reduce the risk of infection. To function optimally, the immune system needs essential nutrients such as vitamins A, C, D, E, B6, B12, zinc, iron and selenium [8, 9]. At the same time, overeating in relation to physical activity can lead to weight gain, which in turn can lead to health problems such as obesity. Studies have shown that obesity leads to a weakened immune system [10]. In addition, obesity can lead to metabolic disorders, immune disorders and other diseases such as hypertension and diabetes [11-13]. On the other hand, nutritional deficiencies can lead to reduced immunity and make individuals more vulnerable to infections [14, 15]. For all cells to function optimally, including those of the immune system, adequate and appropriate nutrition is necessary. Maintaining a healthy diet is therefore essential to promote overall health and well-being.

B) STRESS

For the immune system to function effectively, it is essential to have a healthy environment free from factors that can interfere with its functioning, such as stress. Prolonged exposure to stress can have a variety of adverse effects on health [16, 17]. Many of the health effects of stress are mediated by the immune system [18-20]. Although short-term stress can be beneficial in preparing the body for challenges and improving cognitive performance [21], chronic stress is generally detrimental to health.

Stress is an unavoidable part of life and can take many forms and dimensions, including psychological stress, which can make the body more vulnerable to disease. However, research has shown that a stress-free life is not always beneficial [22]. It is therefore essential to manage chronic stress in order to maintain a robust immune system and good general health.

C) PHYSICAL ACTIVITY

Although physical activity can provide several benefits, it is essential to engage in the one appropriate to one's ability. Among these benefits is increased blood flow to vital organs including the spleen, which is essential for immune function [23]. It can also increase immune cell production and reduce chronic inflammation. However, excessive or high-intensity exercise without adequate rest can lead to decreased cellular immunity and increased susceptibility to infectious diseases [24, 25]. Research has shown that the immune response associated with exercise is influenced by several factors, including the frequency, intensity, duration, and type of activity [26, 27]. In addition, excessive exercise can cause intense fatigue which can negatively impact the capacity of the immune system [28]. Conversely, a sedentary lifestyle, i.e. little or no physical activity, is considered to be one of the main risk factors for immune function [29]. Studies have shown that inactivity can weaken the immune system and make sedentary people more susceptible to infections and chronic health conditions [30, 31]. Therefore, it is crucial to engage in regular physical activity appropriate to individual abilities with sufficient recovery time to prevent any potential negative effects on overall health.

D) SLEEP

Age-appropriate sleep is not only essential for supporting the immune system, but also plays a vital role in promoting physical, mental and emotional health [32]. Given its importance as a modulator of the immune response, research has shown close links between sleep and the immune system [33]. In addition, it allows mental and physical recovery.

Sleep deprivation can weaken immunity and make the body more vulnerable to infection. Chronic deprivation of this factor can be considered as a state of non-specific chronic stress, which in turn has an impact on immune function and general health [18, 22, 34].

Excessive sleep, on the other hand, is associated with a number of health problems such as type 2 diabetes, heart disease, obesity and so on.

To avoid any complications, optimal sleep has been recommended for its valuable physiological processes, which include restorative and regulatory properties [35, 36].

E) ALCOHOL

The link between alcohol consumption, the immune response and infectious and inflammatory processes remains controversial and is not yet fully understood. Studies highlight the effects of excessive alcohol consumption, which can lead to immune deficiency and increased susceptibility to certain diseases. In contrast, moderate alcohol consumption has been associated with no risk [37] or a reduced risk of upper respiratory tract infections [38]. It has been suggested that moderate alcohol consumption has a beneficial impact on the immune system compared with alcohol abuse or abstinence [39- 43]. Some studies have added that moderate alcohol consumption may have favourable effects on health, such as reducing the risk of cardiovascular disease [44]. However, it is important to note that the effects of alcohol can vary from one person to another due to a number of factors that can influence these effects on an individual. In conclusion, it is strongly advised to approach alcohol consumption responsibly and to be aware of the potential risks and differences in reaction between individuals.

F) CLEANLINESS

Cleanliness can have both positive and negative effects on the immune system. On the positive side, exposure to a diverse range of microbes in the environment can contribute to strengthening the immune system. Additionally, it has been shown that exposure to certain types of microbes has a beneficial effect on health [45, 46]. Some studies suggest that exposure to microbes in early childhood is necessary for the proper development of the immune system [47]. On the other hand, excessive cleanliness can weaken the immune system, and it needs to be exposed to a variety of microbes to develop and maintain its capacity.

In summary, the balance between cleanliness and exposure to microbes is important for the proper development and functioning of the immune system. While it is important to maintain good hygiene practices, excessive cleanliness should be avoided, and exposure to a diverse range of microbes should be encouraged as much as possible.

G) SMOKING

Each of the factors discussed above has its positive, negative, and optimal aspects, except for smoking. Smoking is one of the leading causes of preventable death and disease [48] due to the many harmful chemicals found in cigarettes, including nicotine, tar, and carbon monoxide [49, 50], as well as addictive additives. This highly addictive habit has numerous negative health consequences, weakens the body's ability to fight disease, and increases the risk of immune system problems [51]. However, banning smoking in public places has been shown to significantly reduce the exposure of non-smokers to second-hand smoke [52]. Smoking has no benefit for any part of the body, including the immune system. Quitting smoking, on the other hand, offers numerous benefits, such as improved lung function, a reduced risk of disease, and better overall health and well-being. By monitoring and implementing the positive aspects of the other factors mentioned, individuals can strengthen their immune system, promote good health, and reduce the risk of autoimmune diseases.

AUTOIMMUNE DISEASES

Autoimmune diseases are caused by a malfunction of the immune system, which accidentally attacks the body instead of protecting it. The exact causes of this failure are not fully understood, but they probably result from a combination of genetic and environmental factors such as excessive exposure to chemicals [53] or solvents. These diseases can have a variety of symptoms depending on the type and organs affected, but certain signs are common, such as fatigue, joint pain, skin rashes, digestive and neurological disorders, weight loss and inflammation. There are more than 80 types of autoimmune disease that affect different organs and tissues of the body. Some are more serious than others and can cause lasting tissue damage, while others only affect a person's quality of life without causing significant physical damage. In addition, many of these diseases have similar symptoms or can occur simultaneously in the same individual.

Studies have shown that people with a family history, certain ethnic groups [54] and those who have been exposed to certain environmental factors are more likely to develop an autoimmune disease. It is true that many autoimmune diseases affect women more frequently than men, with ratios varying according to the disease. The reasons for this gender disparity are not fully understood, but hormonal factors and the strength of women's immune systems may play a role.

Autoimmune diseases are considered multifactorial because of their complexity and the involvement of multiple factors in their origin, which makes their prevention and effective management difficult. The variation in symptoms of these diseases from person to person makes diagnosis difficult. Although treatments are available to manage these symptoms and reduce

inflammation, autoimmune diseases are generally considered incurable [55, 56] and often require ongoing management and care.

Treatment goals generally focus on reducing inflammation and suppressing the immune system to prevent organ and tissue damage. However, there are some exceptions to this rule, such as certain types of autoimmune diseases that can go into remission or be effectively treated with drugs or other therapies [57, 58]. Although autoimmune diseases remain complex, ongoing research efforts aim to elucidate their underlying mechanisms, improve diagnostic methods and develop more targeted and effective treatments. In the meantime, improving the quality of life of people suffering from these enigmatic diseases is essential. This includes cultivating a positive frame of mind in these individuals so that they accept their fate, implementing effective symptom management strategies, adopting a nutritious diet, encouraging them to engage in regular physical activity and reducing stress levels to a minimum.

SOME FACTORS INVOLVED IN TRIGGERING AUTOIMMUNE DISEASES

Autoimmune diseases are complex conditions. Although the exact causes of these diseases are not fully understood, studies point to several factors that can contribute to their development and trigger their appearance. Here are just a few of the factors known to be involved:

a) Environmental triggers: Various environmental factors have been implicated in the onset of autoimmune diseases [59, 60]. These may include infections (viral or bacterial), exposure to certain chemicals [53] or toxins, or even physical or emotional stress [61].

b) Genetic factors: There is some evidence to suggest that certain genetic factors may predispose individuals to autoimmune diseases [62]. A family history of autoimmune disease increases the risk of developing one.

c) Hormonal factors, particularly in women, also play a role, with fluctuations during puberty [63], pregnancy or the menopause influencing the development or progression of the disease.

d) Immune system dysfunction: Autoimmune diseases result from dysfunction or disruption of the immune system. It is thought that certain events can upset the balance of immune cells and the signals they receive, leading to an inappropriate immune response against the body's own tissues.

e) Gut microbiome: The composition and diversity of the gut microbiome, the collection of micro-organisms living in the digestive tract, can have an impact on immune function [64]. Imbalances in the intestinal microbiome, such as dysbiosis (alteration of normal microbial communities), have been associated with autoimmune diseases.

Understanding these factors and their interactions can provide valuable insights for improving diagnosis, treatment, and prevention strategies for autoimmune diseases.

CURRENT KNOWLEDGE OF THE MECHANISMS OF CERTAIN AUTOIMMUNE DISEASES AND THEIR TARGETS

Autoimmune diseases occur when the immune system, responsible for protecting against foreign invaders such as bacteria and viruses, mistakenly attacks its own cells and tissues. These diseases can affect various parts of the body and have various manifestations, and all share a common underlying mechanism of immune dysfunction.

The exact mechanisms by which autoimmune diseases develop are not fully understood, but significant progress has been made in unravelling some of the key factors involved. Researchers have identified some autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, type 1 diabetes, lupus and celiac disease, Myasthenia gravis (MG) and have gained a better understanding of their causes and effects.

In rheumatoid arthritis, the immune system primarily targets the synovial membrane [65], which lines the joints. The immune cells misperceive the synovial tissue as a threat and trigger an inflammatory response, resulting in joint pain, stiffness and swelling. Over time, this chronic inflammation can damage the joints and surrounding tissue.

Multiple sclerosis is characterised by the immune system attacking the myelin sheath, a protective covering around the nerve fibres of the central nervous system. When myelin is damaged, nerve signals are disrupted, resulting in a wide range of neurological symptoms such as muscle weakness, impaired coordination and cognitive difficulties.

Type 1 diabetes results from a mistaken attack by the immune system on the insulin-producing cells of the pancreas, called beta cells. As a result, the body can no longer produce enough insulin, which leads to high blood sugar levels.

Lupus is a systemic autoimmune disease that can affect multiple organs and tissues throughout the body. [66] It involves the immune system producing auto-antibodies that target various components, such as DNA, red blood cells, and cell membranes. This generalized immune response leads to inflammation and damage in the affected organs, resulting in symptoms that vary widely from individual to individual.

Celiac disease involves the immune system targeting the lining of the small intestine in response to the ingestion of gluten, a protein found in wheat, barley and rye [67]. The immune response triggered by gluten damages the intestinal lining, leading to malabsorption of nutrients and causing symptoms such as abdominal pain, diarrhoea and weight loss.

Myasthenia gravis (MG) is also an autoimmune disease that affects the neuromuscular junction (NMJ), the point where nerve cells communicate with the muscles they control. In this disease, the immune system mistakenly produces antibodies that target and attack specific proteins in the postsynaptic membrane of the neuromuscular junction [68- 70]. As with all autoimmune diseases, the exact cause of MG is not yet fully understood.

Research into autoimmune diseases is ongoing and new knowledge about their mechanisms continues to emerge. Scientists are exploring the roles of specific immune cells, signalling pathways and genetic variations to better understand these complex disorders. Ultimately, advances in research will contribute to the development of more effective treatments and strategies to manage autoimmune diseases.

CONCLUSION

Autoimmune diseases encompass a wide range of conditions that occur when the immune system mistakenly attacks healthy cells and tissues in the body. There are more than 80 known autoimmune diseases, and each can have different symptoms, affect different organs or systems and have varying underlying causes.

It is important to note that autoimmune diseases are complex and can have multiple contributing factors. Each autoimmune disease has its own triggers and mechanisms. Further research is needed to fully understand the complexities of these conditions.

Given the complexity and diversity of autoimmune diseases, it is essential to approach each condition individually and take into account the specific factors involved in its development. Understanding these factors can help to improve diagnosis, develop targeted treatments and manage these diseases more effectively.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

REFERENCES

[1]   THEOFILOPOULOS, Argyrios N., KONO, Dwight H., et BACCALA, Roberto. The multiple pathways to autoimmunity. Nature immunology, 2017, vol. 18, no 7, p. 716-724.

[2]   YU, Cong, GERSHWIN, M. Eric, et CHANG, Christopher. Diagnostic criteria for systemic lupus erythematosus: a critical review. Journal of autoimmunity, 2014, vol. 48, p. 10-13.

[3]   ANAYA, Juan-Manuel. Common mechanisms of autoimmune diseases (the autoimmune tautology). Autoimmunity reviews, 2012, vol. 11, no 11, p. 781-784.

[4]   MIFFLIN, Katherine A. et KERR, Bradley J. Pain in autoimmune disorders. Journal of neuroscience research, 2017, vol. 95, no 6, p. 1282-1294.

[5]   JAWAHEER, Damini, SELDIN, Michael F., AMOS, Christopher I., et al. A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases. The American Journal of Human Genetics, 2001, vol. 68, no 4, p. 927-936.

[6]   QUINTERO, Olga L., AMADOR-PATARROYO, Manuel J., MONTOYA-ORTIZ, Gladys, et al. Autoimmune disease and gender: plausible mechanisms for the female predominance of autoimmunity. Journal of autoimmunity, 2012, vol. 38, no 2-3, p. J109-J119.

[7]   MAGGINI, Silvia, MALDONADO, Paola, CARDIM, Paula, et al. Vitamins C, D and zinc: synergistic roles in immune function and infections. Vitam Miner, 2017, vol. 6, no 167, p. 2376-1318.1000167.

[8]   MAGGINI, Silvia, PIERRE, Adeline, et CALDER, Philip C. Immune function and micronutrient requirements change over the life course. Nutrients, 2018, vol. 10, no 10, p. 1531.

[9]   CALDER, Philip C., CARR, Anitra C., GOMBART, Adrian F., et al. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients, 2020, vol. 12, no 4, p. 1181.

[10]   MILNER, J. Justin et BECK, Melinda A. The impact of obesity on the immune response to infection. Proceedings of the Nutrition Society, 2012, vol. 71, no 2, p. 298-306.

[11]   SOROF, Jonathan et DANIELS, Stephen. Obesity hypertension in children: a problem of epidemic proportions. Hypertension, 2002, vol. 40, no 4, p. 441-447.

[12]   RAGHAVAN, Somasundaram, SINGH, Nikhlesh K., GALI, Sivaiah, et al. Protein kinase Cθ via activating transcription factor 2-mediated CD36 expression and foam cell formation of Ly6Chi cells contributes to atherosclerosis. Circulation, 2018, vol. 138, no 21, p. 2395-2412.

[13]   WEST-EBERHARD, Mary Jane. Nutrition, the visceral immune system, and the evolutionary origins of pathogenic obesity. Proceedings of the National Academy of Sciences, 2019, vol. 116, no 3, p. 723-731.

[14]   WATSON, Ronald R. Nutrition, disease resistance, and immune function. M. Dekker, 1984.

[15]   CHANDRA, Ranjit Kumar. Nutrition, immunity and infection: from basic knowledge of dietary manipulation of immune responses to practical application of ameliorating suffering and improving survival. Proceedings of the National Academy of Sciences, 1996, vol. 93, no 25, p. 14304-14307.

[16]   MCEWEN, Bruce S. Protective and damaging effects of stress mediators. New England journal of medicine, 1998, vol. 338, no 3, p. 171-179.

[17]   ADER, R. Psychoneuroimmunology, International Encyclopedia of the Social & Behavioral Sciences. 2001.

[18]   DHABHAR, Firdaus S. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. Neuroimmunomodulation, 2009, vol. 16, no 5, p. 300-317.

[19]   DHABHAR, Firdaus S., MALARKEY, William B., NERI, Eric, et al. Stress-induced redistribution of immune cells—From barracks to boulevards to battlefields: A tale of three hormones–Curt Richter Award Winner. Psychoneuroendocrinology, 2012, vol. 37, no 9, p. 1345-1368.

[20]   PADRO, Caroline J. et SANDERS, Virginia M. Neuroendocrine regulation of inflammation. In: Seminars in immunology. Academic Press, 2014. p. 357-368.

[21]   DHABHAR, Firdaus S. Effects of stress on immune function: the good, the bad, and the beautiful. Immunologic research, 2014, vol. 58, p. 193-210.

[22]   MCEWEN, Bruce S. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiological reviews, 2007, vol. 87, no 3, p. 873-904.

[23]   SIMPSON, Richard J., CAMPBELL, John P., GLEESON, Maree, et al. Can exercise affect immune function to increase susceptibility to infection?. Exercise immunology review, 2020, vol. 26, p. 8-22.

[24]   PEDERSEN, Bente Klarlund et HOFFMAN-GOETZ, Laurie. Exercise and the immune system: regulation, integration, and adaptation. Physiological reviews, 2000.

[25]   LEANDRO, Carol Góis, CASTRO, Raul Manhães de, NASCIMENTO, Elizabeth, et al. Adaptative mechanisms of the immune system in response to physical training. Revista Brasileira de Medicina do Esporte, 2007, vol. 13, p. 343-348.

[26]   LADDU, Deepika R., LAVIE, Carl J., PHILLIPS, Shane A., et al. Physical activity for immunity protection: Inoculating populations with healthy living medicine in preparation for the next pandemic. Progress in cardiovascular diseases, 2021, vol. 64, p. 102.

[27]   SIMPSON, Richard J. et KATSANIS, Emmanuel. The immunological case for staying active during the COVID-19 pandemic. Brain, behavior, and immunity, 2020, vol. 87, p. 6.

[28]   WALSH, Neil P., GLEESON, Michael, PYNE, David B., et al. Position statement part two: maintaining immune health. 2011.

[29]   SIMPSON, Richard J., KUNZ, Hawley, AGHA, Nadia, et al. Exercise and the regulation of immune functions. Progress in molecular biology and translational science, 2015, vol. 135, p. 355-380.

[30]   NIEMAN, David C. et WENTZ, Laurel M. The compelling link between physical activity and the body's defense system. Journal of sport and health science, 2019, vol. 8, no 3, p. 201-217.

[31]   CAMPBELL, John P. et TURNER, James E. Debunking the myth of exercise-induced immune suppression: redefining the impact of exercise on immunological health across the lifespan. Frontiers in immunology, 2018, vol. 9, p. 648.

[32]   LUYSTER, Faith S., STROLLO JR, Patrick J., ZEE, Phyllis C., et al. Sleep: a health imperative. Sleep, 2012, vol. 35, no 6, p. 727-734.

[33]   BORN, Jan. Sleep and immune functions. Psychoneuroimmunology: An interdisciplinary introduction, 1999, p. 417-442.

[34]   MEERLO, Peter, SGOIFO, Andrea, et SUCHECKI, Deborah. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep medicine reviews, 2008, vol. 12, no 3, p. 197-210.

[35]   BENINGTON, Joel H. et HELLER, H. Craig. Restoration of brain energy metabolism as the function of sleep. Progress in neurobiology, 1995, vol. 45, no 4, p. 347-360.

[36]   MACKIEWICZ, Miroslaw, SHOCKLEY, Keith R., ROMER, Micah A., et al. Macromolecule biosynthesis: a key function of sleep. Physiological genomics, 2007, vol. 31, no 3, p. 441-457.

[37] ENGS, Ruth C. et ALDO-BENSON, Marlene. The association of alcohol consumption with self-reported illness in university students. Psychological Reports, 1995, vol. 76, no 3, p. 727-736.

[38] DOLL, Richard, PETO, Richard, BOREHAM, Jillian, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. Bmj, 2004, vol. 328, no 7455, p. 1519.

[39] COHEN, Sheldon, TYRRELL, D. A., RUSSELL, Michael A., et al. Smoking, alcohol consumption, and susceptibility to the common cold. American journal of public health, 1993, vol. 83, no 9, p. 1277-1283.

[40] Mendenhall, C.L., et al. «Biphasic in vivo immune function after low-versus high-dose alcohol consumption.» Alcohol, vol. 14, no. 3, 1997, pp. 255-260.

[41] Diaz, L. E., et al. «Influence of alcohol consumption on immunological status: a review.» European journal of clinical nutrition, vol. 56, no. 3, 2002, pp. S50-S53.

[42] Romeo, J., et al. «Changes in the immune system after moderate beer consumption.» Annals of Nutrition and Metabolism, vol. 51, no. 4, 2007, pp. 359-366.

[43] Romeo, J., et al. «Effects of moderate beer consumption on first-line immunity of healthy adults.» Journal of physiology and biochemistry, vol. 63, no. 2, 2007, pp. 153-159.

[44] Brien, S. E., et al. «Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies.» Bmj, vol. 342, 2011.

[45] Lowry, C. A., et al. «Identification of an immune-responsive mesolimbocortical serotonergic system: potential role in regulation of emotional behavior.» Neuroscience, vol. 146, no. 2, 2007, pp. 756-772.

[46] Rook, G. A., et al. «Microbial 'Old Friends', immunoregulation and stress resilience.» Evolution, medicine, and public health, vol. 2013, no. 1, 2013, pp. 46-64.

[47] Rook, G. A., et al. «Hygiene and other early childhood influences on the subsequent function of the immune system.» Brain research, vol. 1617, 2015, pp. 47-62.

[48] Centers for Disease Control and Prevention (CDC. «Annual smoking-attributable mortality, years of potential life lost, and economic costs--United States, 1995-1999.» MMWR. Morbidity and mortality weekly report, vol. 51, no. 14, 2002, pp. 300-303.

[49] Rennard, S. I. «Cigarette smoke in research.» American journal of respiratory cell and molecular biology, vol. 31, no. 5, 2004, pp. 479-480.

[50] Talhout, R., et al. «Hazardous compounds in tobacco smoke.» International journal of environmental research and public health, vol. 8, no. 2, 2011, pp. 613-628.

[51] Qu, J., et al. «Recent developments in the role of reactive oxygen species in allergic asthma.» Journal of thoracic disease, vol. 9, no. 1, 2017, pp. E32.

[52] Gorini, G., et al. «Smoke-free policy development in Italy through the legislative process of the ban 2000-2005, and press media review 1998-2008.» Annali dell'Istituto superiore di sanità, vol. 47, 2011, pp. 260-265.

[53] Samih, M., and Ahami, A. O. T. «Research Article Excessive Pesticide Use Likely to Cause the Onset of Myasthenia Gravis in the Moroccan Agricultural Population.» Population, vol. 23, 2020, pp. 917-921.

[54] Anaya, J. M., et al. «The autoimmune tautology: from polyautoimmunity and familial autoimmunity to the autoimmune genes.» Autoimmune Diseases, 2012.

[55] Stroehla, B. C. «The epidemiology of autoimmune diseases.» Autoimmunity Reviews, vol. 2, 2003, pp. 119-125.

[56] Cooper, G. S., et al. «Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases.» Journal of Autoimmunity, vol. 33, no. 3-4, 2009, pp. 197-207.

[57] Feng, X., et al. «Association of increased interferon-inducible gene expression with disease activity and lupus nephritis in patients with systemic lupus erythematosus.» Arthritis Rheum, vol. 54, 2006, pp. 2951-2962.

[58] Crow, M. K. «Type I interferon in systemic lupus erythematosus.» Current Topics in Microbiology and Immunology, vol. 316, 2007, pp. 359-386.

[59] Miller, F. W., et al. «Criteria for environmentally associated autoimmune diseases.» Journal of Autoimmunity, vol. 39, no. 4, 2012, pp. 253-258.

[60] Cho, J. H., and Gregersen, P. K. «Genomics and the multifactorial nature of human autoimmune disease.» New England Journal of Medicine, vol. 365, no. 17, 2011, pp. 1612-1623.

[61] Anaya, J. M. «The autoimmune tautology.» Arthritis Research & Therapy, vol. 12, no. 6, 2010, pp. 1-3.

[62] Stojanovich, L., and Marisavljevich, D. «Stress as a trigger of autoimmune disease.» Autoimmunity Reviews, vol. 7, no. 3, 2008, pp. 209-213.

[63] Patton, G. C., and Viner, R. «Pubertal transitions in health.» The Lancet, vol. 369, no. 9567, 2007, pp. 1130-1139.

[64] Guarner, F., and Malagelada, J. R. «Gut flora in health and disease.» The Lancet, vol. 361, no. 9356, 2003, pp. 512-519.

[65] Biwaters, E. G. L. «Lesions of bursae, tendons and tendon sheaths.» Clinical Rheumatology and Related Research, vol. 5, 1979, pp. 883-925.

[66] Diamond, B., and Volpe, B. T. «A model for lupus brain disease.» Immunological Reviews, vol. 248, no. 1, 2012, pp. 56-67.

[67] Losowsky, M. S. «A History of Coeliac Disease.» Digestive Diseases, vol. 26, no. 2, 2008, pp. 112-120.

[68] Meriggioli, Matthew N., and Sanders, Donald B. «Autoimmune Myasthenia Gravis: Emerging Clinical and Biological Heterogeneity.» The Lancet Neurology, vol. 8, no. 5, 2009, pp. 475-490.

[69] Drachman, Daniel B. «Myasthenia Gravis.» New England Journal of Medicine, vol. 330, no. 25, 1994, pp. 1797-1810.

[70] Patrick, J., and J. Lindstrom. «Autoimmune Response to Acetylcholine Receptor.» Science, vol. 180, no. 4088, 1973, pp. 871-872.