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Etiopathology of autoimmune disease and dental perspectives

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ETIOPATHOLOGY OF AUTOIMMUNE DISEASE
AND DENTAL PERSPECTIVES

by

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B.S., University of Massachusetts, Dartmouth, 2012

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ETIOPATHOLOGY OF AUTOIMMUNE DISEASE
AND DENTAL PERSPECTIVES

MELISSA SEIF

ABSTRACT

The main and most critical function of the immune system is to distinguish between self and non-self and react accordingly. Differentiating self-reactive immune cells as soon as they develop is the phenomenon of tolerance against self-antigens and is a highly regulated process. The development of autoantibodies is a sign of the breakdown of tolerance and may be the harbinger of the onset of an autoimmune disease.

It is well-known fact that many systemic autoimmune diseases (AUIDs) first manifest in the oral cavity. If proven that oral infections trigger AUIDs, then improving oral health may be a potential therapeutic strategy to reduce autoimmune disease incidence. Although etiology and pathogenesis of specific AUIDs may vary, presentation in the oral cavity often involves oral lesions manifested at early stages of systemic inflammatory and autoimmune disease. Therefore regular dental and medical checkups may provide an opportunity for clinicians, in particular dentists, to contribute to earlier detection of AUIDs thereby improving long-term treatment options and overall patient prognosis.
Mechanisms leading to the onset of autoimmune disease are still being considered. Epidemiological inquiries and the increasing numbers of genome-wide association studies have analyzed the breakdown of tolerance and the causes behind autoimmunity. The role of the environment is crucial in the onset of autoimmunity via the breakdown of tolerance; through toll-like receptors that mediate innate immunity which in turn triggers the adaptive autoimmune response, T regulatory cells and Th17 differentiation, through changes in the spleen autoantibody production due to a change in the B cell count, and through self antigen and epigenetic deviations induced by environmental spurs. In spite of many research efforts and the accumulation of innovative data, there are still multiple gaps in knowledge pertaining to this subject matter.

The autoimmune process begins with the activation of T cells by antigen presenting cells (APC) and progresses to CD4+ CD25+ T cells and forkhead box P3 (Foxp3), which stimulate Th1 and Th2 responses and finally B cell activation, which plays a role in autoimmune development. This paper will review the etiopathogenesis of autoimmune diseases and different cell players as well as transcription factors such as TGF-β, IL-6, IL-10, IL-17, Th-17, T reg cells, B reg cells, Th-1, Th-2, and INF-γ.
This paper aims to review published evidence and further explore the etiopathology of individual autoimmune diseases such as Behcet’s, Crohn’s disease, Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis and the subsequent dental implications and therapeutic management. This review also aims to study the most relevant autoimmune, auto-inflammatory, and systemic chronic inflammatory diseases, as well as mechanisms of autoimmune manifestation with respect to oral health.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>APC</td>
<td>Antigen Presenting Cells</td>
</tr>
<tr>
<td>AUlDs</td>
<td>Autoimmune Diseases</td>
</tr>
<tr>
<td>B cells</td>
<td>B lymphocytes</td>
</tr>
<tr>
<td>Breg</td>
<td>Regulatory B cells</td>
</tr>
<tr>
<td>FoxP3</td>
<td>Forkhead Box P3</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>INF</td>
<td>Interferon</td>
</tr>
<tr>
<td>MCTD</td>
<td>Mixed Connective Tissue Disease</td>
</tr>
<tr>
<td>MHC</td>
<td>Major Histocompatibility Complex</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>NK cells</td>
<td>Natural Killer cells</td>
</tr>
<tr>
<td>NOD</td>
<td>Non-Obese Diabetic</td>
</tr>
<tr>
<td>PAMPs</td>
<td>Pathogen-Associated Molecular Patterns</td>
</tr>
<tr>
<td>PRRs</td>
<td>Pattern Recognition Receptors</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic Lupus Erythematosus</td>
</tr>
<tr>
<td>T cells</td>
<td>T lymphocytes</td>
</tr>
<tr>
<td>TCR</td>
<td>T cell Receptor</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Transforming Growth Factor</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
</tr>
<tr>
<td>Th1</td>
<td>Type 1 T helper cells</td>
</tr>
<tr>
<td>Th2</td>
<td>Type 2 T helper cells</td>
</tr>
<tr>
<td>TLRs</td>
<td>Toll-like receptors</td>
</tr>
<tr>
<td>TNFR</td>
<td>Tumor Necrosis Factor Receptor</td>
</tr>
<tr>
<td>Tr1</td>
<td>T regulatory Type 1 cells</td>
</tr>
<tr>
<td>Treg</td>
<td>Regulatory T cells</td>
</tr>
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</table>
INTRODUCTION

Epidemiology is the study of distribution of patterns, causes, and effects of disease within a population. It is basically identifying risk factors for a certain disease and targets for preventative healthcare (Walsh et al. 2000). Studying the epidemiology of autoimmune diseases indicates that these diseases have a diverse demographic profile with the common factor that is their impairment to tissues and organs that result from the response to self-antigens (Cooper et al. 2009).

Autoimmunity is described as the failure of an organism in recognizing self, where a misdirected immune response is initiated against the organism’s own cells. It is characterized by a trigger of both the adaptive and immune systems in the failure of distinguishing “self” from “nonself”. This is evidenced by the existence of autoantibodies and T lymphocytes responsive to host antigens. Autoimmunity when progressed from a benign to a pathogenic response due to both environmental influences and genetic predispositions, to result in a wide range of illnesses, is defined as autoimmune disease (Lleo et al. 2010; Romagnani 2000).
Innate and Adaptive Immune Systems

The adaptive and innate immune systems are both players in fighting external microbes entering the body. The innate system is a series of non-specific responses that trigger the release of chemokines and cytokines (Si-Tahar et al. 2009). It is the primary defense mechanism in the protection from pathogens; it functions through a network of systems that includes the recognition of pathogen-associated molecular patterns (PAMPs) present on pathogens surface via pattern recognition receptors (PRRs). This system allows for rapid screening and determination of "self" from "non-self" and initiates quick immune responses accordingly.

Toll-like receptors (TLRs) are a family of PRRs, which recognize PAMPs trait of pathogenic microorganisms (Selmi et al. 2012). TLRs have a major role in the interaction of innate and adaptive immune responses. According to Selmi et al. recent studies have suggested an association between TLRs and autoimmune disease, where the hypothesis states that a distorted innate immune response as well as an altered TLR signal is a prominent step in the initiation of autoimmune disease (Selmi et al. 2012).

The adaptive immune response recognizes pathogens based on memory and acts via T cells antigen presenting cells (APCs) and dendritic cells (Parija 2009).
Antibodies constitute a major part of acquired immunity (Selmi et al. 2012; Selmi 2013). B lymphocytes (B cells) are responsible for antibody production and T lymphocytes (T cells) serve either as helper or regulatory cells. B lymphocytes are a large component of the adaptive immune system that generate their repertoire in the bone marrow through V(D)J recombination, which is characterized by the pairing of heavy and light chains to further increase diversity (Salinas et al. 2013; Selmi et al. 2012). During this combination some auto-reactive immunoglobulin (Ig) cannot be efficiently purged, however checkpoints in B cell development ensure that auto-reactive B lymphocytes are discounted, through deletion, receptor editing, or rendered anergic, from the peripheral lymphocyte population (Salinas et al. 2013).

**Autoimmune Diseases**

Autoimmune diseases occur when pattern recognition receptors (PRRs) fail in recognizing pathogen-associated molecular patterns (PAMPs) and erroneously identify a part of self as pathogens. This pathology as a group manifests an extensive variability in terms of age of onset, tissues targeted, and response to treatments suppressing the immune system. There are more than seventy distinctive autoimmune disorders affecting roughly five percent of Western populations (Mays et al. 2012). Autoimmune diseases are generally thought of as rare, however they are the leading causes of death among young and middle-
aged women in the United States (Walsh et al. 2000). Of the many categories and different types of diseases, the most prevalent and the ones discussed mainly in this article include Behcet’s syndrome, Rheumatoid Arthritis (RA), Sjögren’s syndrome, Systemic Lupus Erythematosus, Multiple Sclerosis, and Crohn’s disease.

Autoantibodies have been established as indicators of the presence of autoimmune occurrence; however, several studies have demonstrated that patients may carry autoantibodies for years before they manifest any clinical signs (Lleo et al. 2010).

**Behcet’s syndrome**

Behcet's is a chronic inflammatory disease that is characterized by ulcers in the oral mucosa as well as frequent muco-cutaneous lesions, defined by a yellowish necrotic base with a red rim surrounding (Mays et al. 2012). The symptomology can be more or less severe in different individuals and can result in serious issues such as meningitis, blood clots or issues with the central nervous system (Mendes et al. 2009)

The etiology of Behcet’s disease is poorly defined, however, pathology of oral ulceration is evident. Tumor Necrosis Factor alpha (TNF-α) is involved in the pathogenesis as well as the recruitment of IL-12, IL-17 and IL-21 (Mendes et al. 2009).
2009). Most patients acquire hypersensitivity in the oral cavity and trigger an IL-12 mediated delayed-type hypersensitivity response (Mays et al. 2012).

**Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is an autoimmune condition characterized for an increased number of autoantibodies and a hyper response to anti-TNFα. Recent advances employ B cell depleting treatments such as rituximab (Edwards, 2004). RA is the one condition that demands for both clinical and basic evidence to be sought hand in hand in order to provide an ample understanding (Selmi 2013).

Immunologically, it involves Rheumatoid factor, TNFα, IL-1, IL-6, and IL-17. Oral manifestations in RA are distinguished from other disease by the presence of periodontal disease (Mays et al. 2012).

An experimental therapy study conducted on patients with RA consisted of treatment for 6 months with oral dnaJP1, epitope-specific immunotherapeutic molecule derived from heat shock proteins that initiate proinflammatory T cell responses in naïve RA patients, showed result of increased Foxp3+CD4+CD25+T cells (Chen et al. 2002). These results suggest that treatment with an antibody against proinflammatory inducing peptide enhances T regulatory cell stimulation.
This study allows envisioning the feasibility of manipulating T regulatory cells for therapeutic advantages (Chen et al. 2002; Nakamura et al. 2001).

**Sjögren’s Syndrome**

Sjögren’s syndrome is an autoimmune disease characterized by the destruction of salivary and lacrimal exocrine glands (Tapinos et al. 1999). It involves IL-6, IL-12, IL-17 and IL-23, and is distinguished specifically by frequent caries, the presence of Xerostomia (Mavragani et al. 2006), and candidiasis.

In Sjögren syndrome, Selmi et al. has demonstrated that memory B cells are quantitatively reduced in target organs. T cells have a large role in determining B cell activation, tolerance and B cell receptor (BCR) signaling, particularly in lupus-prone mice (Selmi et al. 2012).

The major messengers that mediate inflammatory stimuli, tolerance and autoimmunity are cytokines. In autoimmune disease, targeting TNF-α elicits autoimmune manifestations, particularly in terms of antinuclear (ANA) and anti-dsDNA antibodies (Atzeni et al. 2012). Cytokines such as IL-2, IL-6, and IL-21 play a key role in autoimmunity whether as therapeutic targets or otherwise (Teichmann et al. 2012; Ray et al. 2012).
**Systemic Lupus Erythematosus**

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease leading to many abnormalities that involve the synthesis of autoantibodies that denote the breakdown of tolerance to self-antigens (Park et al 2002; Tsakos 2001).

Numerous environmental aspects, such as ultraviolet radiation, contribute to the pathogenesis of SLE (Yurasov et al. 2005). SLE involves TNF-α, IL-6, IL-10, CD4+ T cells and is distinguished in the oral cavity by the presentation of white and red plaque as well as recurrent aphthous stomatitis (Pijpe et al. 2009).

**Crohn’s Disease**

Crohn’s disease is an inflammatory bowel disease that affects alimentary canal with a particular focus on the mouth. Characteristic granulomatous lesions as well as oral ulcerations are present (Rousseay et al. 2008).

The cause of Crohn’s is multifactorial in addition to interaction between environmental risk factors and variations in the patient’s immune system onset the disease in a genetically prone host (Selmi 2013).
**Multiple Sclerosis**

Multiple sclerosis (MS) is an inflammatory disease mainly affecting the central nervous system, leading to the imparity of the sensory and the neurocognitive function. MS occurs mainly in younger adults with a predisposed genetic trait, which most likely requires a triggering environmental offense. Damage of the target tissue and the inability to repair are characteristic features, which may have several dental implications in case of injury. Damage is followed by the activation of CD4$^+$ T cells and their differentiation into a Th1 phenotype (Lucchinetti et al. 2000).

**Manifestation**

Recently, a study uncovered that exposure to TLR agonists and xenobiotics can result in synergistic effects and the release of IL-6. This mechanism is not directly related to autoimmune disease per se but the liaison between unregulated TLR signaling and inflammation is evident and suggested research claims that it could lead to autoimmune endpoints (Selmi et al. 2012). Environmental contaminants, UV light exposure and chemical contact influence the Th17 response leading to a possible development of autoimmune disease in susceptible individuals. This was seen after the evaluation of Th17 in multiple
sclerosis, rheumatoid arthritis, and Crohn’s disease patients, where the data is convincing that involvement of environmental toxins has a direct correlation to the exacerbation of autoimmune disease through Th17 cells (Selmi et al. 2012).

Table 1 illustrates the proposed environmental considerations and the assumed virus-induced type I diabetes, triggering of TLR pathways intensifies the disease. Another example is the stimulation of the type I interferon pathway in Sjögren’s syndrome, which triggers autoantigen presentation and autoantibody production. Functional changes in TLRs have also been correlated with Systemic Lupus Erythematosus.
Table 1. The major categories of putative environmental agents and possible mechanisms of autoimmune disease. Amended from Selmi et al. 2012

<table>
<thead>
<tr>
<th>Environmental factors that have been associated with autoimmune diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious agents (bacteria, viruses)</td>
</tr>
<tr>
<td>Chemicals/xenobiotics</td>
</tr>
<tr>
<td>Adjuvants</td>
</tr>
<tr>
<td>Physical elements (ultraviolet radiation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyclonal B cell activation;</td>
</tr>
<tr>
<td>Direct effect impairing the immune response (Th17 cells);</td>
</tr>
<tr>
<td>Effects on innate immunity (TLR, adjuvants);</td>
</tr>
<tr>
<td>Direct interaction with regulatory cells (T regulatory cells);</td>
</tr>
<tr>
<td>Modification of self antigens (post-translational modifications);</td>
</tr>
<tr>
<td>Alterations of DNA methylation (epigenetics)</td>
</tr>
</tbody>
</table>
Etiology, Prevalence, and Incidence of Autoimmune Disease

The exact etiology of autoimmune diseases is not well defined, however it is generally accepted that ethnicity, geography, and demographic location play an important role for certain autoimmune diseases (Cooper et al. 2009; Walsh et al. 2000).

Some autoimmune diseases are more prevalent than others ranging from 5 to 500 cases diagnosed per 100,000 individuals: For example, rheumatoid arthritis has an incidence rate of 20 per 100,000 people, while multiple sclerosis is a rarer condition with less than one diagnosis per year (Cooper et al. 2009). There is an estimate of combined incidence rate for autoimmune diseases of 90 per 100,000 people and prevalence rate of around three percent; some diseases cannot be accurately accounted for and therefore these estimates are conservative ones (Cooper et al. 2009). These chronic diseases have a significant impact on the economic costs, the medical care needs and the patient’s quality of life (Løva˚s et al. 2002).

Patterns with respect to disease incidence show that more than three fourth of Sjögren’s disease, Multiple Sclerosis (MS), and Systemic Lupus Erythematosus (SLE) patients are primarily female and are detected and diagnosed between childhood and mid-adulthood but can also be found to affect woman at later
stages of life (Mavragani et al. 2006; Pijpe et al. 2009).

Noteworthy variances have been observed in the age distribution among autoimmune diseases. Autoimmune disease could occur at any age, however it is important to note that some diseases have peaks at different ages (Gottenberg et al. 2009; Mavragani et al. 2006; Pijpe et al. 2009).

Juvenile RA and Type 1 diabetes occur between the ages of eight and ten while Myasthenia Gravis appears and Rheumatoid Arthritis occurs later in mid-adult years.

Myasthenia Gravis, MS, and Grave’s disease tend to occur at average between thirty and fifty years of age. Older age between forty and seventy is seen at diagnosis of thyroiditis, Sjögren disease, RA, and Wegener granulomatosis (Gottenberg et al. 2009; Mavragani et al. 2006; Pijpe et al. 2009).

In addition, patterns of differences of specific autoimmune diseases among countries or different ethnic groups are not consistent across autoimmune diseases. For example, northern Europe is where multiple sclerosis and Type 1 diabetes are more frequently seen. Furthermore, an increased risk of SLE has been reported amongst Asian and Afro-Caribbean immigrants in the United
Kingdom as well as the black population in the US. On the other hand, blacks tend to have a lower rate of Type I diabetes and multiple sclerosis as compared to whites. Rates for rheumatoid arthritis are quite similar among whites, blacks and Hispanics (Cooper et al. 2009; Løva˚s et al. 2002; Walsh et al. 2000).

Temporal changes in incidence have occurred between several autoimmune diseases. Autoimmune pattern incidences differ in type I diabetes that shows an increase in the last 10 to 50 years, and RA that seem to have declined, as seen in the studies in the Pima Indians (Cooper et al. 2009).

Jacobson et al. (1997) completed a study collecting data on 19 of the 24 selected diseases; Table 2 (Amended from Cooper et al., 2002) summarizes this analysis with information including Addison’s disease, adult-onset Type 1 diabetes, rheumatoid arthritis, systemic sclerosis, Wegener granulomatosis, vasculitis, and Sjögren disease. The estimated incidence numbers range from 1 per 100,000 for chronic active hepatitis, scleroderma, primary biliary cirrhosis, and Myasthenia Gravis to 20 per 100,000 people for adult rheumatoid arthritis, and thyroiditis. The prevalence ranged from about 5 per 100,000 for chronic active hepatitis and Wegener granulomatosis to more than 500 per 100,000 for Grave’s disease, thyroiditis, and rheumatoid arthritis.

More than three fourth of thyroiditis, Sjögren, scleroderma, and systemic lupus
erythematous patients are female, however, in multiple sclerosis and rheumatoid arthritis the percent of female patients is around sixty. In autoimmune diseases that begin in childhood, such as diabetes type 1, there is a relatively equal risk between females and males (Cooper et al., 2002).
### Table 2. Autoimmune Disease Incidence And Prevalence

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence Per 100,000 person years</th>
<th>Prevalence Per 100,000</th>
<th>Percent female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Addison’s disease</strong></td>
<td>0.6</td>
<td>14.0</td>
<td>93</td>
</tr>
<tr>
<td><strong>Chronic active Hepatitis</strong></td>
<td>0.7</td>
<td>0.4</td>
<td>88</td>
</tr>
<tr>
<td><strong>Glomerulonephritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>3.6</td>
<td>40.0</td>
<td>32</td>
</tr>
<tr>
<td>IgA</td>
<td>2.4</td>
<td>23.2</td>
<td>67</td>
</tr>
<tr>
<td><strong>Diabetes Type 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;20</td>
<td>12.2</td>
<td>192.0</td>
<td>48</td>
</tr>
<tr>
<td>Age 20 and up</td>
<td>8.1</td>
<td>No Data</td>
<td>35</td>
</tr>
<tr>
<td><strong>Grave disease/ hyperthyroidism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>13.9</td>
<td>1151.5</td>
<td>88</td>
</tr>
<tr>
<td>Ages 10-19</td>
<td>No Data</td>
<td>106.9</td>
<td>67</td>
</tr>
<tr>
<td><strong>Multiple Sclerosis</strong></td>
<td>3.2</td>
<td>58.3</td>
<td>64</td>
</tr>
<tr>
<td><strong>Myasthenia Gravis</strong></td>
<td>0.4</td>
<td>5.1</td>
<td>73</td>
</tr>
<tr>
<td><strong>Myocarditis</strong></td>
<td>0.1</td>
<td>No Data</td>
<td>45</td>
</tr>
<tr>
<td>All ages</td>
<td>4.1</td>
<td>No Data</td>
<td>44</td>
</tr>
<tr>
<td>Ages &lt;15</td>
<td>No Data</td>
<td>150.9</td>
<td>67</td>
</tr>
<tr>
<td><strong>Pernicious Anemia</strong></td>
<td>1.8</td>
<td>5.1</td>
<td>67</td>
</tr>
<tr>
<td><strong>Rheumatoid Arthritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile (age &lt;16)</td>
<td>17</td>
<td>148</td>
<td>68</td>
</tr>
<tr>
<td>Adult</td>
<td>23.7</td>
<td>860.0</td>
<td>75</td>
</tr>
<tr>
<td><strong>Systemic Sclerosis</strong></td>
<td>1.4</td>
<td>4.4</td>
<td>92</td>
</tr>
<tr>
<td><strong>Sjögren disease</strong></td>
<td>3.9</td>
<td>14.4</td>
<td>94</td>
</tr>
<tr>
<td><strong>Systemic Lupus Erythematosus</strong></td>
<td>7.3</td>
<td>23.8</td>
<td>88</td>
</tr>
<tr>
<td><strong>Thyroiditis/ hypothyroidism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ages &gt;19</td>
<td>21.8</td>
<td>791.7</td>
<td>95</td>
</tr>
<tr>
<td>Ages 10-19</td>
<td>No Data</td>
<td>532.1</td>
<td>83</td>
</tr>
<tr>
<td><strong>Wegener granulomatosis</strong></td>
<td>1.0</td>
<td>3.0</td>
<td>51</td>
</tr>
<tr>
<td><strong>Primary Systemic Vasculitis</strong></td>
<td>2.0</td>
<td>14.5</td>
<td>43</td>
</tr>
</tbody>
</table>
Specific Cell Involvement in Autoimmunity

Maintaining immune homeostasis, tolerance and inhibition at the onset of autoimmune disease is the main function of suppressor T cells (Chen et al. 2003b; Wahl et al. 2005). Regulatory T cells (Tregs) are immunoregulatory cells derived either from the thymus: CD4+ CD25+ FoxP3 also known as natural Tregs, or in the peripheral blood also known as induced Tregs (Anuradha et al. 2013).

Treg control both the innate and adaptive immune responses. When a pathogen invades the body, Toll-like receptors are expressed which in turn lead to the stimulation of dendritic cells. Dendritic cells produce IL-6 and TGF-β that further influence the development of Treg, it basically functions as a cycle (Pasare et al. 2003; Verhasselt et al. 2004). T regulatory cells develop after antigen and TGF-β stimulation; IL-10 secreting T regulatory type 1 cells (Tr1) are produced after TGF-β, IL-27, and antigen exposure. T regulatory (Treg) cells have a characteristic expression of CD4, CD25 and forkhead box P3 that have a vital role in the maintenance of immune tolerance (Selmi et al. 2012).

The main function of T reg cells is protecting the host from unbalanced T cell activation. Regulatory T cells CD4+CD25+ mediate inflammatory and immune
reactions and can suppress CD4+CD25− T cell responses to antigens with the help of TGF-β through an antigen-nonspecific mechanism (Chen et al. 2003b; Oida et al. 2003; Shevach et al. 2002). Experiments in mice have shown that a reduction in CD4+ CD25+ T cells by neonatal thymectomy results in spontaneous progression of organ specific autoimmune diseases particularly autoimmune gastritis, wasting, and thyroiditis. Adoptive transfer of Treg can reverse the progress of these autoimmune complications (Sakaguchi et al. 2001).

T cell proliferation is inhibited in HIV-1 immunodeficiency and in lung cancer patients by regulatory cells due to the increased number of CD4+ CD25+. Thus, regulatory T cells have an essential role in the maintenance of tolerance through the suppression of the immune system (Wahl et al., 2005).

T regulatory cells are a heterogeneous family of type 3 Th (Th3) cells, T regulatory 1 (Tr1) cells, and CD4+CD25+ T cells, "naturally-occurring" regulatory T cells. Type 1 regulatory T (Tr1) cells are a subset of T reg cells that play a vital role in the maintenance of tolerance. The main mechanism is by secretion of high levels of IL-10 but minimal amounts of IL-2, IL-4 and IL-17. This aspect sets Tr1 cells apart from Th2 and Th17 cells. Similar to other T cell subsets, Tr1 cells can express FoxP3 when activated (Gregori et al. 2012). Th3 cells mainly produce transforming growth factor beta (TGF-β) and therefore have a TGF-β -dependent regulatory mechanism.
By contrast, CD4+CD25+ T cells act via a contact-dependent mechanism that involves the activity of TGF-β and IL-2. These cells do not divide; instead they play a role in significantly increasing the numbers of CD4+CD25- cells that eventually become CD4+CD25+ cytokine-independent suppressor cells by mechanisms that require both IL-10 and TGF-β (Chen et al. 2003a). Another feature of CD4+CD25+ T cells is the expression of the products of FoxP3 (Zheng et al. 2004).

There are two subsets of CD 4+ T helper cells, Th1 and Th2 (Cooney et al. 2013). Type 1 T helper (Th1) and type 2 T helper (Th2) are two cell-mediated specific immune responses; one is for isotype switching in B cells and the other is for clonal expansion. These responses develop against infections sustained by viruses and intracellular bacteria (Romagnani 2000). The differentiation of these subsets is regulated by multiple cytokines; IL-12 and interferon (IFN) α produced by APCs, propagating cellular immunity which eventually leads to tissue damage. Cytokines such as IL-4 perpetuate stimulation of the humoral immune response (Sakaguchi et al. 2001). The probability of determining the incidence of Th1- or Th2-dominated responses in pathologic or under normal conditions is limited. T cells produce most cytokines in small amounts, which are either transmitted from cell to cell or released in the environment (Romagnani 2000).
B regulatory cells and Natural Killer (NK) cells have been shown to produce IL-10, a cytokine that produces Tr1. IL-10 and TGF-β, which secrete Th3, are subdivisions of induced T regulatory cells (Osnes et al. 2013).

In autoimmunity, T helper 17 (Th17) synthesis cells occurs via factors, cells, transcription factors and cytokines including regulatory B cells (Breg), Interleukin 6 (IL-6), regulatory T cells (Treg), B cells, Interleukin 23 (IL-23), transforming growth factor beta (TGF-β), and forkhead box P3 (FoxP3) (Ian et al. 2006; Mays et al. 2012; Salinas et al. 2013).

Th17 cells are characterized by the secretion of IL-17 and their activation is enhanced through TLR signaling (Anuradha et al. 2013; Bedoya et al. 2013). A few correlations to autoimmune disease include the experimental animal model of multiple sclerosis where TLR agonists increased disease incidence, as well as suggested evidence that Th17 cell activation association with exacerbation of multiple sclerosis (Miossec et al. 2009; Selmi et al. 2012).

Th17 plays a very distinct role in certain autoimmune diseases with its function being a vital defense against bacterial and fungal infections (Atianand et al 2013; Cooney et al. 2013). Th17 cells act against pathogens and participate in response to extracellular bacteria and fungi infections, meanwhile Treg suppress the immune response to normal microbial flora and antigens; however,
unregulated Th17 activity leads to chronic inflammatory diseases (Miossec et al. 2009; Selmi et al. 2012).

**Mechanisms of Regulatory T cell Suppression and Autoimmunity**

Treg are immunosuppressive and anergic and therefore CD4+ CD25+ Treg suppress T cell proliferation and cytokine production when activated. TGF-β is a potent cytokine and growth factor, and blocking it with a soluble TGF-β receptor, with neutralizing antibodies or with recombinant peptides interrupts the capacity of TGF-β to intervene responder T cell proliferation (Sakaguchi 2000; Wahl et al. 2005). This reiterates that TGF-β is used for suppression (Chen et al. 2003b; Nakamura et al. 2001). TGF-β receptor type II allows for membrane-bound TGF-β to interact with the CD4+ CD25–responder cells and therefore providing the link via which TGF-β present on the Treg manages the suppression of responder cells (Chen et al. 2003b; Nakamura et al. 2001).

In healthy individuals CD4+CD25+ Treg cells have shown to be increased compared to patients where CD4+IL-10 Tr1 cells are increased. CD4+CD25+ high Treg cells reduction is a key effect attributed to immunoregulatory disruption in individuals with MCTD (Gregory et al. 2012). Tr1 cells increase in order to restore equilibrium between type 1 and type 2 cytokines in MCTD (Osnes et al. 2013).
The relationship between CD4+CD25+ Treg and Th1-dependent pathogenesis in Rheumatoid Arthritis has no significant difference in suppressive activity between CD4+CD25+ T cells from peripheral blood of RA patients and healthy individuals (Chattopodhyay et al 2013). CD4+CD25+ T cells from peripheral blood reported to have significantly lower suppressive activity than those in the synovial fluid of RA patients. However, ongoing inflammation in the joints suggests the complex mechanisms of RA pathogenesis (Chen et al. 2002; Nakamura et al. 2001).

The most prevalent immunological abnormality that patients with human SLE manifest is the production of pathogenic autoantibodies. Unrestrained T cell hyper-responsiveness leads to uncontrolled B lymphocyte activation and therefore more antibody production, this in turn results in the production of antidouble-stranded DNA and antinuclear antibodies in SLE patients (Pijpe et al. 2009). Upregulation of proinflammatory cytokines IFN-γ, IL-6, IL-10, and IL-12 elevate Th1 and Th2 responses. The abnormalities in T and B lymphocytes are viewed as the consequence of defective TGF-β production (Mavragani et al. 2006). The most prevalent immunological abnormality that patients with human SLE manifest is the production of pathogenic autoantibodies. Unrestrained T cell hyper-responsiveness leads to uncontrolled B lymphocyte activation and therefore more antibody production, this in turn results in the production of antidouble-stranded DNA and antinuclear antibodies in SLE patients (Nakamura et al. 2006).
et al. 2001). Upregulation of proinflammatory cytokines IFN-γ, IL-6, IL-10, and IL-12 elevate Th1 and Th2 responses. The abnormalities in T and B lymphocytes are somewhat the consequence of defective TGF-β production (Anuradha et al. 2013).

Studies indicate that CD4+CD25+ T cells decrease significantly in number and function in patients with active SLE as opposed to patients with an inactive stages subjects and normal individuals (Crispin et al. 2003; Valencia et al. 2003). Having said this, an association between inactive SLE and the levels of CD4+CD25+ Treg is needed to define the exact role of decreased CD4+CD25+ Treg levels in the pathogenesis of the disease (Liu et al. 2004; Wahl et al. 2005).

Consequently, any alteration in the population of these key cells and cytokines will lead to the triggering or onset of an autoimmune disease such as SLE, RA or Mixed Connective Tissue Disease (MCTD), as well as immunodeficiency or autoimmunity in general (Osnes et al. 2013).

Patients with autoimmune diseases (AUIDs) such as SLE, RA or even mixed connective tissue disease (MCTD) have been reported to have a diminished number or activity of NK cells and Th17 cytokines (Chen et al. 2003b; Nakamura et al. 2001). In MCTD, CD4+ and CD8+ T cells make more IL-10, an effort by immune system, to down regulate the inflammatory reaction (Nakamura et al.
Whether the humoral or cellular immunity is activated in a AUIDs patient, understanding the mechanism will aid in identifying the immunological pathways that lead to advancement of disease, therefore improvement of therapeutic outcomes (Osnes et al. 2013).

**Pathogenic Infections and Autoimmune diseases**

One of the unresolved queries in immunology is how pathogenic infections contribute to the etiology of autoimmune diseases. The concept of antigen mimicry is considered. Antigen mimicry is defined as sequences in microbial proteins resembling that of the host’s own protein molecules (Leo’na et al. 2003). In contrast, some studies propose a contrary association between the occurrences of autoimmunity and infections, as in; infection seems to prevent the onset of autoimmunity. This theory is called “the hygiene hypothesis”, which states that the increased occurrence of autoimmune disease is correlated to the diminished incidence of infection (Okada et al. 2010). The basis of this theory states that if low-grade infections are repeated, immune system will respond without aggression. A theoretical model of tolerance driven by regulatory T cells helps clarify both ideas. To determine whether infections may be causing or preventing autoimmune diseases, mechanisms of natural tolerance to host-antigens must be observed. Regulatory T cells, CD4+ CD25+, naturally synthesized in the thymus, are dependent on major histocompatibility complex
(MHC)-Class II expression. Regulatory T cells, overpower the activity of other pathogenic auto-reactive T cells (Chattopodhyay et al. 2013; Leo’na et al., 2003). The results have shown that an inverse correlation exists between the occurrence of autoimmunity and incidence of infection. This could be viewed based on regulatory T cell, and also accounting for the role of antigen mimicry in the etiology of some autoimmune disorders (Leo’na et al. 2003).

APCs displaying MHC-self-peptide complexes, proinflammatory autoreactive T cells that can possibly incite autoimmunity, and regulatory autoreactive T cells, which suppress proinflammatory T cells were studied. Fast surge in antigen presenting cells reduce interaction between proinflammatory and regulatory autoreactive T cells leading to the onset of autoimmunity (Jonuleit et al. 2001; Leo’na et al. 2003). Regulatory autoreactive T cells inhibit the proliferation proinflammatory autoreative T cells at the APC surface (Leo’na et al. 2003). Slow APC increase allows for adaptation of the regulatory cell population size, therefore reinforcing tolerance (Figure 1). Therefore the concepts of immunity and tolerance are explained as the competitive seclusion of regulatory autoreactive T cells as proinflammatory autoreactive T cells increase in population as well as the concomitance of both T cells types at balance (Leo’na et al. 2003).
Fig 1. Illustration of T cell mediated immune tolerance or autoimmunity development. Amended from Leoń et al., 2004 (A), Interactions relating regulatory T cells, proinflammatory T cells and Antigen Presenting Cells. (B), Fast surge in antigen presenting cells reduce interaction between proinflammatory and regulatory autoreactive T cells leading to the onset of autoimmunity. (C), Slow APC increase allows for adaptation of the regulatory cell population size, therefore reinforcing tolerance.
**Infection and Response: APC proliferation**

When an infection occurs in the body, at first the innate immune system is triggered to clear the microorganism, which provokes a rapid burst in the recruitment of antigen presenting cells that rush to the site of the infection for proper control. Differentiation and proliferation of antigen presenting precursors ensues which will then lead to the processing and presentation of foreign antigens (Leo’na et al. 2003). If the proliferation of APCs is rapid, it causes an increase in pro-inflammatory autoreactive T cells and therefore a collapse of tolerance. On the other hand, if there is proliferation of APCs but it occurs rather slowly, there will still be an increase in pro-inflammatory autoreactive T cells, which is controlled by the proliferation of regulatory T cells, however no break in tolerance occurs (Leo’na et al. 2003).

Significant improvement in self-antigen presentation would either provoke or prevent autoimmunity when accompanied by rapid or slow kinetics, respectively. Inoculation of Non-Obese Diabetic (NOD) mice with different doses of antigen presenting cells from the spleen of non-treated NOD mice and checking the incidence of animals developing diabetes indicated that treatments including a significant inoculum with those APCs would quicken the early onset of diabetes (Leo’na et al. 2003).
According to recent reports by Leo’na et al., when the innate immune system is activated, dendritic cells produce IL 2, a cytokine that serves as a resource for regulatory T cells. If there happens to be excess in IL 2 synthesis in pathological situations with infectious basis, the balance between regulatory and proinflammatory cells would become subverted, resulting in generalized immunodepression (Leo’na et al. 2003; Oida et al. 2003).

T cell responses to foreign antigens are vital for the protection of organism against pathogenic agents, however T cell response to self-antigens is detrimental. The lack of regulation of T cell activation and development results in autoimmune diseases, which entails inflammation and the destruction of tissue (Sakaguchi 2000; Jonuleit et al. 2001).
Dental Management of Autoimmune Diseases

To date, no clear correlation has been demonstrated between AUIDs and oral manifestation. It has been suggested that the increase in bacteria on the tooth surface may serve to trigger the immune system mobilizing T cells, B cells, mast cells, NK cells and macrophages as a defense mechanism of against these invading bacteria perceived as foreign bodies (Manakil 2012).

Conventionally, most autoimmune diseases are treated through medical specialties depending on the type of organ involved. Due to this fact, there are many missed opportunities to study autoimmune diseases as an entity (Cooper et al. 2009). To understand the etiology of autoimmune diseases, further studies of the relationships among them is necessary.

The general principles for treatment of autoimmune diseases with oral manifestations include oral hygiene reinforcement using antiseptics, antibiotics, and corticosteroids. Specifically, corticosteroids are used to manage the oral ulcers in Behcet’s syndrome (Gottenberg et al. 2009). Dentists address the difficulties that RA patients face due to their limited manual dexterities by performing regular oral hygiene checkups, more preventative oral hygiene maintenance as well as diagnosis and treatment of periodontal disease as early as possible. Dental care with fluoride and routine checkups, azole, antifungal
treatment, is utilized for patients with Sjögren’s syndrome and mouthwashes, special toothpastes and mouth rinses are used to alleviate Xerostomia (Mays et al. 2012). However, care must be taken in utilizing azole antifungal agents because many chemicals in medications interact with this type of mouth rinse. For treatment of plaque and stomatitis in SLE, clobetasol and tacrolimus ointment are used as well as systemic administration of immunodeficiency drugs such as Rituximab, a B-cell inhibitor (Mendes et al. 2009).
DISCUSSION

The presence of auto-reactive B and T lymphocytes in the periphery characterize the physiological process in autoimmunity and it can be concluded that environmental factors, physical elements and chemical adjuvant trigger the transformation from autoimmunity to autoimmune disease.

When discussing the effects of innate immunity and their role in linking environmental factors and autoimmune disease it is important to mention the two major pathways highlighted, TLR and adjuvants. The activation of the innate immune system through toll-like receptors and their interaction between xenobiotics is predisposed by the interaction of environmental factors and therefore has a direct link on autoimmunity development (Anuradha et al. 2013; Selmi et al. 2012) Moreover, it is clear that adjuvants stimulate the innate and adaptive immune system and therefore prompt the release of cytokines and chemokines, as well as induce non-antigen-specific signals that identify adaptive responses triggering for autoimmune pathology. However it is not clear whether deregulation of TLR is a prominent step in triggering autoimmunity, or whether genetic predisposition has a more ponderous role in relation to these factors.

Given the previous discussion on environmental factors influencing autoimmune development, it can be postulated that this influence occurs via production or
activation of Treg cells. Treg cells (suppressor T cells) are concluded to be responsible for active immunosuppression of responses to foreign and self-antigens leading to autoimmune disease. Therefore, stating that down-regulation of Treg subsets or their alteration by any environmental or chemical factor is a direct correlation with the onset of autoimmune disease is accurate (Chen et al. 2002; Nakamura et al. 2001).

The nature of interface between T cells and antigen presenting cells (APCs) predicts production of efficient Th1, Th2, Th17 and Treg cells. Therefore, environmental queues also have a significant effect on APC and vis a vis an effect on Treg cells (Chen et al. 2002).

The phenomenon of autoimmunity includes the loss of B cell anergy, the failure of T regulatory cells, and the synthesis of auto-reactive T cells and autoantibodies. These mechanisms eventually lead to tissue injury that begins from the synthesis of pro-inflammatory cytokines and continues toward chemotaxis of immune cells to the target sites.

Figure 2. summary description of the mechanisms of immunity and therefore serves as a step forward in understading the mechanisms and pathology behind autoimmunity.
Figure 2. Illustration of the Immune Response Mechanism.


(A) T cells are part of both innate and adaptive immunity, on the contrary to B cells, which only exist when the adaptive immune response comes into play. Natural Killer cells also play a significant role in the rapid innate immune response (Osnes et al., 2013). Natural T regulatory cells include cells that express CD4+ CD25+ and forkhead box P3 (Foxp3) stimulate the formation of Th1 and Th2 helper cells, where cellular and humoral response is initiated respectively. Antigen Presenting cells also play a role in stimulating Th1 and th2 cells by secreting cytokines such as IL-12, Interferon-Gamma, and IL-14. Th1 response leads to Interferon-γ anti-infection cytokine, phagocytosis, Th2 response doesn’t activate anti-infective action macrophages, however this pathway leads to antibody production via B cells.

(B) A Naïve T cell in the presence of TGF-β and IL-6 leads to the formation of Th17. In the presence of TGF-β only, a naïve T cell will progress to T regulatory cell leading to lower inflammation and a reduced immune response.

(C) B cell activation eventually leads to ectopic germinal center activation, if TGF-β and IL-10 are involved, B regulatory cells will play a role in autoimmune suppression. Otherwise, B cell activation will move forward to somatic hypermutation and immune pathogenesis.
To further elaborate on the process that occurs it must be mentioned that early expression of IL-4 during an immune response is very important in the determination of Th2 development. When a weak T-cell receptor (TCR) signal is received, naïve CD 4 cells seem to be receptive to CD28-dependent IL-4 production. When IL-4 levels reach a certain threshold, differentiation of Th cells into T helper 2 cells occurs. Moreover, Th17 is a vital part and plays a rather significant role in autoimmunity through its pro-inflammatory T helper cytokine production of IL-17. Th17 is very crucial since the defense against fungal and bacterial infections mainly relies on this cell population, therefore, IL-17 can be either protective or damaging. The study of Th17 and T regulatory cells as well as IL-17 has been found to act on both neutrophil chemotaxis and endothelial activation therefore associating two major chronic inflammation mechanisms (Ray et al. 2012). A few studies mentioned earlier have supported the target of Th17 in the treatment of autoimmunity however the mechanisms of periodontal infections may complicate this process. This is complicated due to evidence of an IL-2 dependent mechanism, the expression of dopamine receptor (D5) by dendritic cells, and the altered expression of TGF-β (Selmi et al. 2012).

In discussing T regulatory cells, it is important to re-emphasize that they are crucial to prevention of autoimmunity; they have many functional features and one in particular is to preserve self-antigen tolerance. However, this can cause fulminant infection when viral infections invade the central nervous system. Th1
cells producing Interferon, tumor necrosis factor, and IL-2 lead to evoke cell-mediate immunity. Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. These cells induce strong antibody responses; however, also play a role in inhibiting phagocytic cell functions.

Autoimmune responses such as Crohn’s disease are Th1-dominated responses. On the other hand, Th2 allergen-specific responses are responsible for atopic disorders in genetically predisposed individuals (Romagnani 2000). Therefore in order to distinguish whether a Th1 or a Th2 response is involved, both environmental and genetic factors need to be evaluated.

T regulatory cells are the main driving force for autoimmune control and therefore the pathogenesis of inflammation, infections and autoimmunity is constrained by cluster of differentiation CD4+ CD25+ regulatory T cells that facilitate suppression of the immune system. As we stated earlier, CD4+ CD25+ act via a contact-dependent, antigen-specific means with the aid of TGF-β, which holds a dual function in mediating suppression between CD4+CD25– as well as the conversion of CD4+ CD25- into the regulatory phenotype ((Chen et al. 2003b; Leo’na et al. 2003).

By the immune system responding to pathogens, a risk of autoimmunity is a direct price to pay. Epidemiological and experimental models till today have failed
to pinpoint the etiology of autoimmune diseases. The only hypothesis viable today, concluded by a genome-wide association study is that autoimmunity generates from a combination of genetic and environmental factors.
CONCLUSION

The failure of self-recognition that leads to immune responses triggered against an organism’s own cells is described as autoimmunity. Autoimmunity progresses from a benign to a pathogenic response due to both environmental influences and genetic predispositions. As was seen in Table 1, in the context of autoimmunity, adjuvants retain the capacity to stimulate the release of proinflammatory chemokines and cytokines as well as induce non-antigen-specific signals that identify adaptive responses triggering for autoimmune pathology. Further inquiries should also focus on genetic predisposition and its relation to these factors.

Autoimmune diseases are among the leading causes of death in young and middle-aged women. With the exception of Type I diabetes, autoimmune disease is seen to affect predominantly women. Autoimmune pattern incidences differ, where some in the example of type I diabetes tend to have increased in the last half century, while others like RA seem to have declined over the same period.

In terms of mechanisms of autoimmunity, it can be concluded from this review that CD4+ CD25+ forkhead box P3 (Foxp3) regulatory T cells can suppress responder T cell proliferation and cytokines and stimulate the formation of Th1 and Th2 helper cells, where cellular and humoral response is initiated.
respectively. Th1 response leads to phagocytosis, while the Th2 response leads to antibody production via B cells.

A characteristic feature of CD4+CD25+ Tregs is their ability to suppress a range of different responses mediated by both innate and adaptive immune systems. Therefore the reduction of CD4+CD25+ T cells in an organism affects the development of spontaneous autoimmune disorders, emphasizing the importance of Treg and their protective role against autoimmunity. These natural Tregs act mainly by Tcell to APC contact in a cytokine-independent manner where mechanisms of suppression are facilitated by the production of inhibitory cytokines, such as IL 10 and TGF-β. Mechanisms of regulation of these Tregs are also possible in order to diminish, and not just enhance, their numbers and activity to reverse immunodeficiency.

B regulatory cells play a role in autoimmune suppression and their activation with the involvement of IL 10 and TGF-β leads to germinal center activation. B cell activation eventually leads to ectopic germinal center activation, if TGF beta and IL10 are involved (Osnes et al. 2013). B cell development checkpoints guarantee that auto-reactive B cells are discarded. Correspondingly, autoimmune disease is directly related to tolerance checkpoint dysfunction. We can also conclude that Th17 is another important immune checkpoint where their unregulated activity can result in immunopathology. Alterations in the Th17
response will hopefully be a significant therapeutic focus in autoimmune disease patients.

The presence of oral ulcerations is almost always an autoimmune indication and is similar in the many autoimmune disease presented, the pathogenesis of these ulcerations, however, may differ. No clear association has been proven between AUIDs and oral manifestation. From the data suggest by Manakil 2012 it can be concluded the increased bacterial layer on tooth surfaces may have a role in the onset an immune response.

As Mays et al. reported in 2012 our studying corroborates their findings that early detection by dental professionals will allow both the healthcare provider and the patient to communicate an approach to moderate, alleviate or prevent disease development. Early detection and management of autoimmune diseases is not easy, and therefore dentists play a significant role to manage the multidisciplinary medical complexity such as autoimmune diseases. Managing inflammatory issues is not unique to each disease and can be applied with the use of steroids or antimicrobial treatment. Persistent and developed examination of autoimmune diseases will improve our understanding of disease burden and progressive trends.
In conclusion, a common effort in research is needed to determine whether common immunological pathways might be significant in several conditions. Next generation sequencing and pathway analyses must be envisioned in terms of autoimmunity in general and might help provide mutual aims for new therapies. Studying monozygotic twins, with one being the control and the other as the patient, is optimal idea for determining the significance of environmental, genetic, and epigenetic aspects in the susceptibility to autoimmune diseases.
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REFERENCES


Romagnani S (2000). T-cell subsets (Th1 versus Th2). Department of Internal Medicine, Section of Immunoallergology and Respiratory Diseases.


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Programme in collaboration with the International Student and Scholar Center

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Nov 2011-May 2012

International Orientation Leader  Leadership Training Camp, International Student Orientation
UMASSD  Aug 29-Sept3 2011

UNDPI Internship  United Nations Headquarters New York City NY, USA  May- June 2011

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  - Lectures by experts in peace and international conflicts including representatives of NATO

Research  
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Fall 2010- Spring 2011

- The study of cranio-facial/ maxillo-facial development in zebra fish: Morphological and histological analysis of the effects of Sodium Fluoride on zebra fish dental tissue; Dissection of the pharyngeal teeth and microscopic analysis of both treated and untreated fish.
  - Developed motor and spatial skills, enhanced hand-eye coordination, and trained for assessment in 3D dimension

Harvard Longwood Seminars  
Harvard Medical School
Fall –Spring 2010

- Mini-Med School Classes for a Large Audience about diverse topics and innovation in the field of Medicine

Chairperson General Assembly (GA) Third Committee Global Model United Nations 2009  
June 16-19/Aug1-8, 2009

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President of the UMD Model UN Club  
UMASSD North Dartmouth, MA USA  
December 2011-2012

Cambridge Hospital  
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Sept 2010-May 2012

- Surgical/Medical Volunteer
  - Patient rounds, shadowing RNs, CNAs, Interns and MDs and following up on patient history, current symptoms and admission status- Innovative work around the Surgical floors and ICU, such as surveys, timely rounds, etc., to enhance the overall patient experience- Operating Room time/ Surgery observation

Notre Dame Maritime Hospital Lebanon  
ER Volunteer - Patient Contact, ER experience, Shadowing MDs and RNs  
July- Aug 2010

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Byblos, Lebanon  
Summer 2010

- Internship, Shadowing, Patient Contact- Office Work; Clinical Observation of Dental Implant Surgery, Periodontal Surgery and Bone grafting; Panoramic and X-ray development

President of the Pre-Medical/Pre-Health Society  
UMASSD Elected by the Pre-Health society in June 2010  
June 2010-June 2012

MaryAnne Thomas D.M.D.- Boston University Graduate  
Quincy Dental- Quincy MA USA  
Fall 2009-2010
Shadowing/Volunteering Experience - Prep-ing rooms according to procedure/breaking down rooms after surgical procedure is done. Assisting in Amalgam restorations, crown preps, and extractions and other procedures

**Louis P. Kenyon D.M.D., P.C., FAGD, FICOI-UPenn Graduate**

**LPK Dental – Mattapoisett, MA USA**

*Fall 2009-2010*

- Shadowing/Volunteering Experience- Coordination of patients for treatment, observing the operation of the office, processing health forms, insurance information and payments Patient operation prep, sanitation, taking and developing films. Observed sinus lifts, surgical placement of dental implants and various other procedures

**Star Kids Charity**

*New Bedford MA USA*  

*Feb 2010*

- Provides educational opportunities to high-risk, low income children who have at least one parent with a history of incarceration and/or substance abuse - Events coordinator and volunteer

**Ehden & Bentael Natural Reserve and Habitat**

*Ehden, North Lebanon*  

*Summer 2007*

- Volunteer- Research in biodiversity and ecosystems of plants and animals present in the reserve

**Bentaël Natural Reserve and Habitat**

*Bentaël, Lebanon*  

*Volunteer - Community work/Management team*  

*Summer 2006*

**Global Classroom**

*UNA-USA LAU Model UN*  

*Trainer, Director, Chairperson*  

**www.laumun.info**  

*Dec 2007-2008-2009*

**ACTIVITIES & ORGANIZATIONS**

- **Presidential Member** The National Society of Leadership and Success Sigma Alpha Pi (ΣΑΠ)  
  *As of Feb 2012*

- **President** of the UMD Model UN Club  
  *UMASSD*  
  *Dec 2011-June 2012*

- **President** of the Pre-Medical/Pre-Health Society  
  *UMASSD*  
  *June 2010-June 2012*

- **Surgical/Medical Volunteers** Cambridge Hospital Cambridge Health Alliance (CHA)  
  *Sept 2010-May 2012*

- **Member** Student Health Advisory Board- ISSC Representative  
  *UMASSD*  
  *Sept 2010-May 2012*

- **Bronze Member, Ambassador** of the Donald C. Howard Leadership Program  
  *UMASSD*  
  *Fall 2010-May 2012*

- **Chair Global Model United Nations**-Alumni New York/Geneva  
  *Summer 2009*

- **Executive Board & Head of Youth** Human environmental association for development (HEAD)  
  *2008-Present*

**AWARDS & RECOGNITIONS**

- Most Outstanding Woman of the Year honorary award  
  *The University of Massachusetts Dartmouth*

- Certificate of acknowledgment in recognition of outstanding accomplishments and efforts in the field of sustainable development  
  *The Lebanese Minister of Environment Mr. Mohammed Rahal and Director of UNDP in Lebanon Mr. Edgard Chehab.*

- Global Model UN General Assembly Official, representative of the Asian continent as Chairperson of the Third Committee General Assembly  
  *UN Headquarters.*

**LANGUAGES-**

**ENGLISH, FRENCH, ARABIC – PROFICIENT**