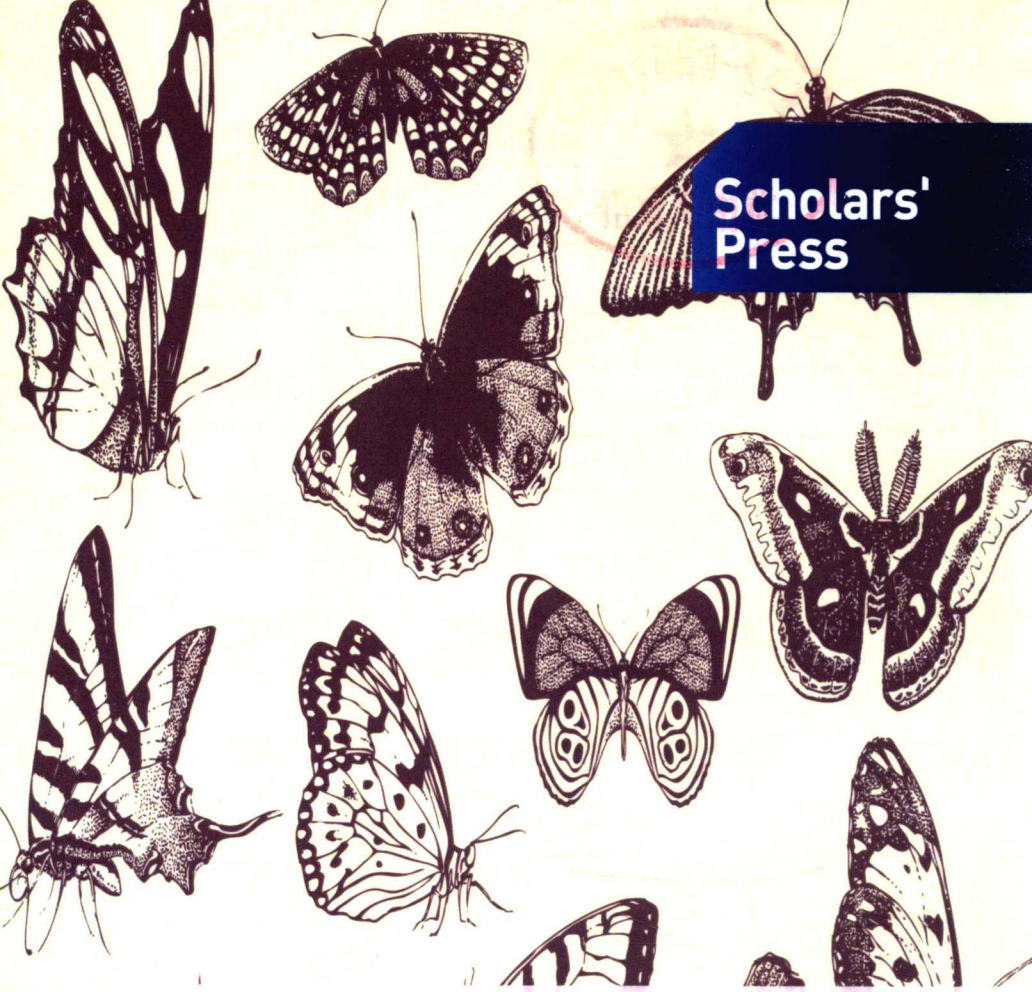

Scholars' Press

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Immunological Modulation of Auto-Immune Systemic Lupus Erythematosus (SLE) in Female BWF1 Mice Infected with Malaria

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ABSTRACT

Autoimmune diseases are the third leading cause of morbidity and mortality, after heart disease and cancer, in the industrialized world. Systemic lupus erythematosus (SLE), is a prototypic multi-system autoimmune disease that can affect the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. There is no one specific cause of SLE but the impact of infections on the development of SLE is substantial and the relationship between infections and autoimmunity in general is a complex phenomenon that has been the focus of much research. This study was designed to evaluate the effect of either live or gamma irradiated malaria infection on the autoimmune female BWF1 mice model of lupus. We observed many positive consequences of infection with live malaria parasite while gamma irradiation has diminished this effect. Some negative effects of infection were also observed. Taken together, our data reveal that infection of lupus mice with live malaria decrease apoptosis in renal tissue and confers protection against lupus nephritis the effect that couldn't occur in case of gamma irradiated parasite infection.

Keywords: Autoimmune diseases, Systemic lupus erythematosus, Malaria, Apoptosis, Lupus nephritis.

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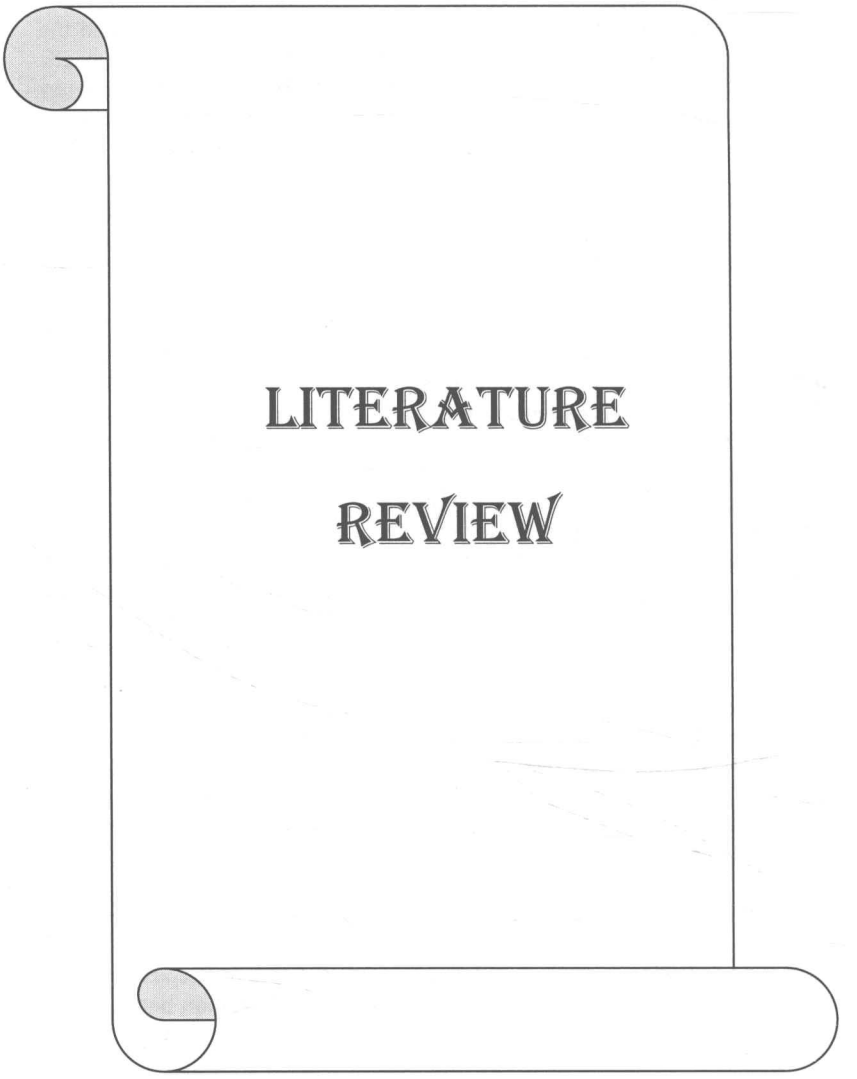
INTRODUCTION AND AIM OF THE WORK

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease affecting multiple organs including skin, joints, vessels, kidney and the central nervous system. SLE can arise from a combination of genetic susceptibility, allergies and infections (Cooper et al., 2002). Infections by pathogens, such as viruses, bacteria or parasites are prime candidates for enhancing autoimmune disease in susceptible candidates (Bach, 2005). Traditionally, this was thought to occur because of the structural cross-reactivity between the pathogenic micro-organism and self antigens (theory of molecular mimicry) (Blank et al., 2007). Alternatively, microbial products may induce autoimmunity by triggering the bystander activation of the immune system, which, if not regulated, can break the anergic state, leading to the expansion of dormant autoreactive clones (Bach, 2005, Sfriso et al., 2010). Evidence for the Epstein Barr virus to act as an infectious precursor of SLE was recently demonstrated in mice that were immunized with either the initial auto-antigenic epitope recognized in SLE patients or the cross-reactive Epstein Barr virus nuclear antigen-1 (Sundar et al., 2004). The occurrence of SLE has also been associated with parvovirus B-19 infection (Severin et al., 2003). On the other hand, infection may also protect from autoimmune disease. Western countries are being confronted with a disturbing increase in the incidence of most immune disorders, including autoimmune and allergic disease, inflammatory bowel disease, etc. Epidemiological evidence indicates that this increase is linked to improvement of the socio-economic level of these countries, more specifically, to the decrease of infections observed over the last decades. This "hygiene hypothesis" postulated that infection by microbes and inflammation will protect rather than induce and/or accelerate autoimmune diseases (Yazdanbakhsh et al., 2002; Liu and Leung, 2006; Vercelli, 2006). There are numerous murine models of SLE. One of the best characterized SLE models is the F1 hybrid between the New Zealand Black (NZB) and New Zealand White (NZW) it usually called (BWF1) which develops overt SLE with features reminiscent of those observed in human SLE, such as high anti-dsDNA titers and a high incidence of glomerulonephritis (GN).

The aim of the present study was to examine possible histological, biochemical and immunological alterations in SLE female BWF1 hybrid mice following experimental infection with the rodent live and gamma-irradiated malaria parasite *P. chabaudi* and studying the relation between the infection and the disease parameters.



LITERATURE REVIEW

1- Autoimmune diseases

One of the most important functions of the immune system is to protect organisms against infections. However, in some individuals, the immune system attacks the tissues of its own host, destroying them and thereby causing disease. There are more than 80 different so-called autoimmune diseases (AIDs) in human beings (Rubtsov et al., 2010). It is estimated that 5 % of the general population worldwide are suffering from AIDs (Shoenfeld et al., 2008; Selmi, 2010b), AIDs are reported as the third leading cause of morbidity and mortality after heart disease and cancer, in the industrialized world (Kivity et al., 2009). What causes the breakdown of immune tolerance that is necessary for the development of autoimmunity remains largely unknown (Ansari and Gershwin, 2009), particularly for more rare diseases (Leuschner et al., 2009; Mendes et al., 2009), however it is largely accepted that pathogenesis of AIDs is multi factorial; with genetic and environmental factors interplaying to determine disease onset and progression (Villalta et al., 2007; Davies, 2008; Lleo et al., 2008; Morahan et al., 2008; Invernizzi and Gershwin, 2009). Many mechanisms are being proposed for T regulatory cells (Treg) (Morris et al., 2009), oral tolerance (Peron et al., 2009; Reynoso et al., 2009; Yamada et al., 2009), macrophages (Fairweather and Cihakova, 2009; Wermeling et al., 2009), or vitamin D (Albert et al., 2009; Barna et al., 2009; Kalsch et al., 2009; Motrich et al., 2009; Smolders et al., 2009; Selmi, 2007; 2010a; 2011). Some cytokines are also linked to AIDs for example; IL-6 plays a number of critical roles in the pathogenesis of autoimmune diseases (Mihara et al., 2012).

Since the first reports on AIDs during the 1950s, it was clear the striking female prevalence in these disorders with a female to male ratio up to 10:1 (Whitacre, 2001; Gleicher and Barad, 2007; Zandman-Goddard et al., 2007; Lleo et al., 2008). Aside from genetic and environmental factors, estrogens and other steroid hormones play a fundamental role in the expression of these AIDs. (Whitacre, 2001).Indeed, women with most AIDs are known to have abnormal estrogen or prolactin metabolism and these diseases strike generally after puberty and before the menopause (Invernizzi, 2009). Indeed, women experience a more intense cellular and humoral immune response than men, making them more resistant to certain infections but also suffer higher incidence of autoimmune diseases. In animal models, females also reject grafts faster than males (Ansar et al., 1985; Ansar and Talal, 1991). The fact that women suffer from more AIDs than men could also be attributed to the stimulation of T helper (Th) 2 response by estrogens (Gleicher and Barad, 2007). An estrogen hormonal environment stimulates Th lymphocytes to secrete type 2 cytokines that promote the synthesis of antibodies (Beagley and Gockel, 2003; Tanriverdi et al., 2003). On the other hand, androgens stimulate Th cells to produce type 1 cytokines, which reduces Th2 activity and stimulates T CD8 cells (Grimaldi et al., 2002). During pregnancy, there is a shift towards the Th2 response (Marzai et al., 1996), which can be attributed to the increase in circulating levels of 17β-

estradiol (E2) and progesterone (Piccini et al., 1995; González et al., 2010). However both organ-specific and systemic autoimmunity are associated with an increased prevalence of recurrent miscarriage (RM), the precise mechanism for this is unclear, as cross-reactivity between trophoblastic and maternal host autoantigens has not been demonstrated. In many types of both systemic and organ-specific immunity, a disturbed T-helper cell profile is seen. This is also evident in women with RM. In both cases, reduced numbers of T reg. cells have been reported. These are required to regulate excessive activity of the Th1 and the pro inflammatory Th17 subsets that, when operating through excessive natural killer cell activity, may have anti pregnancy effects (Bansal et al., 2011).

Each autoimmune disease is primarily defined by the tissue being attacked and can be divided into two main categories: single organ or multi-organ. Examples of single target organ autoimmune diseases include type I diabetes, in which the immune response destroys the beta cells that produce insulin in the pancreas. In patients with multiple sclerosis, the immune response attacks cells in the brain, while in rheumatoid arthritis; the immune response causes inflammation and destruction of the joints. The situation is more complicated in multi-target organ or systemic diseases such as SLE. In patients with lupus, the immune system makes antibodies against DNA and other material present in the nuclei of all cells. These antibodies bind their targets and give rise to problems in organs such as the kidneys, causing inflammation and leading to tissue damage and malfunction (Rubtsov et al., 2010).

The treatment of autoimmune diseases has significantly changed during the past years with the development of numerous monoclonal antibodies that target specific mechanistic effectors such as tumor necrosis factor- α (TNF-α) (Anolik and Aringer, 2005; Caporali et al., 2009; Robak and Robak, 2009; Galarza-Maldonado et al., 2010; Traczewski and Rudnicka, 2011; Yildirim-Toruner and Diamond, 2011) that currently represents the cornerstone of the treatment of RA (Bazzani et al., 2009) or newly established molecules such as rituximab to deplete B cells (Dörner et al., 2009; Moreno et al., 2010). A large number of biologics are currently in advanced experimental phases and are expected to rapidly change the management of autoimmune disease-patients in the next few years (Mount and Gilliland, 2008; Cairoli et al., 2010; Dall'era and Wofsy, 2010; Postal et al., 2012), as in the case of the newest TNF-α and other cytokine inhibitors, hematopoietic stem cell transplantation (Kushida et al., 2009) or the induction of antigen-specific reactivity (Kanazawa et al., 2009). Nevertheless, there is a wide variability among patients and between clinical conditions in terms of response and tolerability (Favalli et al., 2002; Dall'era and Chakravarty, 2011) and these have not fully replaced more classical therapeutic approaches such as intravenous immunoglobulins (Arnson et al., 2009; Cuadrado, 2009; Selmi, 2010a).

From the genetic standpoint, it is known that in the case of AIDs, there is a complex interaction between the product of various genes, and genomic high-

throughput analyses can tell us which genes are turned on or off in different tissues from patients with autoimmune diseases. Recent genomic and transcriptomic profiling studies have implicated certain cytokines, surface receptors, signalling pathways, and cell types in the pathogenesis of inflammatory diseases (Gottenberg et al., 2006; Potti et al., 2006; Edwards et al., 2007; Wakamatsu et al., 2007; Bartůnková et al., 2009; Devauchelle-Pensec et al., 2010; López-Pedrera et al., 2012).

Infections have an important role in the development of autoimmunity. Almost every autoimmune disease investigated is linked to one or more specific infectious agents (Doria et al., 2008; Pordeus et al., 2008; Shoenfeld et al., 2008). The solid link between infections and autoimmunity has been strengthened by several studies during the past years (Hasni et al., 2011). Such studies have mainly investigated the autoimmune component or consequences of viral infections (Barzilai et al., 2007). In the case of chronic hepatitis C (CHC) infection, AIDs are commonly found and new evidence is needed to prevent their occurrence. The recent report that B lymphocyte activating factor (BAFF) levels could be a useful tool to predict autoimmunity development in CHC is of particular interest (Toubi et al., 2006) while data on the prevalence of serum autoantibodies to microsomal epoxide hydrolase in CHC (Akatsuka et al., 2007) appear to indicate that the AID occurrence in these patients might be currently underestimated. Similar to hepatitis viruses, data have been also obtained on serum autoantibodies occurring during simian immunodeficiency virus (SIV) infection in primates in which viral infection features appear to correlate with autoimmunity serum markers, thus supporting a direct role of the former (Ansari et al., 2007), evidence has been provided on the type 1 diabetes severity to be linked with internal virus infection (Mäkelä et al., 2006). Lastly, AIDs are presented as complications of vaccines (Orbach and Shoenfeld, 2005). It is of particular interest, for example, the proposed correlation between the use of vaccines and the onset of fibromyalgia (Ablin et al., 2006), and the use of that new antibody-based treatments for chronic viral infections (Ejrnaes and Herrath, 2007) might produce important implications for AIDs (Selmi, 2007). It is now well accepted that infections are major players in the environmental factors which modulate the development of autoimmune diseases, both on positive and negative ways (Zaccone et al., 2008). The underlying mechanisms are multiple and complex, probably different according to pathogens (Bach, 2005; Blank et al., 2007). Mimicry of host antigens by infectious agents may induce cross-reactive autoimmune responses to epitopes within host proteins which, in susceptible individuals, may tip the balance of immunological response versus tolerance toward response and subsequently lead to AID.

Chronic diseases, such as inflammatory bowel diseases and rheumatoid arthritis, are characterized by a robust immune response resulting in unresolved inflammation (Afzali et al., 2007). Despite clear evidence that vaccination with mimetic microbial antigens has the potential to activate auto reactive T cells,

crucial evidence for triggering of autoimmunity by mimetic sequences in natural pathogens remains lacking, although they may provoke a prolonged inflammatory response when occurring on a susceptible immunological background. Considering that activation rather than the presence of auto reactive T cells and antigen spreading are the hallmarks of autoimmune disease, the creation of an environment resulting in failure of tolerance and regulatory mechanisms, rather than emergence of novel microbial antigenic determinants, may well be at the root of autoimmunity. Because microbial degradation products, and even bacterial DNA, are present at sites of autoimmunity, this has led to the speculation that the continuous seeding of bacterial products from the gut may eventually favor, on a permissive genetic background, onset of inflammatory autoimmunity. As the vast majority of infections pertain to our resident microbiota, focus has been given toward understanding the mechanisms underlying transition from healthy carrier state to infectious syndromes, including autoimmune diseases (Pordeus et al., 2008). More surprisingly, infections may also protect from autoimmune diseases (Bach, 2005). Western countries are being confronted with a disturbing increase in the incidence of most immune disorders, including autoimmune and allergic diseases, inflammatory bowel diseases, and some lymphocyte malignancies. Epidemiological and clinical data support the hygiene hypothesis according to which the decrease of infections observed over the last three decades is the main cause of the incessant increase in immune disorders. The hypothesis does not exclude an etiological role for specific pathogens in a given immune disorder as might notably be the case in inflammatory bowel diseases. With regard to the mechanisms of protection, antigenic competition, immune regulation, innate and adaptive mechanisms have been considered. Infectious agents stimulate a large variety of regulatory cells (Th2, CD25+, Tr1, and NKT) whose effects extend to other specificities than those which triggered their differentiation, an effect that is usually known as bystander suppression. The term "bystander suppression" is used for an unusually intensive suppression of cells exceeding the normal mechanisms of down regulation or cellular inhibition by direct cell-to-cell contacts or short-range cytokines. This effect takes predominantely place when strong counter regulatory mechanisms are activated in inflammatory or immunologically active environments such as chronic inflammatory or chronic infectious diseases (van Dillen et al., 2002). Infectious agents may also intervene through components which are not recognized as antigens but bind to specific receptors on cells of the immune system.

2- Systemic Lupus Erythematosus (SLE) as a representative example of auto immune diseases:

History of SLE

SLE is not a novel disease, as the cutaneous lesions were described already by Hippocrates under the term herpes esthiomenos (Smith and Cyr, 1988). Lupus, wolf in Latin, a term first associated to disease in the 10th century,

presumably to describe skin lesions reminding of a wolf's bite (Wallace and Hahn, 2002). Due to the large variety of disease manifestations and to the common misinterpretation of lupus as being a variant of tuberculosis, it was not until 1872 that the physician Moriz Kaposi described lupus erythematosus (LE) as an entity of skin lesions with occasional systemic symptoms. In 1906, the Wasserman test for syphilis became widely used and soon false positive tests for syphilis were noted in patients with LE, a sign still included in the American College of Rheumatology (ACR) criteria for SLE today (Tan et al., 1982; Wallace and Hahn, 2002) . The LE cell was discovered in 1948 and was a breakthrough that contributed to the understanding of the pathogenesis of disseminated LE (Hargraves, 1969). Today, the LE cells have been found to contain apoptotic bodies (Schmidt-Acevedo et al., 2000).

Epidemiology, clinical presentation and disease activity indices of SLE

SLE, also termed lupus, is a chronic autoimmune disease with tissue damage caused by auto antibodies and immune complexes. The disease has a wide spectrum of clinical manifestations that include non-erosive arthritis, skin lesions, and inflammation in internal organs that cause nephritis, pleuritis, pericarditis and nervous system involvement. General symptoms such as malaise, fever and fatigue are also common in SLE patients. Most patients have antinuclear antibodies (ANA) and during active disease, leucopenia and/or complement consumption are frequently seen. The disease is also varyingly active, with periods of exacerbations that are followed by remissions (Wallace and Hahn, 2002). For milder SLE, without threatening organ involvement, salicylate, non-steroid anti-inflammatory drugs (NSAID) and glucocorticoids are used for therapy. Anti-malarial drugs are also frequently used in SLE, both for treatment of several manifestations and to prevent relapses (Ruiz-Irastorza et al., 2010). Due to the fact that SLE patients can have many different clinical manifestations, rheumatologists have developed a set of criteria to facilitate collection of data for clinical trials and to compare different patient populations. In 1982, the ACR revised the preliminary criteria from 1971 for the classification of SLE (Table I). A person is considered to have SLE if at least four of the 11 criteria are present which gives a high sensitivity and specificity for presence of SLE (Tan et al., 1982; Hochberg, 1997). Of all individual parameters, anti-dsDNA antibodies were found to be the best discriminator. It is important to make the distinction that these criteria are not intended to be used for diagnosis, because more than 50% of the patients did not fulfill the ACR criteria at a given time point, although all did with time (Levin et al., 1984; Jonsson et al., 1989). Predominantly women (9:1, female: male ratio) during their child bearing years are affected by SLE and the incidence has been estimated to be 4.8/100 000 and the prevalence to be 68/100 000 inhabitants in southern Sweden (Nived et al., 2013). In the US, the overall prevalence has been estimated to be between 14.6 to 50.8 cases per 100 000 persons (Mertelsmann-Voss et al., 2014). An increase in the incidence has been reported, perhaps due to increased use of oral