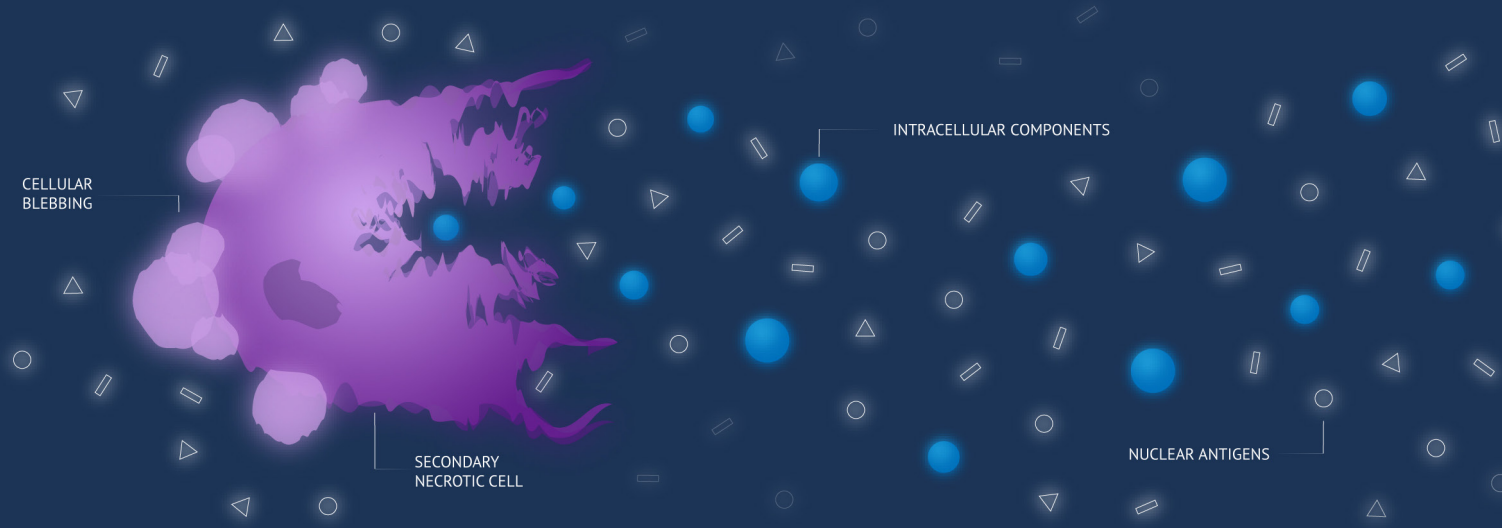
# LUPUS Pathoprofile

**AUTHORS:** Takhliq Amir & Jim Xie
**ARTIST:** Kien Nagales

## When the body attacks itself

## INTRODUCTION

Lupus is a chronic inflammatory autoimmune disease. Of the four main types of lupus, systemic lupus erythematosus (SLE) is the most common, affecting approximately 90 in 100 000 Canadians.[1] In SLE, abnormalities in immunological function induce the production of antibodies that target the body's own cells (autoantibodies), leading to multisystemic inflammation and a wide range of clinical presentations. Symptoms range from skin rashes and arthritis, to nephritis and psychosis.[2] A variety of genetic, hormonal, and environmental factors, including UV radiation and estrogen, are implicated in the etiology of SLE.[3,4]




## DEFICIENCY IN APOPTOTIC CLEARANCE

Typically, apoptosis —a highly controlled form of cell death— occurs as part of the normal cell cycle.[5] In healthy individuals, when apoptotic cells are cleared by macrophages via phagocytosis, their cell membranes remain intact. Membrane impermeability hinders any intracellular substances from leaking out, thereby preventing an immunogenic response.[5-7] However, in certain pathological conditions, secondary necrosis occurs when the cellular membrane disintegrates and releases noxious intracellular components such as nuclear antigens into surrounding tissues.[5] Nuclear antigens elicit a pro-inflammatory cytokine response, which recruit immune cells in a process leading to autoimmunity.[6,7]

In lupus, various factors, such as decreased expression and impaired function of macrophages, cause the accumulation of apoptotic debris to exceed their clearance rate. Subsequently, secondary necrosis occurs wherein cellular blebbing —the formation of vesicles on the surface of apoptotic cells— releases nuclear antigens (e.g. DNA) extracellularly, leading to an immune response.[6,7] As immune complexes and biological wastes accumulate over time, continuous clearance defects contribute to the loss of immune cell self-tolerance, which underlies autoimmunity in SLE.[6,8]

## ANTIBODY PRODUCTION AND INFLAMMATION

Self-antigens released from secondary necrosis stimulate immune cell receptors, such as members of the Toll-like receptor (TLR) family found on B cells.[9] Self-reactive B cells are thus activated and interact with autoantigen-specific T lymphocytes to differentiate into long-lived plasma cells that reside in the bone marrow and produce autoantibodies.[2,10] Of the high-affinity IgG autoantibodies secreted by these B cells, antinuclear antibodies, namely anti-DNA antibodies (ADAs), are the most well-characterized.[11] ADAs bind to apoptosis-derived DNA to produce high plasma levels of DNA-ADA immune complexes.[12,13] Such immune complexes produce a positive feedback loop of multisystemic inflammation. DNA-ADA complexes can cause the secretion of proinflammatory cytokines by activating plasmacytoid dendritic cells, a unique type of secretory immune cells found in peripheral lymphoid organs and the blood.[14] Moreover, immune complexes can deposit in the microvasculature and hyperactivate the complement system via the classical pathway, causing tissue damage and inflammation in a variety of organ systems.[2,15] The overall increase in inflammation, in combination with enhanced recruitment of self-reactive T and B cells caused by apoptotic clearance defects, augments the humoral immune response and drives the production of additional autoantibodies.[2,6,7,12,13]