Crosstalk between B cells and neutrophils in rheumatoid arthritis.

Abstract

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease without known cure that primarily affects synovial joints. RA has a prevalence of approximately 1% of the population worldwide. A vicious circle between two critical immune cell types, B cells and neutrophils, develops and promotes disease. Pathogenic anti-citrullinated protein antibodies (ACPA) directed against a range of citrullinated epitopes are abundant in both plasma and synovial fluid of RA patients. In addition to stimulating numerous cell types, ACPA and other autoantibodies, notably rheumatoid factor, form immune complexes (ICs) that potently activate neutrophils. Attracted to the synovium by abundant chemokines, neutrophils are locally stimulated by ICs. They generate cytokines and release cytotoxic compounds including neutrophil extracellular traps (NETs), strands of decondensed chromatin decorated with citrullinated histones and granule-derived neutrophil proteins, which are particularly abundant in the synovial fluid. In this way, neutrophils generate citrullinated epitopes and release peptidyl arginine deiminase (PAD) enzymes capable of citrullinating extracellular proteins in the rheumatic joint, contributing to renewed ACPA generation. This review article focusses on the central function of citrullination, a post-translational modification of arginine residues in RA. The discussion includes ACPA and related autoantibodies, somatic hyper mutation-mediated escape from negative selection by autoreactive B cells, promotion of the dominance of citrullinated antigens by genetic and lifestyle susceptibility factors and the vicious circle between ACPA-producing pathogenic B cells and NET-producing neutrophils in RA.

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease (reviewed in Ref. [1). This most common form of inflammatory arthritis affects ~1% of the population worldwide and is more prevalent in women than men. RA is a disabling condition characterized by symmetrical inflammation of synovial joints, with small, peripheral joints most commonly affected. The synovial fluid (SF) becomes enriched in leucocytes and cytokines, and the inflamed synovial membrane develops into an inflammatory pannus, an abnormal layer of blood vessel-containing tissue which invades the space between the bones, covering bones and cartilage. Unless treated, RA erodes the joint cartilage and bone, causing chronic pain, stiffness, progressive loss of function, disability and, once fusion of bones has occurred, lasting deformities. Up to 40% of patients develop extra articular RA, which ranges from systemic features, such as vasculitis, to affecting individual organs, for example the lung (e.g., interstitial lung disease) or heart (e.g., pericarditis). With the advent of improved and increasingly sophisticated disease-modifying anti-rheumatic drugs, RA has become more

manageable in recent years. Although it remains incurable, a combination of early intervention, control of inflammation and prevention of joint damage can culminate in reaching a sustained state of remission.

BIOGRAPHY

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