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Review

Rheumatoid arthritis: Recent advances on its etiology, role of cytokines and pharmacotherapy

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ABSTRACT

An autoimmune disease is defined as a clinical syndrome resulted from an instigation of both T cell and B cell or individually, in the absence of any present infection or any sort of distinguishable cause. Clonal deletion of auto reactive cells remains the central canon of immunology for decades, keeping the role of T cell and B cell aside, which are actually the guards to recognize the entry of foreign body. According to NIH, 23.5 million Americans are all together affected by these diseases. They are rare, but with the exception of RA. Rheumatoid arthritis is chronic and systemic autoimmune response to the multiple joints with unknown ethology, progressive disability, systemic complications, early death and high socioeconomic costs. Its ancient disease with an old history found in North American tribes since 1500 BCE, but its etiology is yet to be explored. Current conventional and biological therapies used for RA are not fulfilling the need of the patients but give only partial responses. There is a lack of consistent and liable biomarkers of prognosis therapeutic response, and toxicity. Rheumatoid arthritis is characterized by hyperplasic synovium, production of cytokines, chemokines, autoantibodies like rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA), osteoclastogensis, angiogenesis and systemic consequences like cardiovascular, pulmonary, psychological, and skeletal disorders. Cytokines, a diverse group of polypeptides, play critical role in the pathogenesis of RA. Their involvement in autoimmune diseases is a rapidly growing area of biological and clinical research. Among the proinflammatory cytokines, IL-1α/β and TNF-α trigger the intracellular molecular signalling pathway responsible for the pathogenesis of RA that leads to the activation of mesenchymal cell, recruitment of innate and adaptive immune system cells, activation of synoviocytes which in term activates various mediators including tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-8 (IL-8), resulting in inflamed synovium, increase angiogenesis and decrease lymphangiogensis. Their current pharmacotherapy should focus on their three phases of progression i.e. prearthritis phase, transition phase and clinical phase. In this way we will be able to find a way to keep the balance between the pro and anti-inflammatory cytokines that is believe to be the dogma of pathogenesis of RA. For this we need to explore new agents, whether from synthetic or natural source to find the answers for unresolved etiology of autoimmune diseases and to provide a quality of life to the patients suffering from these diseases specifically RA.

Contents

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1. Introduction

The human immune system work in association with other physiologic systems in order to provide stable interior environment essential for the survival and reproduction of the host. This system distinguishes and responds to dangerous changes in tissue. The two basic triggering elements responsible for the activation of immune system are pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) expressed by microbes and stress respectively [1]. The evolutionary process culminates in a balanced array of homeostatic mechanisms for knowing the external and internal world. During lymphocyte ontogeny and in the form of any immune response, there is a hazard of the genesis and/or activation of autoreactive lymphocytes, disturbing the homeostasis leads various autoimmune diseases [2]. Autoimmune diseases are very rare, but an exception is always there, for example rheumatoid arthritis and autoimmune thyroiditis. According to NIH (The National Institutes of Health) 23.5 million Americans suffer from autoimmune disease. However, these diseases are not yet fully understood, but to pursue them is mesmerizing [3]. These are pathological conditions characterized by abnormal autoimmune responses, autoantibodies production and T-cell responses to self-protein initiated by immune system reactivity [4]. Clonal deletion of auto reactive cells remains the central canon of immunology for decades, keeping the role of T cell and B cell aside, which are actually the guards to recognize the entry of foreign body. Autoantigen helps in the formation of inventory of mature lymphocytes and their continuous exposure in periphery helps the naïve T cell and B cell to survive and grow. The speculation that lymphocytes are meant to differentiate between self and foreign antigen is wrong because both self and foreign antigen have similar structure. Therefore their role is just to respond to the antigen in specific microenvironment in the presence of inflammatory cytokines [5].

Table 1
Specific autoimmune disorder.

List of Autoimmune diseases			
Addison's disease	ChurgStrauss syndrome	Herpes gestationis	Parry Romberg syndrome
Agammaglobulinemia	Crohn's disease	Idiopathic thrombocytopenic purpura (ITP)	ParsonnageTurner syndrome
Alopecia areata	Cogans syndrome	Henoch Schonlein purpura	Pars planitis (peripheral uveitis)
Amyloidosis	Cold agglutinin disease	IgA nephropathy	Pemphigus
Ankylosing spondylitis	Congenital heart block	IgG4 related sclerosing disease	Peripheral neuropathy
AntiGBM/AntiTBM nephritis	CREST disease	Immunoregulatory lipoproteins	Primary sclerosing cholangitis
Antiphospholipid syndrome (APS)	Coxsackie myocarditis	Inclusion body myositis	Perivenous encephalomyelitis
Autoimmune angioedema	Discoid lupus	Interstitial cystitis	Pernicious anemia
Autoimmune aplastic anemia	Dressler's syndrome	Juvenile arthritis	POEMS syndrome
Autoimmune dysautonomia	Demyelinating neuropathies	Juvenile myositis	polyglandular syndromes
Autoimmune inner ear disease (AIED)	Dermatitis herpetiformis	Kawasaki syndrome	Polyarteritis nodosa
Autoimmune myocarditis	Dermatomyositis	Lichen planus	Polymyalgia rheumatica
Autoimmune oophoritis	Devic's disease	Lichen sclerosus	Polymyositis
Autoimmune pancreatitis	Endometriosis	Ligneous conjunctivitis	Postpericardiotomy syndrom
Autoimmune retinopathy	Eosinophilic esophagitis	Linear IgA disease (LAD)	Psoriasis
Autoimmune thrombocytopenic purpura (ATP)	Eosinophilic fasciitis	Lupus (SLE)	Psoriatic arthritis
Autoimmune thyroid disease	Erythema nodosum	Lyme disease, chronic	Pyoderma gangrenosum
Autoimmune hepatitis	Evans syndrome	Lambert Eatons yndrome	Pure red cell aplasia
Autoimmune hyperlipidemia	Experimental allergic	Microscopic polyangiitis	Primary biliary cirrhosis
Autoimmune urticarial	Essential mixed cryoglobulinemia	Mixed connective tissue disease	Raynauds phenomenon
Axonal & neuronal neuropathies	Fibromyalgia	Mooren's ulcer	Reactive Arthritis
Autoimmune immunodeficiency	Fibrosing alveolitis	MuchaHabermann disease	Reflex sympathetic dystrophy
Acute necrotizing hemorrhagic leukoencephalitis	Giant cell arteritis (temporal arteritis)	Multiple sclerosis	Reiter's syndrome
Balo disease	Giant cell myocarditis	Myasthenia gravis	Relapsing polychondritis
Behcet's disease	Glomerulonephritis	Myositis	Restless legs syndrome
Bullous pemphigoid	Goodpasture's syndrome	Meniere's disease	Scleroderma
Cardiomyopathy	Granulomatosis with Polyangiitis	Neuromyelitis optica (Devic's)	Sjogren's syndrome
Castleman disease	Graves' disease	Neutropenia	Sperm & testicular autoimmunity
Celiac disease	GuillainBarre syndrome	Narcolepsy	Stiff person syndrome
Chagas disease	Hashimoto's encephalitis	Ocular cicatricial pemphigoid	Subacute bacterial endocarditis (SBE)
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Hashimoto's thyroiditis	Optic neuritis	Susac's syndrome
Chronic recurrent multifocal osteomyelitis (CRMO)	Haemolytic anemia	Palindromic rheumatism	
Chronic fatigue syndrome	Hypogammaglobulinemia	Paroxysmal nocturnal hemoglobinuria (PNH)	