Autoinflammatory Syndromes: Recent advances in diagnosis and treatment

E S S A Y

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" قالوا سبحانك لا علم لنا إلا ما علمتنا
إنك أنت العليم الحكيم "

صدق الله العظيم

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Dedication

To all the people who ever helped me through out life.

To my parents, who taught me everything I know and whose prayers have accompanied me every step on the road.

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Abstract

Autoinflammatory diseases are characterized by seemingly unprovoked inflammation. These diseases include familial Mediterranean fever; cryopyrin-associated periodic syndromes; tumor necrosis factor receptor-associated periodic syndrome; hyperimmunoglobulinemia-D syndrome; pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; and Blau syndrome.

Recent identification of the susceptibility genes for auto-inflammatory diseases has broadened the clinical spectrum as well as the molecular basis of these diseases. Studies have shown that activation of the interleukin-1β (IL-1β) pathway is a common mechanism in the pathogenesis of autoinflammatory diseases. A major role for the activity of a complex known as the inflammasome in the development of these diseases was established recently.

New pathophysiological insights have led to the development of promising maintenance treatments designed to reduce the number and severity of the inflammatory attacks.

Anakinra, a recombinant human interleukin-1 receptor antagonist, is a promising new biologic agent for the treatment of cryopyrinopathies as well other autoinflammatory diseases.

Key words:

Autoinflammatory diseases, inflammasome, interleukin-1β, cryopyrin, TNFα blocker and interleukin-1 receptor antagonist.

Contents

List of abbreviations

ASC	Apoptosis-associated specklike protein with a CARD
BB	B-Box domain
BS	Blau syndrome
CAPS	Cryopyrin-associated periodic syndrome
CARD	Caspase recruitment domain
CC	Coiled-coil domain
CD2BP1	CD2 binding protein 1
CIAS1	Cold-induced autoinflammatory syndrome on chromosome 1
CINCA	Chronic infantile neurological cutaneous and articular syndrome
CRDs	Cysteine-rich domains
ER	Endoplasmic reticulum
FCAS	Familial cold autoinflammatory syndrome
FMF	Familial Mediterranean fever
HIDS	Hyperimmunoglobulin-D syndrome
HMG-CoA	3-hydroxy-3-methylglutaryl- coenzyme A
ICE	Interleukin-1β-converting enzyme
IgG1	Immunoglobulin-G1
IL-1RA	Interleukin-1 receptor antagonist
IL-1β	Interleukin -1 Beta
IPAF	ICE-protease activating factor
KDa	Kilodalton
LPS	Lipopolysaccharide
LRR	Leucine-rich repeats
MEFV	Mediterranean FeVer
MVK	Mevalonate kinase
MVA	Mevalonic aciduria
MWS	Muckle-Wells syndrome
NAD	NACHT association domain
NALP	NACHT-, LRR- and pyrin-domain-containing protein

NF-κB	Nuclear factor-kappa B
NOD	Nucleoside oligomerization domain
NOMID	Neonatal onset multisystemic inflammatory disease
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAMPs	Pathogen-associated molecular patterns
PAPA	Pyogenic arthritis, pyoderma gangrenosum and acne syndrome
PG	Pyoderma gangrenosum
PRMs	Pattern recognition molecules
PSTPIP1	Proline/ serine /threonine phosphatase-interacting protein 1
PYD	Pyrin domain
SAA	Serum amyloid A
TNF	Tumor necrosis factor
TNFRSF1A	TNF receptor superfamily 1 A
TRAPS	TNF receptor-associated periodic syndrome
UPR	Unfolded protein response

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Introduction

The term autoinflammatory syndromes describes a distinct group of systemic inflammatory diseases apparently different from infectious, autoimmune, allergic and immunodeficient ones. Originally, it was almost synonymous with clinically defined hereditary periodic fever syndromes, including familial Mediterranean fever (FMF) , hyper-immunoglobulin D syndrome (HIDS) with periodic fever and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) ***(Kanazawa and Furukawa, 2007).***

Similar but distinct periodic fever syndromes, the three cryopyrinopathies: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome and neonatal onset multisystem inflammatory disorder / chronic infantile neurological cutaneous articular syndrome (NOMID/CINCA), have all been reportedly associated with mutations in a common gene [cold-induced autoinflammatory syndrome 1 (CIAS1)] ***(Shinkai et al., 2008).***

Consequently, the concept of autoinflammatory syndromes has been spread to contain other systemic inflammatory diseases: rare hereditary diseases with or without periodic fevers, such as pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome (PAPA) and Blau syndrome (BS) ***(Kanazawa and Furukawa, 2007).***

Autoinflammatory diseases are all caused by or associated with mutations of genes regulating innate immunity and have common clinical features accompanied with activation of neutrophils and/or monocytes/macrophages. The main component of autoinflammatory diseases is the group of hereditary periodic fevers which are characterised

by intermittent bouts of clinical inflammation with focal organ involvement mainly: abdomen, musculoskeletal system and skin ***(Grateau, 2006).***

Musculoskeletal manifestations may occur as features of the acute inflammatory attacks or persist for longer periods. Among them, the most common include arthritis of the large and medium-sized joints in FMF and CINCA, arthralgia in HIDS, and myalgia or pseudo-fasciitis in TRAPS. The outcome is usually favorable, although joint destruction may develop in CINCA or at the hip in FMF ***(Stankovic and Grateau, 2007).***

Familial Mediterranean fever, the most frequent of the periodic fever syndromes, is an autosomal recessive disease, predominantly affecting people of Mediterranean descent. The disease is caused by mutations in the MEFV gene, encoding the pyrin protein thought to be associated with the interleukin-1 related inflammation cascade ***(Lidar and Livneh, 2007).***

The cryopyrinopathies are now believed to represent related conditions along a spectrum of disease severity, in which FCAS is the mildest and NOMID is the most severe phenotype. Patients typically present with fever, urticarial rash, conjunctivitis and arthritis ***(Shinkai et al., 2008).***

Hyper-immunoglobulin D syndrome is one of the hereditary auto-inflammatory syndromes characterized by recurrent episodes of fever, increased serum IgD (normal value < 100 U/ml) and generalized inflammation (lymphadenopathy, arthralgias/arthritis, abdominal complaints, skin rash, and headache). HIDS is caused by specific mutations in the gene encoding mevalonate kinase, resulting in depressed enzymatic activity ***(Scolozzi et al., 2004).***

Tumor necrosis factor receptor-associated periodic syndrome is a dominantly inherited disease caused by mutations in the TNF receptor 1 (TNFR1) gene. Patients suffer from periodic bouts of severe abdominal pain, localised inflammation, migratory rashes, muscle pain and fever ***(Kimberley et al., 2007).***

The pyogenic arthritis, pyoderma gangrenosum and acne syndrome, is an autosomal dominant autoinflammatory disease, characterized by recurrent sterile arthritis that usually occurs after minor trauma, but also spontaneously. It is a self-limiting disease, but can lead to serious joint destruction ***(Dierselhuis et al., 2005).***

Blau syndrome is an autosomal dominant inherited disorder with clinical manifestations caused by granulomatous inflammation of joints, eyes, and skin ***(Simon and van der Meer, 2007).***

Although they share many clinical features with autoimmune disorders, the notion that autoinflammatory syndromes are a set of clinical diseases distinct from autoimmune disorders has been largely validated by the recognition that their pathogenesis does not require autoreactive T lymphocytes or immunoglobulins to self antigens. Instead, the autoinflammatory disorders result from aberrant regulation of cytokine signalling pathways leading to persistent or uncurbed inflammation ***(Shinkai et al., 2008).***

The discovery of the genetic basis for these conditions led to the description of intracellular receptors for infectious and noninfectious danger signals. Insights into these conditions have triggered the exploration of the role of innate immunity in common rheumatologic diseases *(Ryan and Goldbach-Mansky, 2008).*

The pivotal roles of interleukin (IL)-1β in cryopyrin-associated periodic syndromes, tumor necrosis factor (TNF) in TNF receptor-associated periodic syndrome, and links to inflammatory cytokine dysregulation in other autoinflammatory diseases have resulted in

effective therapies targeting proinflammatory cytokines IL-1beta and TNF and uncovered other new potential targets for anti-inflammatory therapies *(Glaser and Goldbach-Mansky, 2008).*

Aim of the Work

The aim of this study is to discuss current reviews on clinical manifestations, diagnosis and treatment regimens of autoinflammatory syndromes and to display new avenues in our understanding of the inflammatory response.