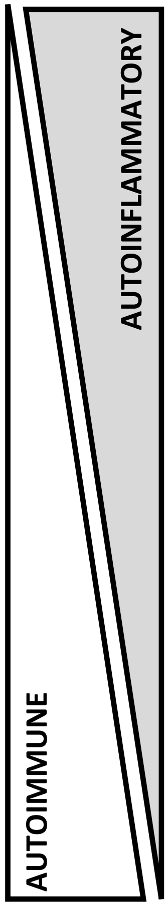
OVERVIEW OF AUTOINFLAMMATORY DISEASES

Supplement

CONTINUUM OF AUTOINFLAMMATORY AND AUTOIMMUNE DISEASES



Monogenic Autoinflammatory Diseases	• FMF: Familial Mediterranean Fever • TRAPS: Tumour Necrosis Factor Receptor associated Period Syndrome • CAPS: Cryopyrin-associated Auto-inflammatory Syndrome • HIDS: Hyper-IgD Syndrome • PAPA: PSTPIP1-associated arthritis, pyoderma gangrenosum and acne • NOD2-associated granulomatous disease (Blau syndrome, IBD)
Polygenic Autoinflammatory Diseases	• IBD: Crohn's Disease, Ulcerative colitis • Sarcoid and other erythema nodosum-associated diseases • Uveitis: Idiopathic • Acne and acneiform associated diseases
Mixed pattern diseases	• Axial spondyloarthritis • Reactive arthritis • Psoriasis, psoriatic arthritis • Behcet's disease • Uveitis: HLA-B27 related
Polygenic Autoimmune Diseases	• RA: Rheumatoid arthritis • SLE: Systemic Lupus Erythematosus • IIM: Idiopathic inflammatory myopathy • SSc: Systemic Sclerosis • SjD: Sjogren's Disease • Uveitis (sympathetic opthalmia) • AAV: ANCA-associated vasculitis • Goodpasture Syndrome • PBC: Primary Biliary Cirrhosis • Celiac Disease • Type 1 Diabetes • Addison Disease • Autoimmune thyroid disease • Myasthenia gravis • Pemphigus, Pemphigoid, Vitiligo
Monogenic Autoimmune Diseases	• ALPS: Autoimmune Lymphoproliferative Syndrome • IPEX: Immunodysregulation Polyendocrinopathy Enteropathy X-linked • APECED: Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy

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	Innate Immunity	Adaptive immunity
Specificity	• "Hard-wired" recognition of molecular patterns shared by pathogens and by damaged host cells	• "Learned" recognition of microbial and non-microbial antigens
Response, Memory	• Rapid initial response (minutes-hours) • None/limited memory: identical subsequent responses	• Slow initial response (days-weeks) • Memory: subsequent responses more rapid and intense
Blood proteins	• Complement, various lectins and agglutinins	• Antibodies
Cellular effectors	• Phagocytes (macrophages, neutrophils), dendritic cells, NK cells, mast cells, innate lymphoid cells	• B- and T-cell lymphocytes
Disease	• "Auto-inflammatory" • Antigen-independent inappropriate activation • No MHC association, no antibodies, equal sex effected	• "Auto-immune" • Self/non-self inappropriate lack of discrimination • MHC association, auto-antibodies, female predominance

In reality: complex interplay between Innate/Adaptive immune system and Auto-Immune/Auto-Inflammatory disease

Auto-inflammatory diseases can be divided into 4 main categories based on pathogenesis and response to empiric treatment

1) Inflammasomopathies: diseases caused by inappropriate activation of the inflammasome; often respond to IL-1i, TNFi, IL-18i

2) Interferonopathies: diseases caused by inappropriate activation of Type 1 interferon; often respond to JAKi

3) NF-κB-opathies/aberrant TNF activity: diseases caused by dysregulation of NF-κB; often responds to IL-1i, IL-6i, TNFi

4) Other: other diverse mechanisms, some diseases do not neatly fit above; our understanding of disease is evolving over time.

OVERVIEW OF AUTOINFLAMMATORY DISEASES

INFLAMMASOMOPATHIES

Mechanism	Disease	Gene	Clinical presentation and therapy	
Pyrin Activation	FMF	MFEV (AR or AD)	Patient	Age at onset <20 years; Eastern Mediterranean (Jewish, Turkish, Armenian, Arab)
			Features	Attacks: fever, polyserositis (peritonitis, pericarditis, pleuritis), inflammatory arthritis; amyloid risk
			Therapy	IL-1i, colchicine; NSAIDs for flares
	MKD (HIDS)	MKV (AR)	Patient	Caucasian children; diagnosis may be delayed to adolescence or adulthood. Also known as HIDS
			Features	Fever, lymphadenopathy, abdominal/joint pain, diarrhea, rash, headache, frequent infections High serum IgD and IgA
			Therapy	IL-1i, TNFi
	PAAND	MEFV (AD)	• Childhood fever, neutrophilic dermatosis, pyoderma gangranosum, arthralgias/myalgias; • IL-1i, colchicine	
	PAPA	PSTPIP1 (AD)	• Juvenile-onset inflammatory arthritis; adolescent/adult pyoderma gangranosum, ulcers, acne • IL-1i, TNFi	
	PFIT	WDR1 (AR)	• Fevers, immunodeficiency, oral inflammation, perianal ulcers, thrombocytopenia • IL-18i	
Cryopyrin activation	FCAS	NLRP3 (AD)	Patient	Variable age onset
			Features	Mildest fever, cold-induced neutrophilic urticaria, arthralgia, extremity pain, conjunctivitis, fever
			Therapy	Il-1i
	MWS	NLRP3 (AD)	Patient	Variable age at onset
			Features	Mild fever, neutrophilic urticaria, inflammatory arthritis, deaf, conjunctivitis, episcleritis; amyloid
			Therapy	IL-1i
	NOMID	NLRP3 (AD)	• Neonatal severe fever, rash, uveitis, various CNS manifestations (ex meningitis, hydrocephalus); high mortality • IL-1i	
	Majeed	LPIN2 (AR)	• Chromic recurrent multifocal osteomyelitis, fevers, rash, anemia • IL-1i	
NLRC4 activation	AIFEC	NLRC4 (AD)	• Infantile enterocolitis, rash, fever, macrophage activating syndrome, arthritis • IL-1i, IL-18i	
	FCAS/ NOMID	NLRC4 (AD)	• Cold urticaria, extremity pain, fever, CNS disease • IL-1i	
NLRP12 activation	FCAS	NLRP12 (AD)	• Cold urticaria, extremity pain, fever , aphthous ulcer • TNFi, IL-1i	
NLRP1 activation	NAIAD	NLRP1 (AD)	• Ocular, laryngeal, skin dyskeratosis, fever, arthritis • IL-1i, TNFi,	
Receptor antagonist deficiency	DIRA	IL1RN (AR)	• Pustular rash, inflammatory arthritis, hepatosplenomegaly, osteomyelitis, periostitis, fever, • Il-1i	
	DITRA	IL36RN (AR)	• Pustular psoriasis, fever, malaise • TNF, IL1i, ?IL-17/12/23	

- FMF: Familial Mediterranean Fever, FCAS: Familial Cold Autoinflammatory Syndrome, MWS: Muckle-Wells Syndrome
- AR = Autosomal recessive. AD = Autosomal dominant.
- Some name inflammasomopathies by genetic mutation, ex: NRP3-AID (AutoInflammatory Disease), NLRP12-AID
- Diseases with amyloid risk (FMF, MWS) require routine urinalyses to screen for renal amyloid involvement

INTERFERONOPATHIES

Mechanism	Disease	Gene	Clinical presentation and therapy
Nucleic acid processing, degradation Disorders	Aicardi-Goutieres Syndrome (AGS)	TREX1, ADAR1, RNASEH2A/B/C, SAMHD1, IFIH1 (AR; AD: IFIH1)	• Neonatal to later-onset fever, neurologic decline, encephalopathy, cerebral calcification, chilblains, hepatosplenomegaly, autoantibodies • JAKi, ?reverse transcriptase inhibitor, ?IFN-RA
	Mono-genic SLE	DNASE1/2/1L3, complements AR (AD: DNASE1)	• Neonatal inflammatory arthritis, cytopenias, glomerulonephritis, rash, mucositis, liver fibrosis • ?JAKi, ?IFN-RA
Nucleic acid sensing enhanced	SMS	IFIH1, DDX58a (AD)	• Early onset calcification of aorta/cardiac valves, osteopenia, acro-osteolysis, dental anomalies • ?JAKi, ?IFN-RA
	SAVI	TMEM173 (AD)	• Infant-onset vasculopathy (Chilblain's, small vessel vasculitis), skin ulcers/necrosis, arthritis, ILD • JAKi, ?IFN-RA
Proteosome dysfunction	CANDLE PRAAS PRAID	PSMB3, PSMB4, PSMB8, PSMB9, POMP (AR, AD: POMP)	• Infant-onset fever, annular plaques and eyelid swelling, joint contractures, hepatosplenomegaly, lipodystrophy, failure to thrive, developmental delay, anemia • JAKi, ?IFN-RA

NF-κB DISORDERS and/or ABERRANT TNF ACTIVITY				
Mechanism	**Disease**	**Gene**	**Clinical presentation and therapy**	
Dysregulated NFκB signaling	HA20	TNFAIP3 (AD)	Patient	• Childhood onset but adolescence/adulthood reported; most common European and Japanese
			Features	• Fever (44%), mouth/genital/GI ulcers (63%), erythema nodosum, psoriasis, folliculitis, diarrhea, arthralgia/arthritis. Can resemble like Behcets, IBD, RA/SLE/sJIA
			Therapy	• Colchicine, TNFi, IL-1i, IL-6i, ?JAK
	RELA haplo-insuff.	RELA (AD)	• Oral and gastrointestinal ulcerations, cytopenias, lymphoproliferative disease • TNFi	
	ORAS	OTULIN (AR)	• Neonatal fever, panniculitis, diarrhea, inflammatory arthritis, failure to thrive • TNFi	
	LUBAC deficient	HOIL1, HOIP (AR)	• Neonatal fever, recurrent infection, Failure to thrive amylopectin-like deposits in muscles • Hematopoietic stem cell transplant, ?TNF	
Dysregulated TNF	TRAPS	TNFRSF1A (AD)	Patient	• Age at onset varies from infancy to adulthood (22%), tends to be childhood
			Features	• Fever flares x1-4 weeks, abdo pain, myalgias, centrifugal rash, conjunctivitis, periorbital edema
			Therapy	• TNFi, IL-1i
	DADA2	ADA2 (AR)	Patient	• Childhood onset, but later and adult onset reported (sometimes due to delayed recognition)
			Features	• Fever, PAN-like vasculitis, young-onset ischemic/hemorrhagic stroke, livedo, cytopenias, hypogammaglobulinemia
			Therapy	• TNFi, Hematopoietic stem cell transplant
	Blau	NOD2 (AD)	• Early-onset familial sarcoid: Granulomatous dermatitis, uveitis, polyarticular arthritis • TNFi	
	CRIA	RIPK1 (AD)	• Fever, lymphadenopathy, hepatosplenomegaly • ?IL-6i	
• HA20: haploinsufficiency of A20, TRAPS: TNF receptor-associated periodic fever syndrome, DADA2: deficiency of adenosine deaminase 2				

OTHER AUTO-INFLAMMATORY DISORDERS (that are more prevalent in adult than paediatric patients)			
Schnitzler's	Patient	• Median age 55-years, slight male predominance.	
	Features	• Recurrent fever (72%), urticaria, bone/joint pain (40%), lymphadenopathy (25%), paraprotein (IgM>IgG) • Urticaria may precede other symptoms by years	
	Treatment	• IL-1i, IL-6i	
CNO/CRMO, SAPHO	• CNO (Chronic nonbacterial osteomyelitis), aka CRMO (Chronic Recurrent Multifocal Osteomyelitis) • May be within the same disease spectrum as SAPHO (Synovitis acne pustulosis hyperostosis osteitis) in adults		
	Mechanism	• IL1RN mutation leading to NLRP3 activation and expression of IL-1β, TNF, IL-18	
	Patient	• May affect adults or children	

	Features	• Bone: swelling and bone pain due to uni- or multi-focal aseptic osteitis commonly at
		  • Metaphyses/epiphyses of long bones
		  • Shoulder girdle (clavicle and sternum)
		  • Vertebral bodies
		  • Mandible (rare)
		• Musculo/cutaneous (20%):
		  • Palmoplantar pustulosis, cystic acne,
		  • Inflammatory arthritis (more in SAPHO)
		• Spondyloarthropathy features:
		  • IBD (10%), Psoriasis, hidradenitis suppurativa
		  • Association of CNO with seronegative spondyloarthropathy may be stronger in adults than in children	

	Imaging	• Diagnostic confirmation of osteitis usually by
		  • X-ray: osteolytic or hyperostotic features
		  • MRI whole-body or regional with STIR: for bone marrow edema signifying osteitis
		• Can evaluate for fracture, sarcoma, metastases, infarction; bone biopsy and culture may be required	

	Treatment of osteitis	First line	• NSAIDs
		Refractory	• Methotrexate, sulfasalazine (±NSAIDs, steroids), ***or*** • TNF-inhibitors: adalimumab, etanercept, other TNFi (±methotrexate), ***or*** • Bisphosphonates: Pamidronate (first choice), zoledronate (±NSAIDs, steroids)

PFAPA	Periodic fever with aphthous stomatitis pharyngitis and adenitis	
	Patient	• Usually pediatric disease, adult cases reported
	Features	• Every 4-6 weeks: fever with aphthous stomatitis, pharyngitis, cervical adenitis lasting 3-6 days • 41% of adults have all 4/4 features, 60% of adults of 2/4 features • Adults may develop exudative pharyngitis
	Treatment	• Single dose of prednisone 0.5mg/kg/d • Colchicine, IL-1i if frequent flares
IRP	Idiopathic recurrent pericarditis	
	Definitions	• Recurrent pericarditis: pericarditis with relapse after at least 4 weeks • Chronic pericarditis: symptoms persisting >3 months without symptom-free interval for 4 weeks
	Features	• Chest pain (100%), pleurisy (36%), fever (30%), ALT elevation (8%), peritonitis (5%) • Recurrence rate: 20-30% after first episode, 20-50% after first relapse • Investigations: ESR/CRP elevation, compatible ECG, echocardiographic evidence of effusion
	Treatment	• Colchicine • If refractory: low-dose corticosteroids • If steroid dependent: methotrexate, azathioprine, anakinra, pericardectomy
AOSD	Adult-onset Still's Disease: see dedicated chapter	