Year in Review 2019

Auto inflammatory syndromes

Basic science papers- by Hal Hoffman

New Monogenic Diseases

Immunodysregulation (immunodeficiency)

Heterozygous Truncating Variants in POMP Escape Nonsense-Mediated Decay and Cause a Unique Immune Dysregulatory Syndrome.
Poli, M. C., Ebstein, F., Nicholas, S. K., et al. S.; Am J Hum Genet. 2018 Jun 7;102(6):1126-1142. doi: 10.1016/j.ajhg.2018.04.010.
Describes a novel interferonopathy with features of immunodeficiency

Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors.
Giannelou A, Wang H, Zhou Q, et al. Ann Rheum Dis. 2018 Apr;77(4):612-619. doi: 10.1136/annrheumdis-2017-212401.
Describes a new autoinflammatory disease with a novel mechanism of action involving RNA processing.

Mechanism of Inflammasome mediated disorders

Gasdermin D mediates the pathogenesis of neonatal-onset multisystem inflammatory disease in mice
Xiao, J., Wang, C., Yao, J. Cet al. PLoS Biol. 2018 Nov 2;16(11):e3000047. doi: 10.1371/journal.pbio.3000047. eCollection 2018 Nov.; PMCID PMC6235378; PMID 30388107.

GSDMD is critical for autoinflammatory pathology in a mouse model of Familial Mediterranean Fever.
Kanneganti A, Malireddi RKS, Saavedra PHV, et al. J Exp Med. 2018 Jun 4;215(6):1519-1529. doi: 10.1084/jem.20172060. PubMed PMID: 29793924; PubMed Central PMCID: PMC5987922.
*These 2 papers demonstrate that GSDMD plays an important role in mouse models of **inflammasomopathy***

Caspase-1 self-cleavage is an intrinsic mechanism to terminate inflammasome activity
Boucher D, Monteleone M, Coll RCet al. J Exp Med. 2018 Mar 5;215(3):827-840; PMCID PMC5839769; PMID 29432122.
This is the first potential molecular explanation for the self limited nature of many autoinflammatory diseases

Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome.
Weiss ES, Girard-Guyonvarc'h C, Holzinger D, et al. Blood. 2018 Mar 29;131(13):1442-1455. doi: 10.1182/blood-2017-12-820852. PubMed PMID: 29326099; PubMed Central PMCID: PMC5877443
This demonstrates the mechanistic and diagnostic role of IL-18 in MAS

TNF/TNFR axis promotes pyrin inflammasome activation and distinctly modulates pyrin inflammasomopathy.
Sharma, D, Malik, A, Guy, C, Vogel, P, Kanneganti, T. D., Journal: J Clin Invest, 129: 1, 150-162, Epub Date: 2018/11/21, Date: Jan 2, PMC6307946, PMID 30457980.
*This elucidates the role of the TNF pathway in **pyrin inflammasomopathy** suggesting targeting TNF in FMF*

Metabolic Induction of Trained Immunity through the Mevalonate Pathway.
Bekkering, S., Arts, R. J. W., Novakovic, et al. Cell. 2018 Jan 11;172(1-2):135-146.e9. doi: 10.1016/j.cell.2017.11.025; PMID 29328908.
*Describes innate immune disease mechanisms of **mevalonate kinase deficiency***

Mechanism of interferon driven disorders

STING-associated vasculopathy develops independently of IRF3 in mice.
Warner JD, Irizarry-Caro RA, Bennion BG, et al. J Exp Med. 2017 Nov 6;214(11):3279-3292., PMC5679177, PMID 28951494.
*Demonstrates a role for IFR3 pathway in mouse model of **SAVI***

Cryo-EM structures of STING reveal its mechanism of activation by cyclic GMP–AMP
Shang, G., Zhang, C., Chen, Z. J., et al..; eng; England; Nature. 2019 Mar;567(7748):389-393. doi: 10.1038/s41586-019-0998-5. Epub 2019 Mar 6.; PMID 30842659.
Novel technology allows for visualization of molecular mechanism of STING function

Novel Pre Clinical Therapies

NLRP3

NLRP3 inflammasome inhibitor OLT1177 suppresses joint inflammation in murine models of acute arthritis. Marchetti C, Swartzwelter B, Koenders MI, et al. Arthritis Res Ther. 2018 Aug 3;20(1):169. doi: 10.1186/s13075-018-1664-2.PMID:30075804
Novel NLRP3 targeted therapy with potential for treating inflammasomopathies

STING

Targeting STING with covalent small-molecule inhibitors.
Haag SM, Gulen MF, Reymond L, et al. Nature. 2018 Jul;559(7713):269-273. doi: 10.1038/s41586-018-0287-8. Epub 2018 Jul 4.PMID: 29973723
Description of novel STING inhibitors with translational potential

Year in Review 2019- Auto inflammatory syndromes

Clinical papers- by Joost Frenkel

Consensus proposal for taxonomy and definition of the autoinflammatory diseases (AIDs): a Delphi study. Ben-Chetrit E, Gattorno M, Gul A, et al. Ann Rheum Dis 2018;77:1558-65
A novel nomenclature for the autoinflammatory diseases primarily based on pathogenic mechanism

An International Delphi Survey for the Definition of New Classification Criteria for Familial Mediterranean Fever, Mevalonate Kinase Deficiency, TNF Receptor-associated Periodic Fever Syndromes, and Cryopyrin-associated Periodic Syndrome. Federici S, Vanoni F, Ben-Chetrit E, et al. J Rheumatol 2019;46:429-36.

Classification criteria for autoinflammatory recurrent fevers
Gattorno M, Hofer M, Federici S, et al. Ann Rheum Dis 2019
2 papers describing novel clinical and genetic classification criteria for the the major autoinflammatory diseases and the careful process by which these were established

Infantile Onset Intractable Inflammatory Bowel Disease Due to Novel Heterozygous Mutations in TNFAIP3 (A20). Zheng C, Huang Y, Ye Z, et al. Inflamm Bowel Dis 2018;24:2613-20.
Infantile onset IBD as a novel and severe presentation of A20 haploinsufficiency.

A Novel Cryopyrin-Associated Periodic Syndrome Caused by a Mutation in the Nucleotide-Binding Domain, Leucine-Rich Repeat Family, Pyrin Domain-Containing 3 (NLRP3) Gene. Turunen JA, Wedenoja J, Repo P, et al. Keratoendotheliitis Fugax Hereditaria: Am J Ophthalmol 2018;188:41-50.
A completely novel presentation of NLRP3 mutations affecting the cornea

Gradual Symmetric Progression of DFNA34 Hearing Loss Caused by an NLRP3 Mutation and Cochlear Autoinflammation. Nakanishi H, Kawashima Y, Kurima K, et al. Otol Neurotol 2018;39:e181-5.
A phenotype of CAPS predominantly or exclusively affecting the cochlea, responsive to IL-1 blockade.

Biallelic loss-of-function LACC1/FAMIN Mutations Presenting as Rheumatoid Factor-Negative Polyarticular Juvenile Idiopathic Arthritis. Rabionet R, Remesal A, Mensa-Vilaro A, et al. Sci Rep 2019;9:4579,019-40874-2.
A novel phenotype of laccase deficiency: polyarticular JIA.

Familial Mediterranean Fever Is Commonly Diagnosed in Children in Israel with Periodic Fever Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome. Butbul Aviel Y, Harel L, Abu Rumi M, et al. J Pediatr 2019;204:270-4.
A paper describing he overlap between PFAPA and FMF, incidentally proving the increased attack frequency of PFAPA upon glucocorticoid treatment.

Type I interferon-mediated autoinflammation due to DNase II deficiency. Rodero MP, Tesser A, Bartok E, et al. Nat Commun 2017;8:2176,017-01932-3.
A novel interferonopathy due to DNase2 deficiency.

Novel proteasome assembly chaperone mutations in PSMG2/PAC2 cause the autoinflammatory interferonopathy CANDLE/PRAAS4. de Jesus AA, Brehm A, VanTries R, et al. J Allergy Clin Immunol 2019;.
A novel proteasome associated autoinflammatory syndrome caused by deficiency of a chaperone protein.

Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes.De Benedetti F, Gattorno M, Anton J, et al. N Engl J Med 2018;378:1908-19.
*Landmark paper describing the efficacy of canakinumab in **TRAPS, HIDS** and colchicine resistant **FMF**.*

J**AK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies**.Sanchez GAM, Reinhardt A, Ramsey S, et al. J Clin Invest 2018;128:3041-52.
*Elegant prospective study of JAK inhibition in **interferonpathies**.*

The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: A retrospective cases series.Kone-Paut I, Cimaz R, Herberg J, et al. Autoimmun Rev 2018;17:768-74.
Small retrospective case series of IL-1 blockade in Kawasaki, suggesting a favorable effect.

Successful therapy with secukinumab in a patient with generalized pustular psoriasis carrying homozygous IL36RN p.His32Arg mutation. Gabeff R, Safar R, Leducq S, et al. Int J Dermatol 2019;58:e16-7.
*Case report of favorable effect of secukinumab in **DITRA**.*

Colchicine intoxication in familial Mediterranean fever patients using clarithromycin for the treatment of Helicobacter pylori: a series of six patients. Haj Yahia S, Ben Zvi I, Livneh A. Rheumatol Int 2018;38:141-7.
Paper describing serious colchicine toxicity due to interaction with clarithromycin.

Use of colchicine in pregnancy: a systematic review and meta-analysis.Indraratna PL, Virk S, Gurram D, Day RO. Rheumatology (Oxford) 2018;57:382-7.
*A systematic review confirming the **safety of colchicine in pregnancy**.*

Clinical impact of a targeted next-generation sequencing gene panel for autoinflammation and vasculitis.Omoyinmi E, Standing A, Keylock A, et al. PLoS One 2017;12:e0181874.
A paper describingthe yield of a large multigene autoinflammatory panel in clinical practice.

New workflow for classification of genetic variants' pathogenicity applied to hereditary recurrent fevers by the International Study Group for Systemic Autoinflammatory Diseases (INSAID). Van Gijn ME, Ceccherini I, Shinar Y, et al J Med Genet 2018;55:530-7.
A paper with great practical consequences for the determination of pathogenicity of variants in the autoinflammatory genes.

In silico validation of the Autoinflammatory Disease Damage Index.Ter Haar NM, van Delft ALJ, Annink KV, et al. Ann Rheum Dis 2018;
A paper confirming the feasibility and validity of measuring long term damage in autoinflammatory disease using the ADDI index.