A test was done…

- A blood sample was sent for periodic fever genetic testing, which revealed a D350N mutation in the NLRP3 gene, which confirmed the diagnosis of Muckle-Wells syndrome.

Periodic fever syndromes

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Grand rounds

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Conflicts of interest

- None.

Objectives

- 1. To give an overview of periodic fever and autoinflammatory syndromes.
- 2. To discuss 4 relatively common autoinflammatory syndromes.
- 3. To discuss the inflammasome pathway.
- 4. To explain how the inflammasome is relevant to common diseases seen by all doctors.

Periodic fever syndromes

- Periodic fever syndromes are a subset of autoinflammatory syndromes.
- Autoinflammatory=diseases mediated by over-activity of the innate immune system.
- Autoimmune diseases=diseases mediated by over-activity of the adaptive immune system.

Familial Mediterranean fever

- The most prevalent autoinflammatory syndrome, with world-wide prevalence of 1 in 100,000.
- 1 in 1000 in Turkish people.
- 1 in 250-1000 in Sephardic Jews.
- 1 in 500 in people of Armenian descent.
- Caused by a an autosomal recessive mutation in MEFV gene that codes for protein Pyrin.

Familial Mediterranean fever

- Most patients have their first attacks in childhood; 90% have first episode before age of 20.
- Flares last 1-3 days and are self-limited.
- Symptom-free between flares. Flares can happen weekly to every few years.
- Most common manifestations are fever and peritonitis. Less commonly can have pleuritis, pericarditis, non-erosive oligoarthritis, scrotal pain, aseptic meningitis, erysipelas-like rash.
- If untreated, amyloidosis a frequent complication.
- Molecular pathway: inflammasome.
- Treatment: colchicine. Anti-IL-1 in refractory cases.

TNF receptor-associated periodic fever syndrome (TRAPS).

- Formerly known as familial Hibernian fever.
- Prevalence: 1 per 1,000,000.
- 20% present in adulthood.
- Flares are prolonged, with mean of 2 weeks.
- Most common manifestations are fever, peritonitis, pleuritis, myalgia, arthralgia, periorbital edema and conjunctivitis.
- Cause: autosomal dominant mutation in gene that codes for TNFR1.
- Molecular pathway: cellular stress due to accumulation of misfolded proteins, leading to IL-1β production.
- Treatment: Anti-IL-1. Anti-TNF effective in few cases.

Hyper-IgD syndrome

- Prevalence: unknown. Approximately 300 cases reported worldwide.
- Most patients experience first flare before age of 1.
- Flares last 3-7 days and occur every 4-6 weeks.
- Most common manifestations are fever, high IgD levels, non-erosive large joint arthritis, cervical lymphadenopathy, peritonitis, vomiting and diarrhea, various rashes.
- Cause: autosomal recessive mutation in gene that codes for Mevalonate kinase, which is involved in cholesterol synthesis.
- Molecular pathway: cellular stress leading to IL-1β production.
- Treatment: NSAIDs, Anti-IL-1. Anti-TNF effective in few cases.

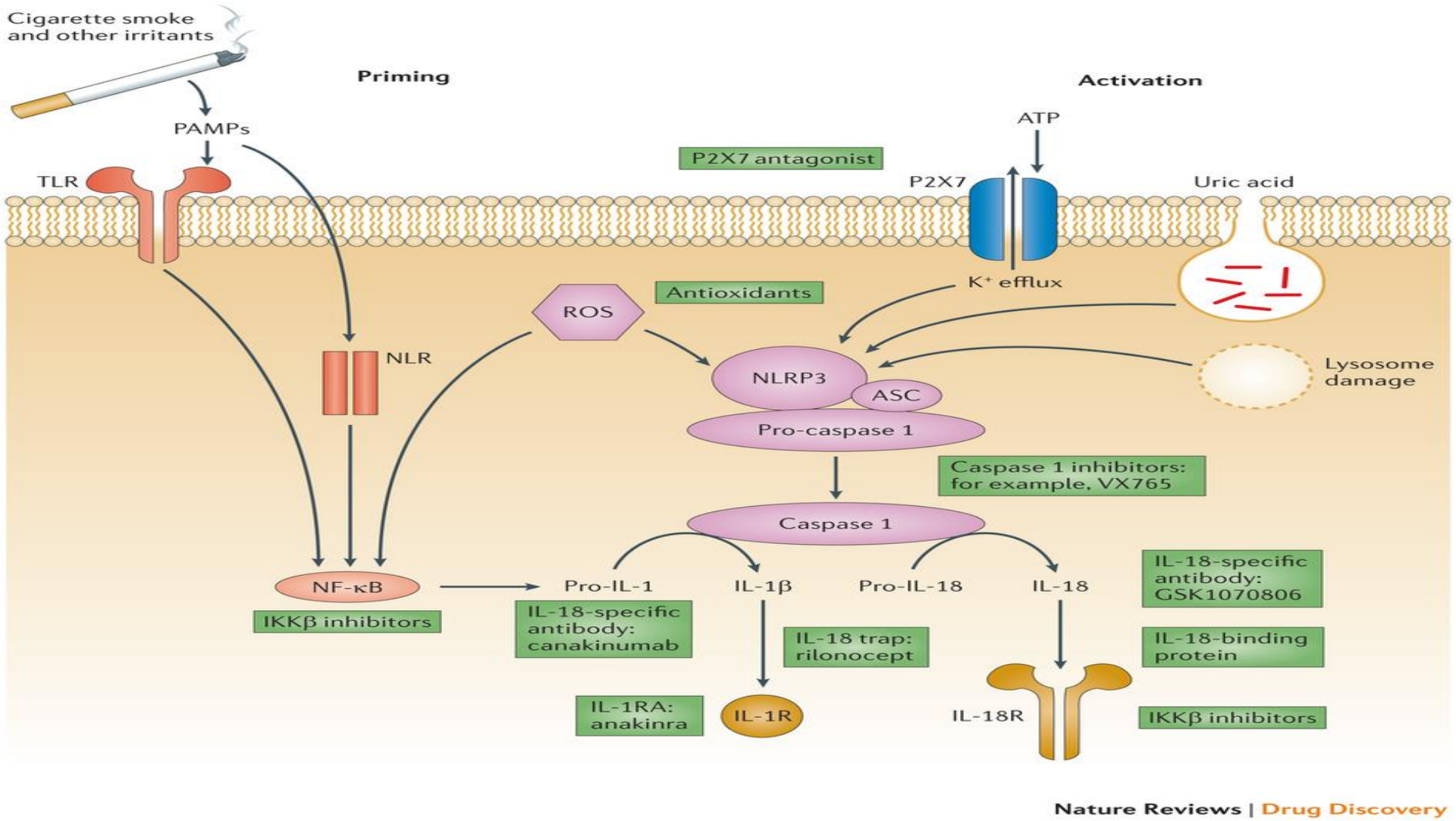
Muckle-Wells Syndrome

- One of three Cryopyrin-associated periodic syndromes (CAPS).
- All three have mutations in NLRP3 (Cryopyrin).
- Other syndromes are familial cold autoinflammatory syndrome (FCAS) and neonatal-onset multisystem inflammatory syndrome (NOMID).
- Combined prevalence of 1-2 per 1,000,000.

CAPS

- Most common manifestations: fever, cold induced skin rashes including urticaria, myalgia, arthralgia, arthritis, ophthalmic inflammation including uveitis, neurosensory hearing loss, CNS inflammation, amyloidosis.
- Molecular pathway: inflammasome.
- Treatment: anti-IL-1, which include Anakinra, Rilonacept and Canakinumab.

The Inflammasome: an important pathway.



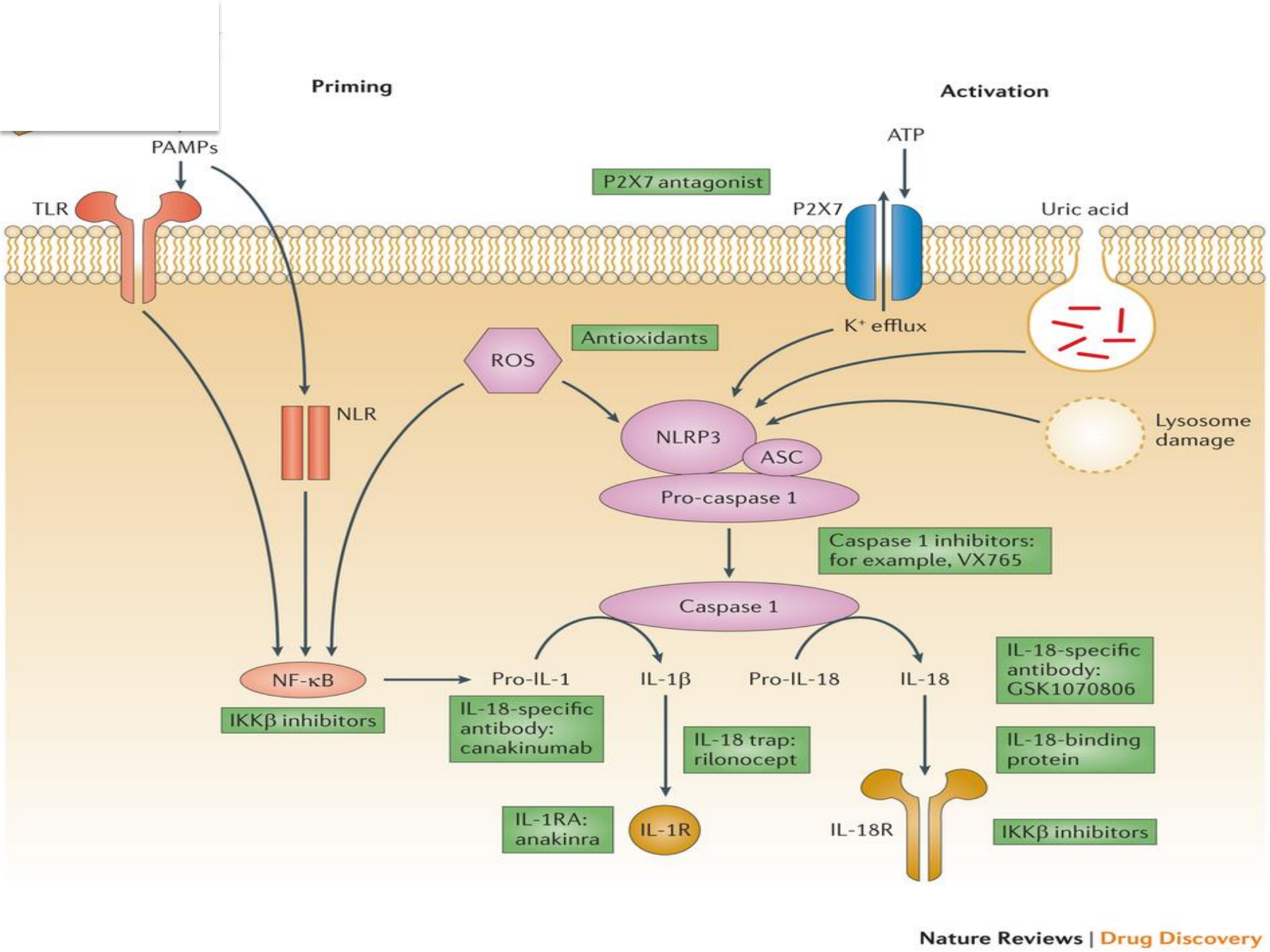
A word about nomenclature

The Human Genome Project

Genome=Gene+Chromosome

- Lipidome.
- Metabolome.
- Connectome.
- Foodome.
- Etc…

HOW DOES A CHROME-DOME GNOME FROM ROME COME HOME?


Priming
Activation
PAMPs
TLR
ATP
P2X7 antagonist
P2X7
Uric acid
K⁺ efflux
Antioxidants
ROS
NLR
NLRP3
ASC
Pro-caspase 1
Lysosome damage
Caspase 1 inhibitors: for example, VX765
Caspase 1
NF-κB
IKKβ inhibitors
Pro-IL-1
IL-1β
Pro-IL-18
IL-18
IL-18-specific antibody: GSK1070806
IL-18-specific antibody: canakinumab
IL-18 trap: rilonocept
IL-18-binding protein
IL-1RA: anakinra
IL-1R
IL-18R
IKKβ inhibitors

Diseases in which the Inflammasome is