VNIVERSITAT DE VALÈNCIA Facultat de Farmàcia

MASTER DEL DEPARTAMENTO DE FAMACOLOGIA:
INVESTIGACIÓN Y USO RACIONAL DEL MEDICAMENTO

FARMACOLOGIA DE LA INFLAMACIÓN

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DEFINITION OF INFLAMMATION

“***Inflammation*** ***is the term used to describe the response of tissue to injury.***

- *Its purpose is to destroy (or at the very least limit) the injurious stimulus, and to begin the process of healing.*
- *Inflammation is a function of the connective tissues, and the immune system (which share a number of cell types in common).*
- *The cells of the CT and the immune response all have specific roles to play in the process: consequently there’s a predictable sequence of events.*

ACUTE versus CHRONIC INFLAMMATION

“An inflammatory response to some insult begins ***acutely,*** that is, within seconds to a couple of hours. It may resolve itself in a fairly short time.

The boundary between the two in terms of time isn’t hard and fast: but as a general, if an inflammation hasn’t resolved itself in a day or two it can be considered ***chronic.***

Chronic inflammations can last a very long time—years, perhaps—but even they may in time resolve, with restoration and/or repair taking place.

WHAT CAUSES INFLAMMATION ?

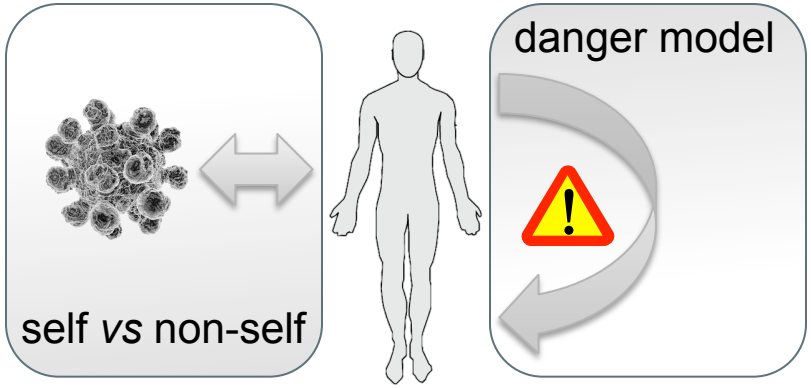
“*Dead cells and cellular debris are powerful inflammatory stimuli:*

- Anything that injures cells and tissues to the point of necrosis causes an inflammatory response.
- It can be the result of infection, of trauma, of ischemia, chemical injury, radiation, etc.
- Regardless of the initial source of injury, the results are the same.
- Occurs in response to **necrosis** (but not apoptosis).

sensing ...

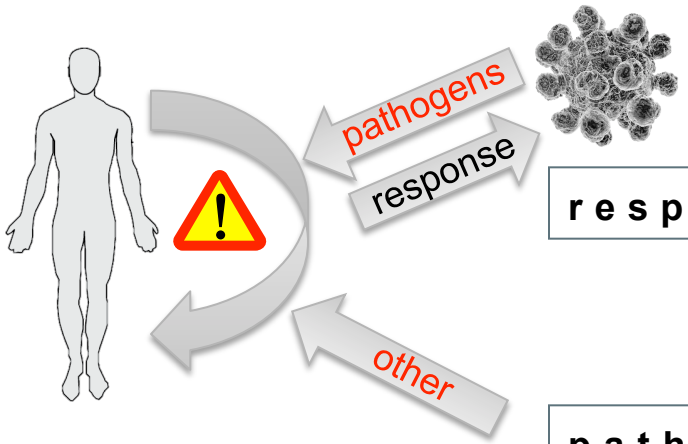
... non-self *or* danger ?

> *two competing hypothesis for immune system activation*



sensing ...

... non-self *or* danger ?



response to INFECTIONS

pathogen-*free* DISEASES

gout, **rheumatoid arthritis**, atherosclerosis, ischemia reperfusion, **type 2 diabetes**, **metabolic syndrome**, obesity, GVHD, alzheimer's, epilepsy, stroke, **COPD**

definition of danger signals

ENDOGENOUS MOLECULES

ARE NOT 'IN PLACE'

ARE MODIFIED

A T P
extracellular

HOMEOSTASIS
i m b a l a n c e

osmolarity
a c i d i t y
glycaemia
h y p o x i a

uric acid
cholesterol
I A P P
β-amyloid

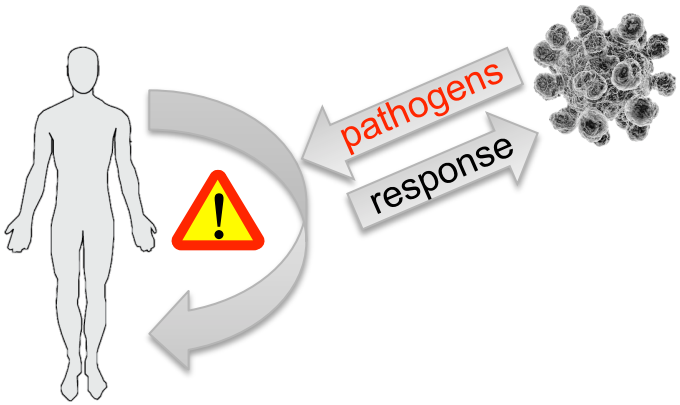
'pathogenic'
C R Y S T A L S

wound

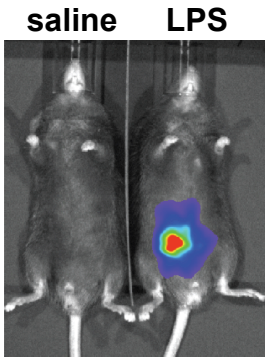
d e g r a d a t i o n
e x t r a c e l l u l a r
M A T R I X

breakdown hyaluronic acid

infection & danger signals



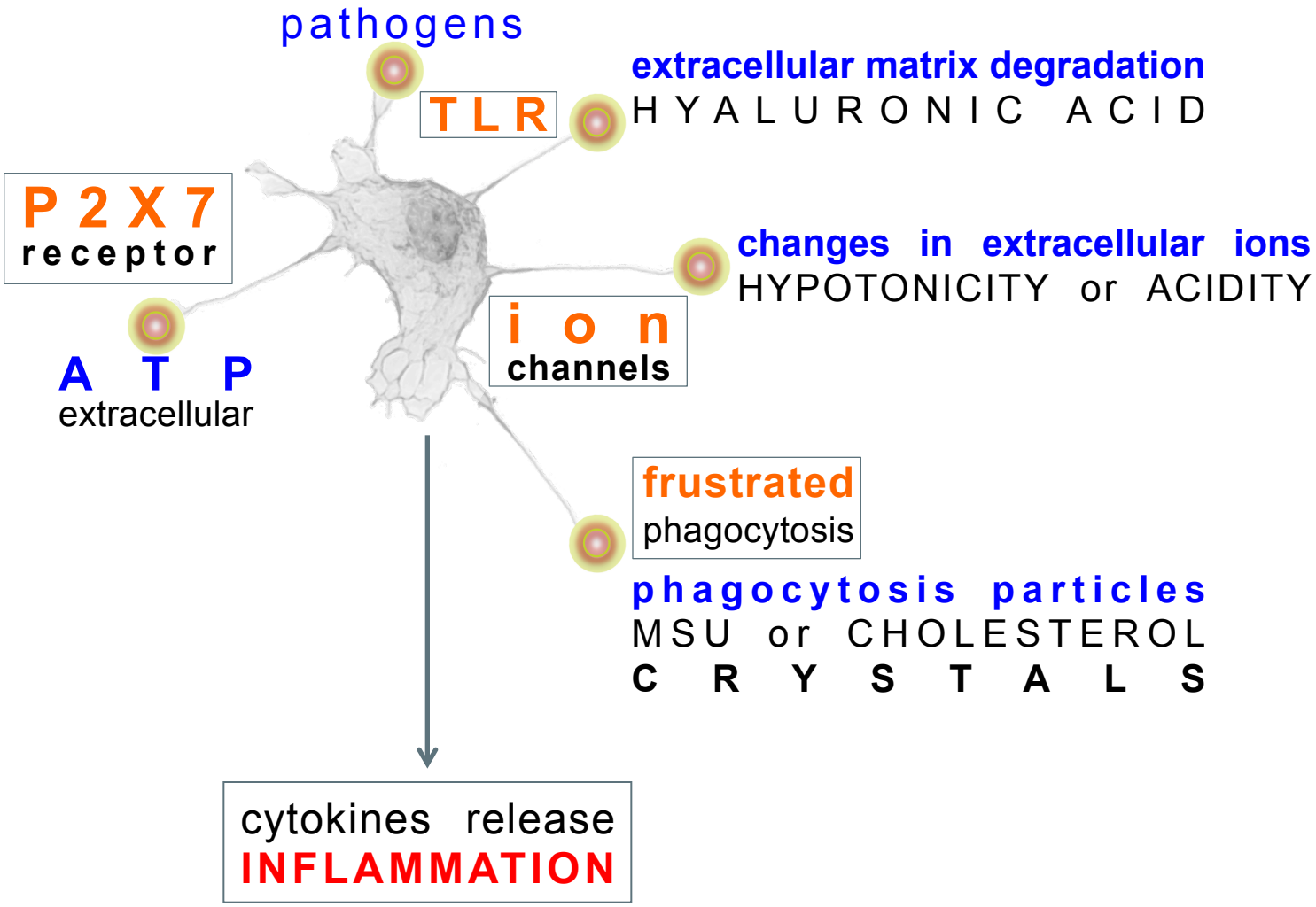
ATP released in response to PATHOGEN SIGNALS



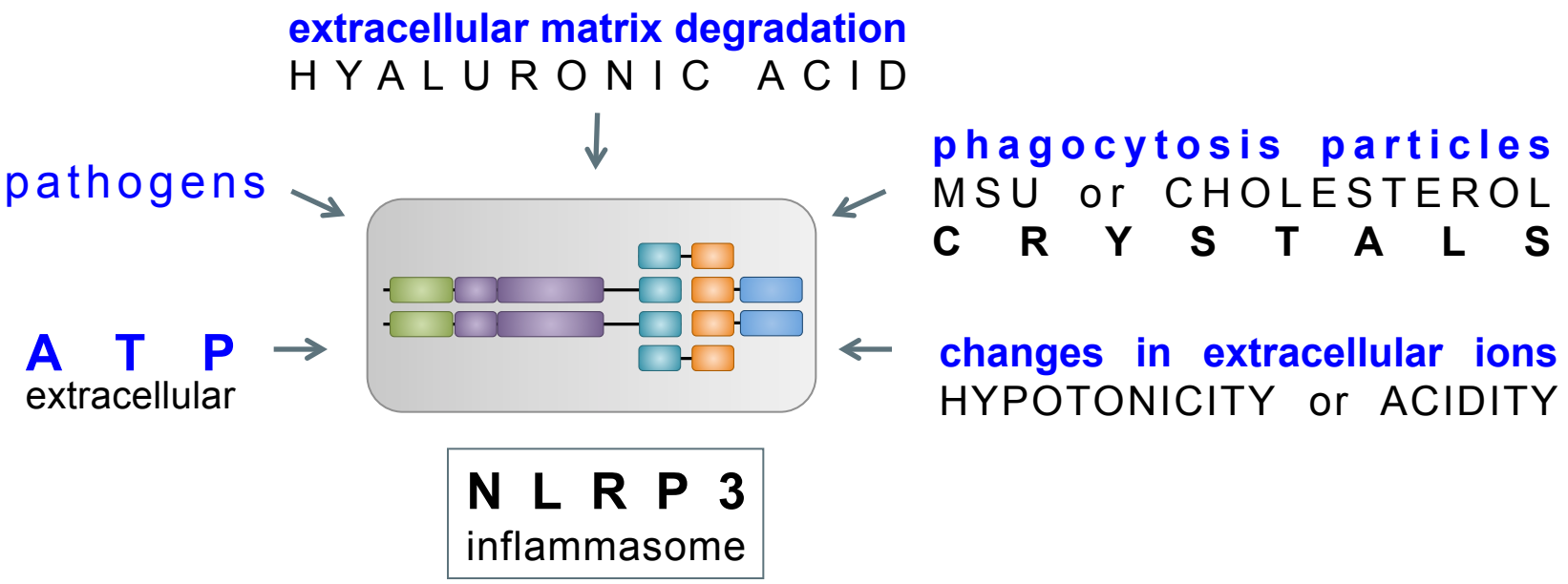
Barberà-Cremades, et al. 2012, FASEB J.

macrophages

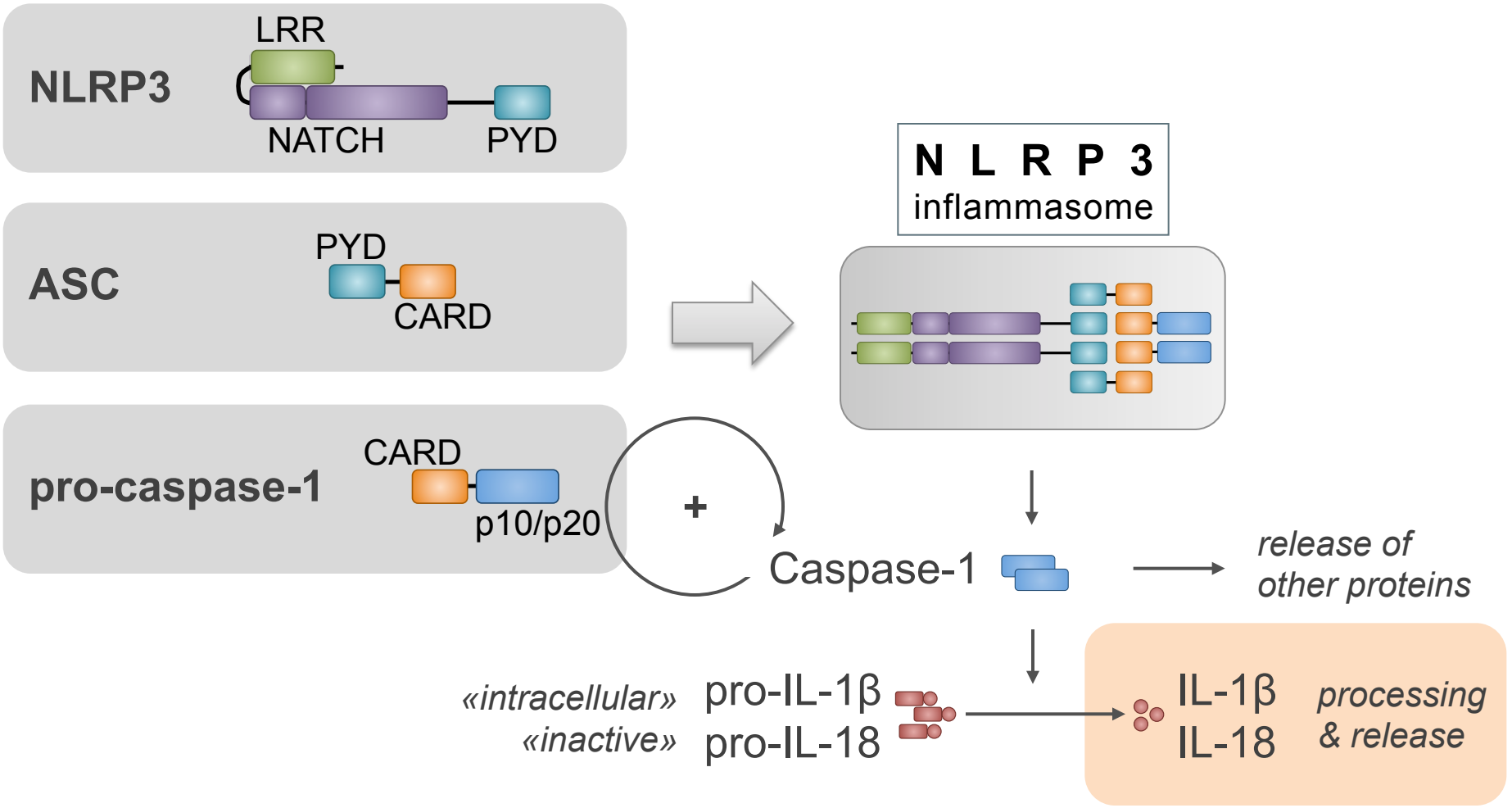
recognize danger



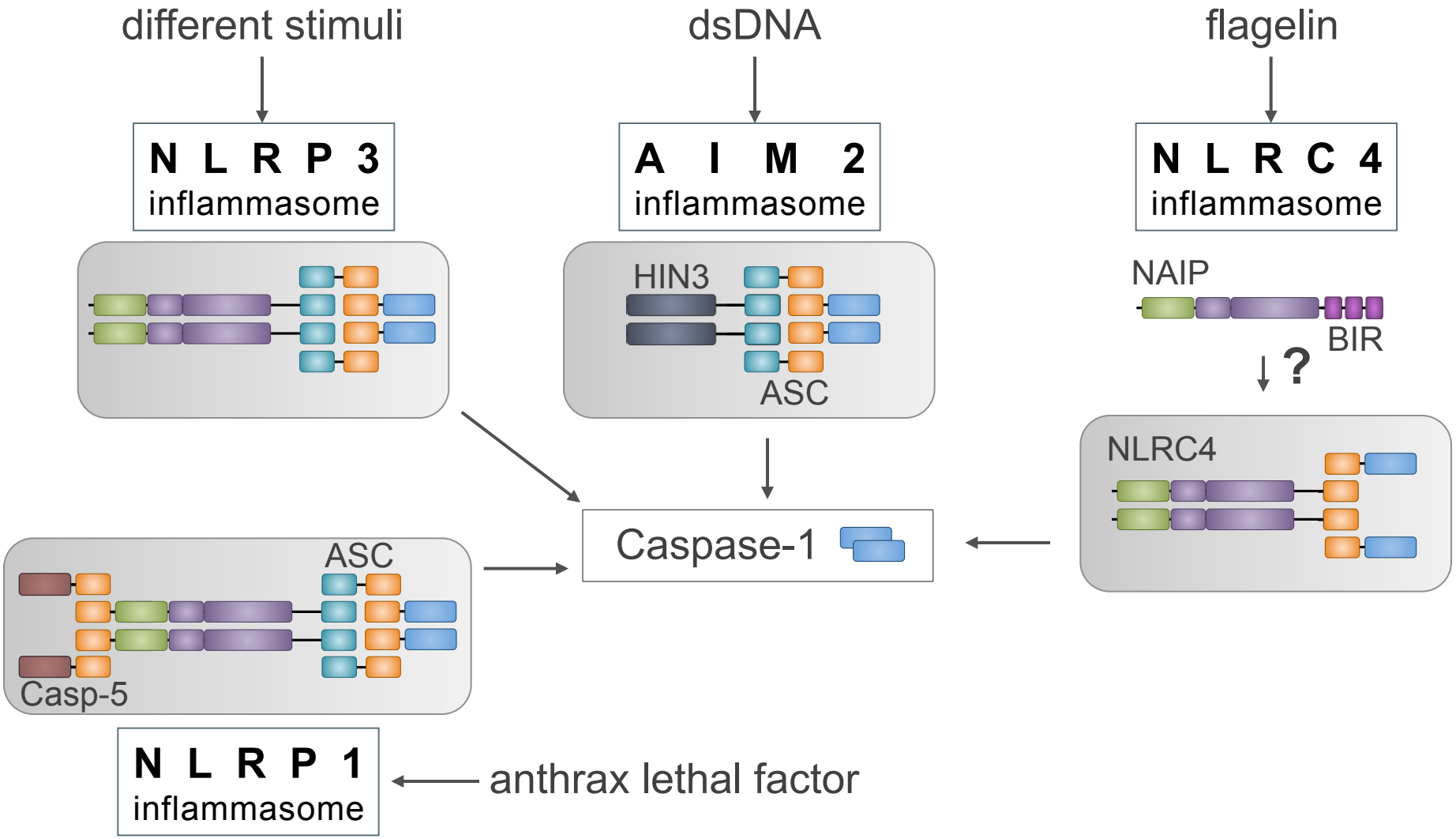
the NLRP3 inflammasome



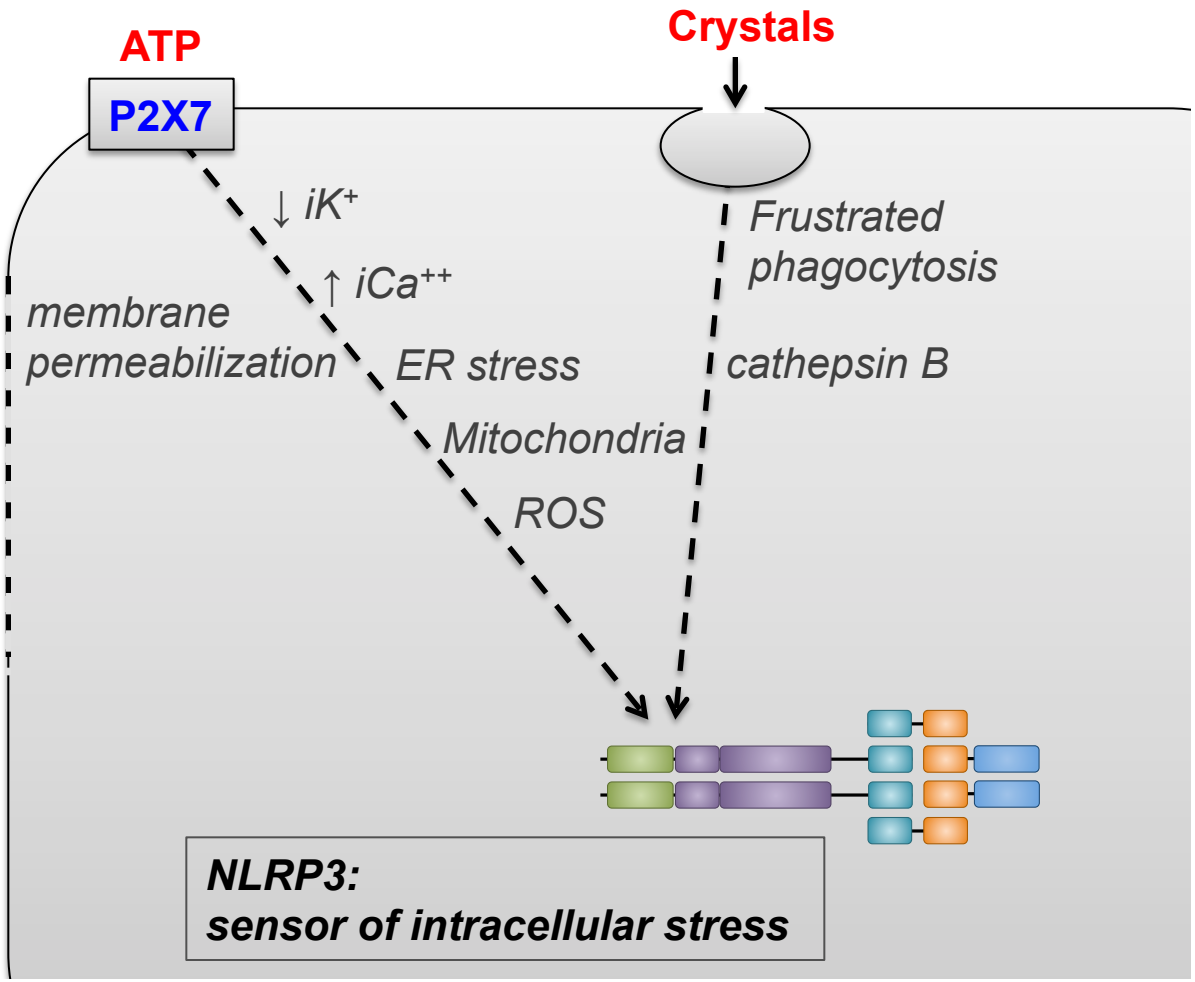
the NLRP3 inflammasome



the different inflammasome scaffolds

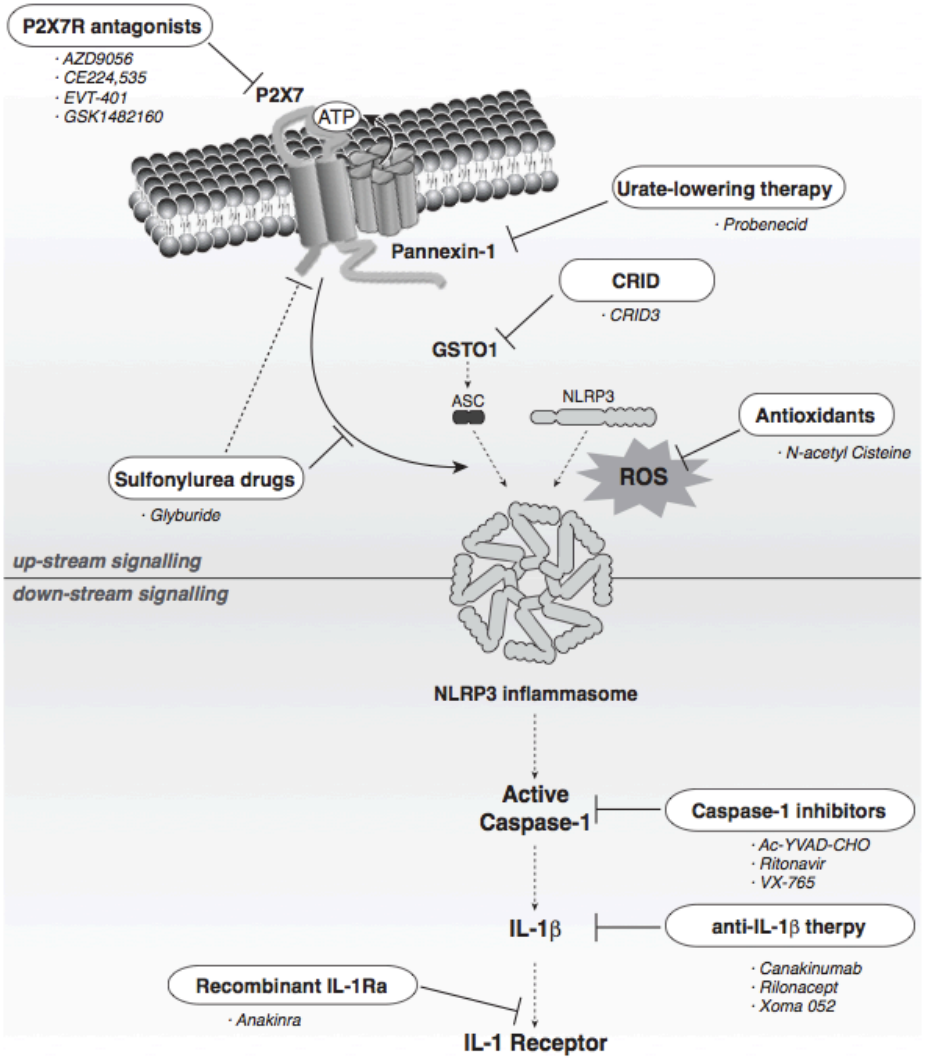


activating the NLRP3 inflammasome



PHARMACOLOGICAL

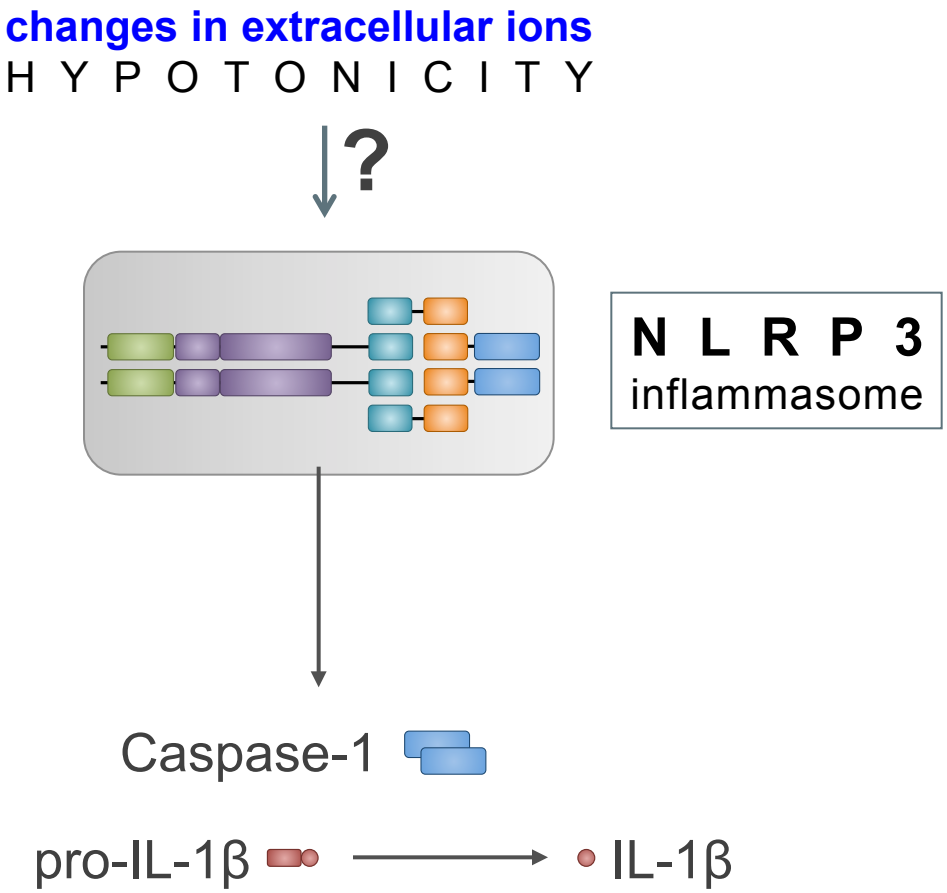
TARGETS FOR INFLAMMATION



SCIENTIFIC CHALLENGE

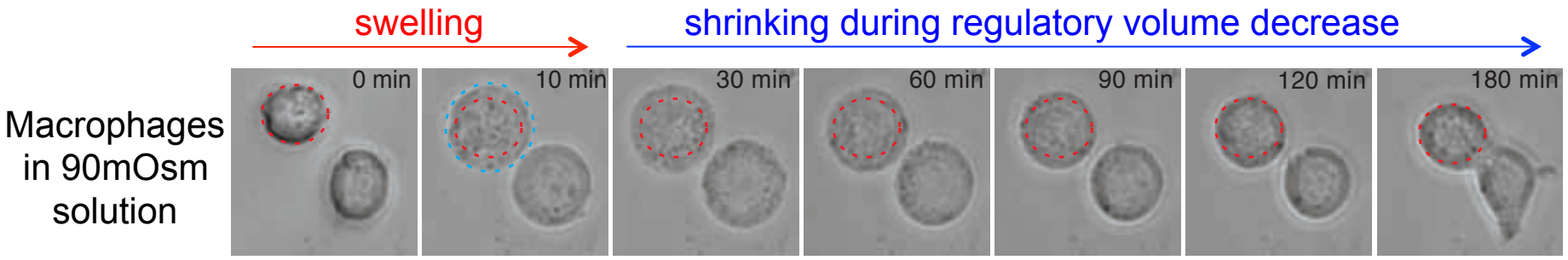
discovering pharmacological targets

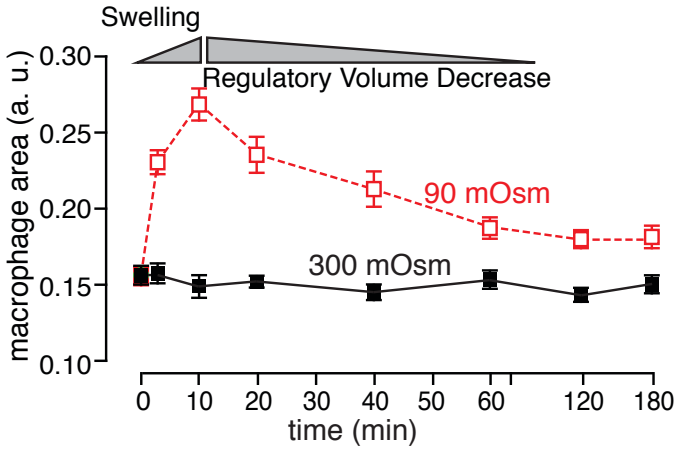
“how NLRP3 sense changes in hypotonicity ?



detecting osmolarity by macrophages

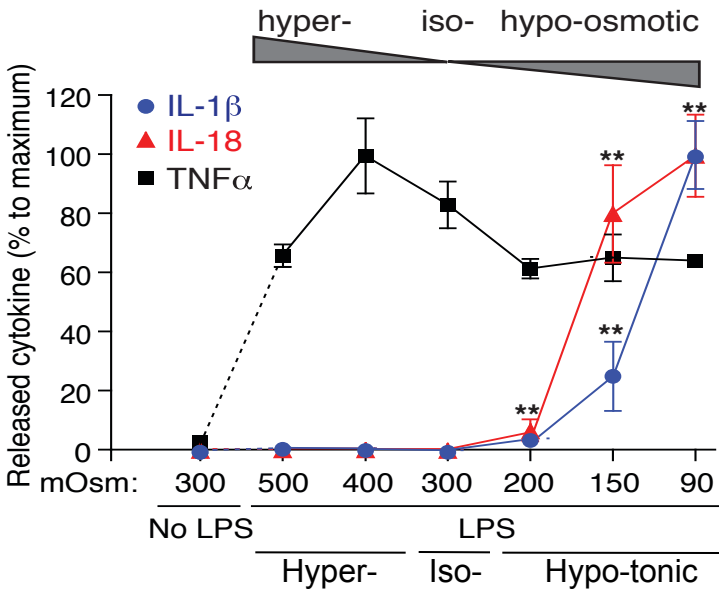
- Extracellular osmolarity is a homeostatic parameter
- However: changes occur during physio- or patho-logical conditions (arthritis)
- Mechanism highly regulated and conserved

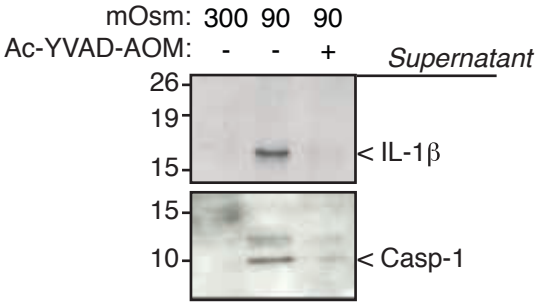


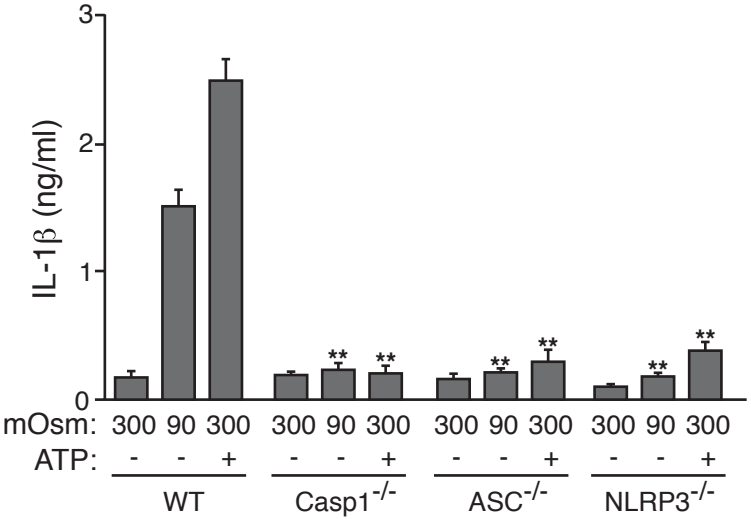


hypotonicity induces

NLRP3-dependent release of IL-1β

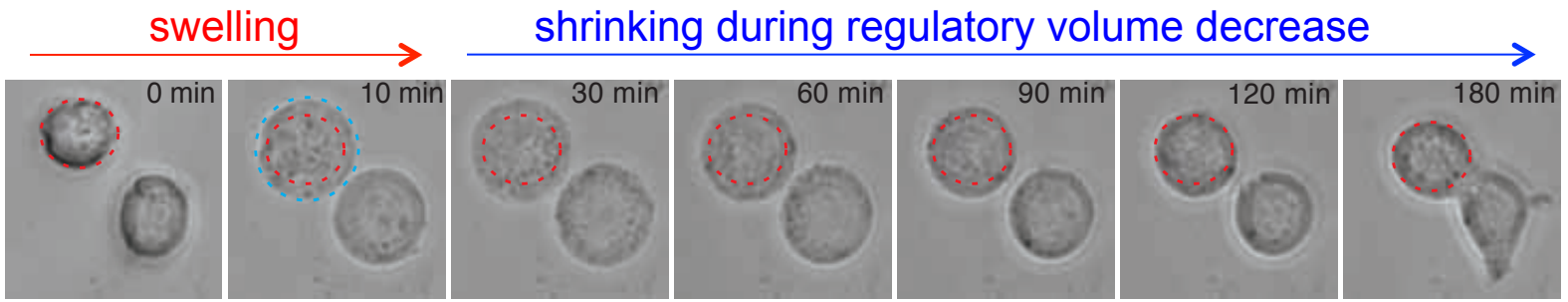






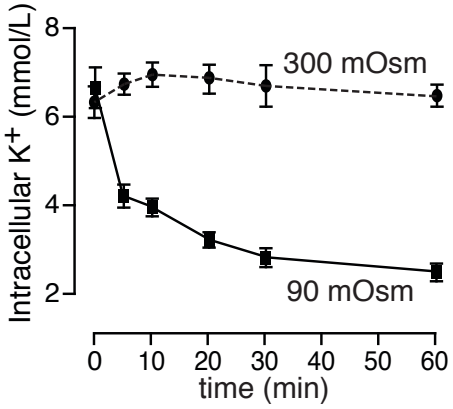
Compan et al., 2012, Immunity

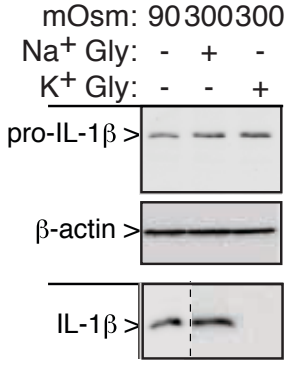
hypotonicity induces decrease of intracellular K^+

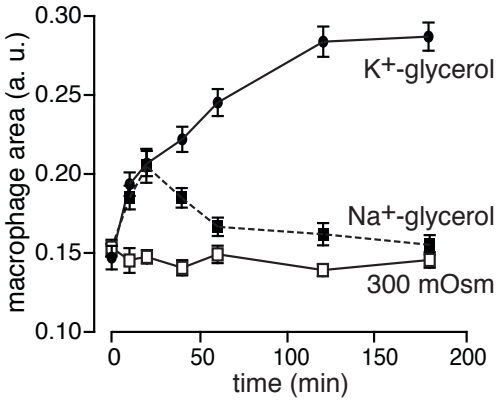


Cl^- Channels

K^+ Channels



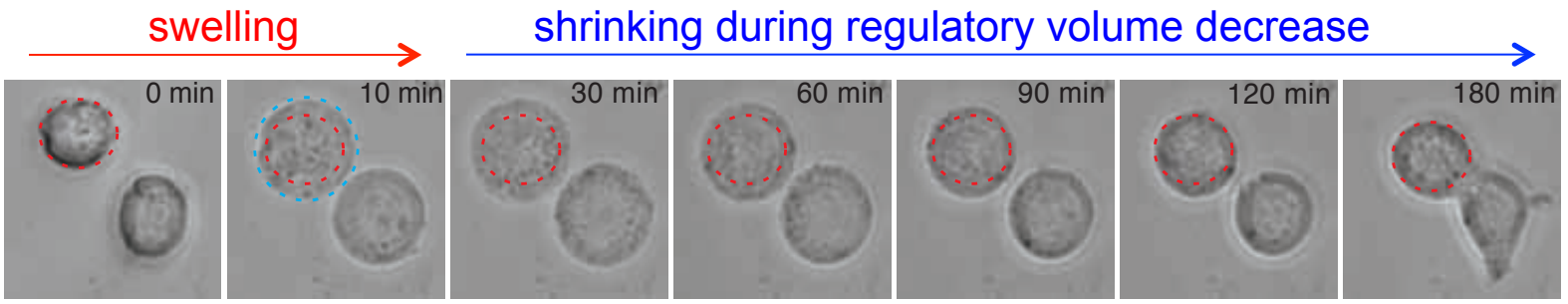




Compan et al., 2012, Immunity

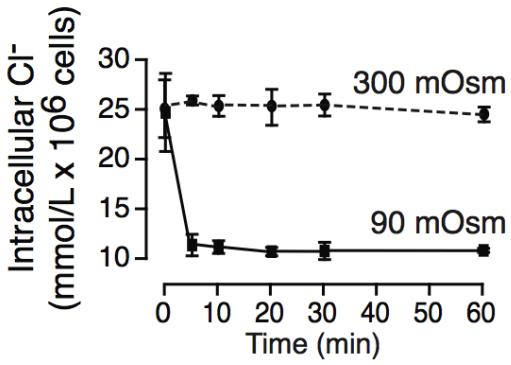
hypotonicity induces

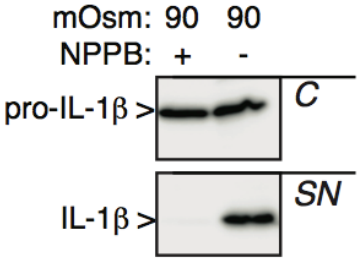
decrease of intracellular Cl^-

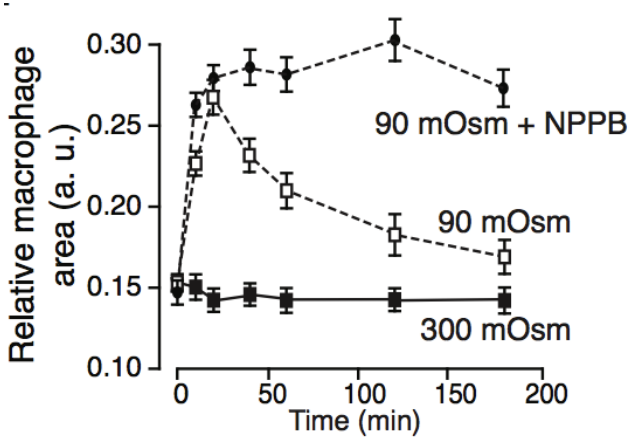


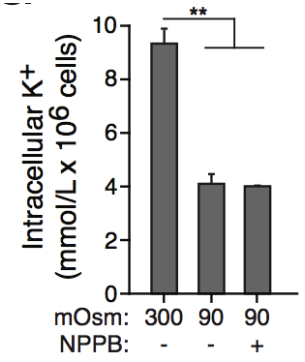
Cl^- Channels

K^+ Channels



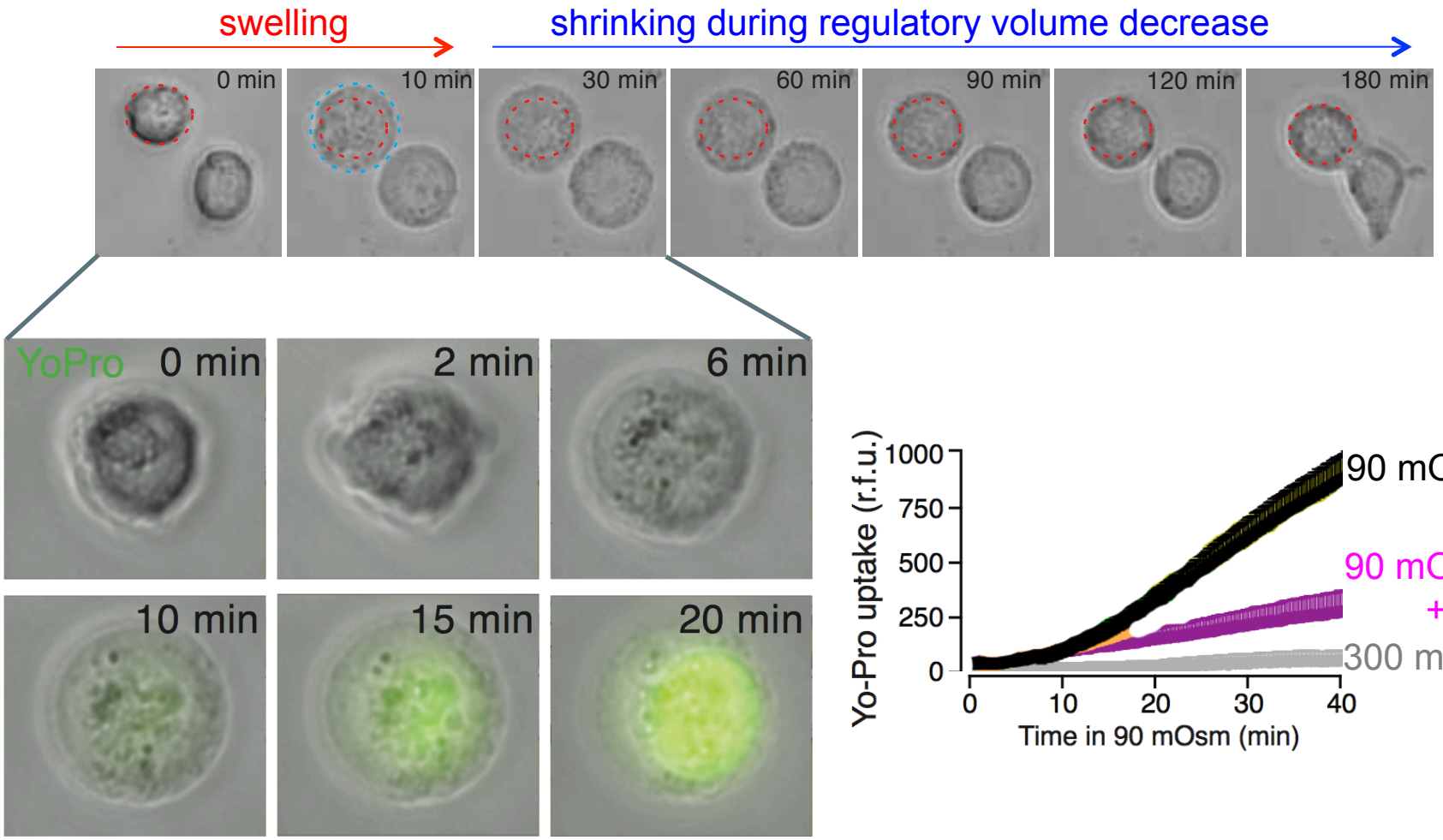






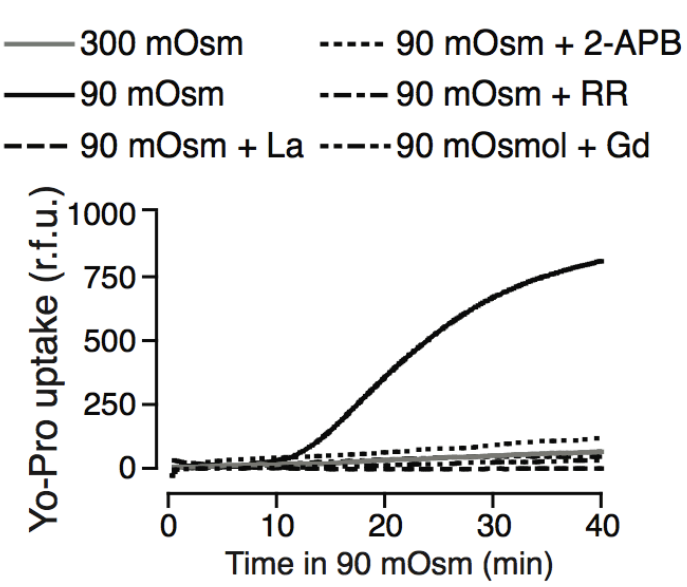
Compan et al., 2012, Immunity

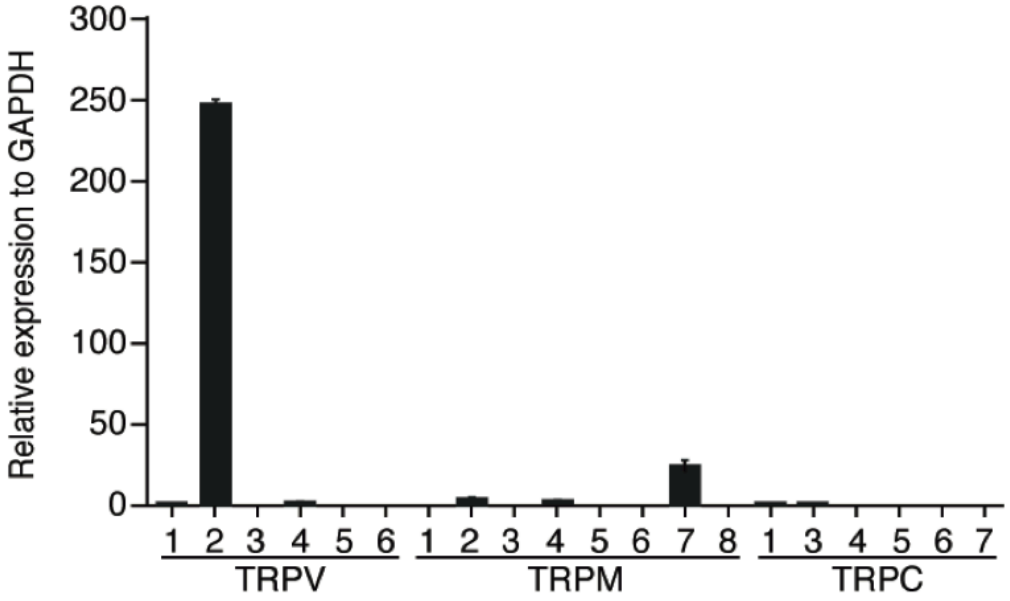
hypotonicity permeabilize cell membrane during RVD

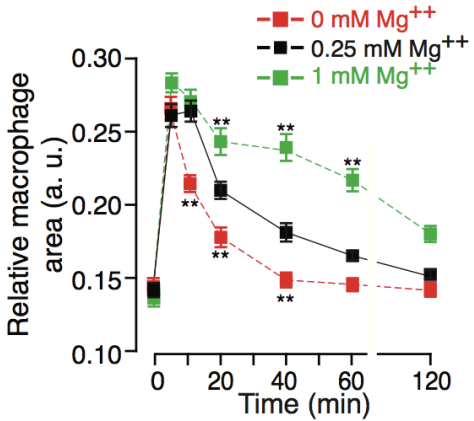


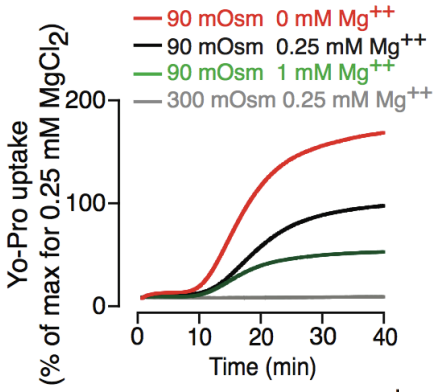
Compan et al., 2012, Immunity

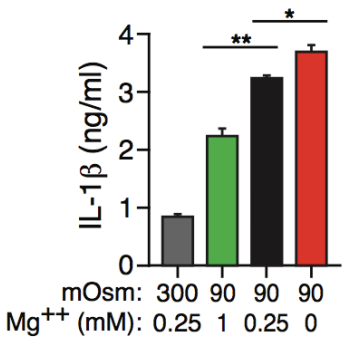
cell permeabilization depends on TRP channels





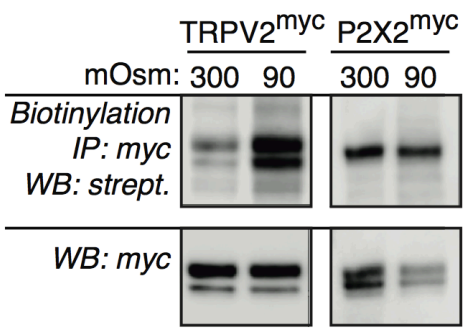


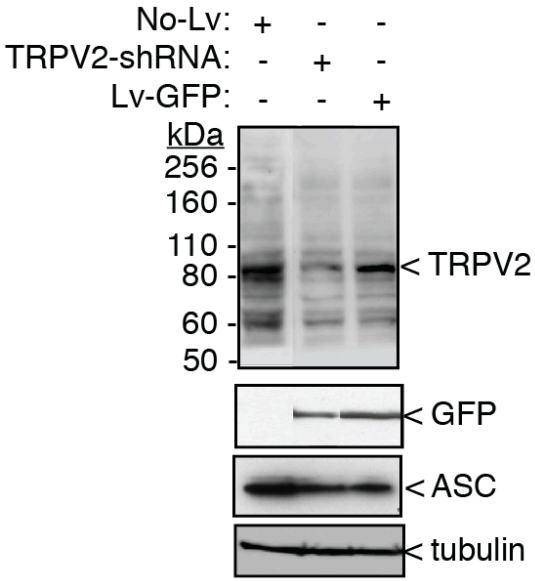


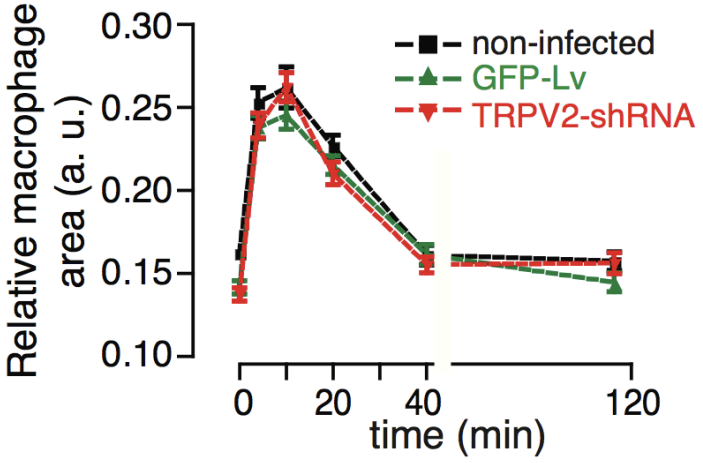


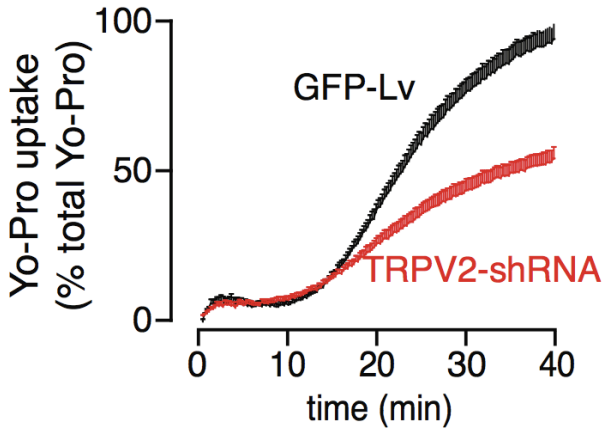
Compan et al., 2012, Immunity

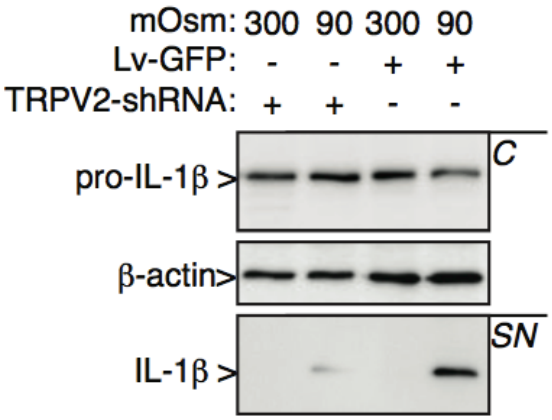
TRPV2 permeabilize plasma membrane during RVD





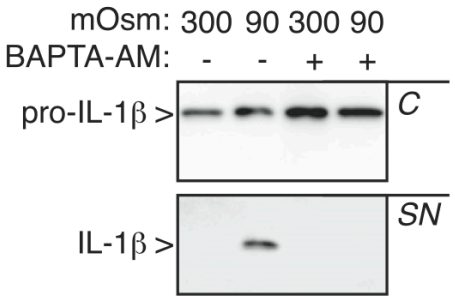


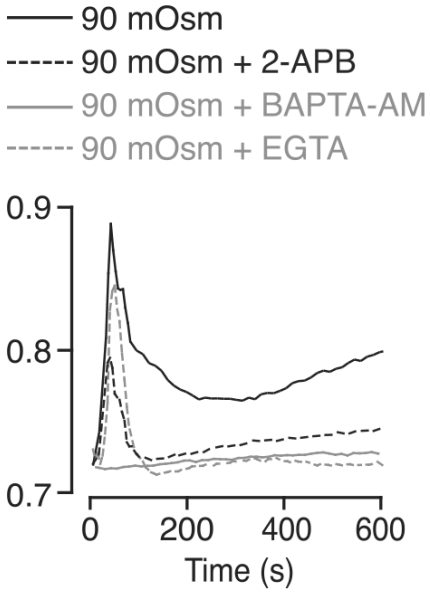


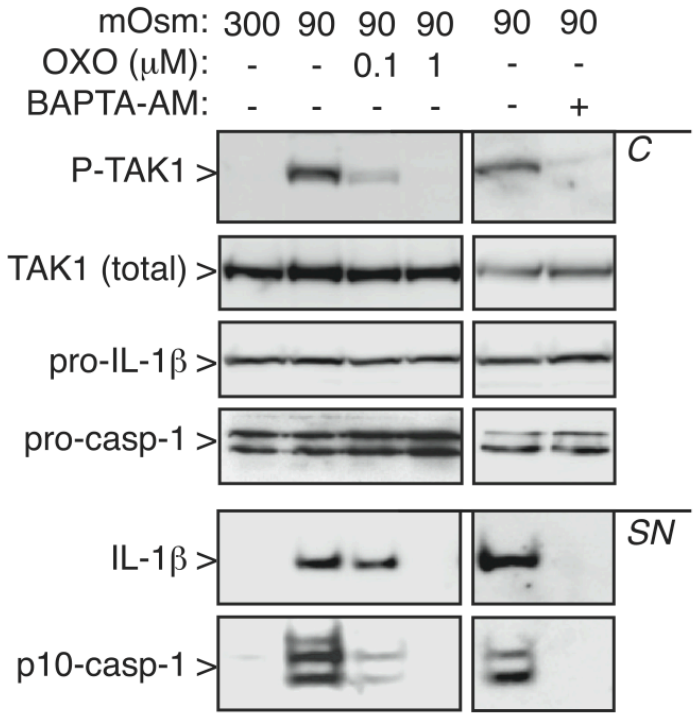


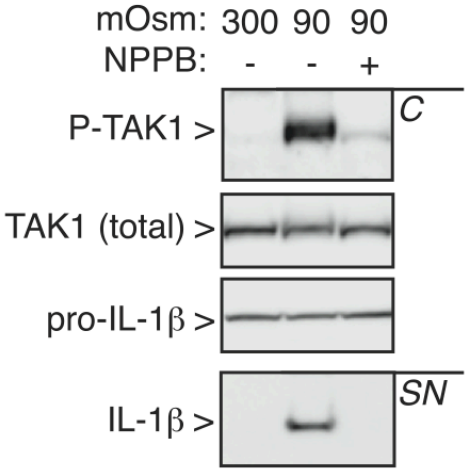
Compan et al., 2012, Immunity

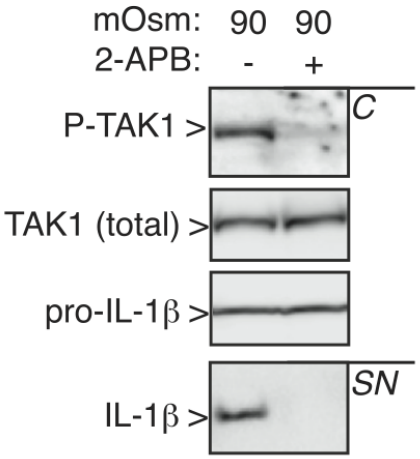
TRP-channel Ca^{++} activates the NLRP3 via TAK1 phosphorylation







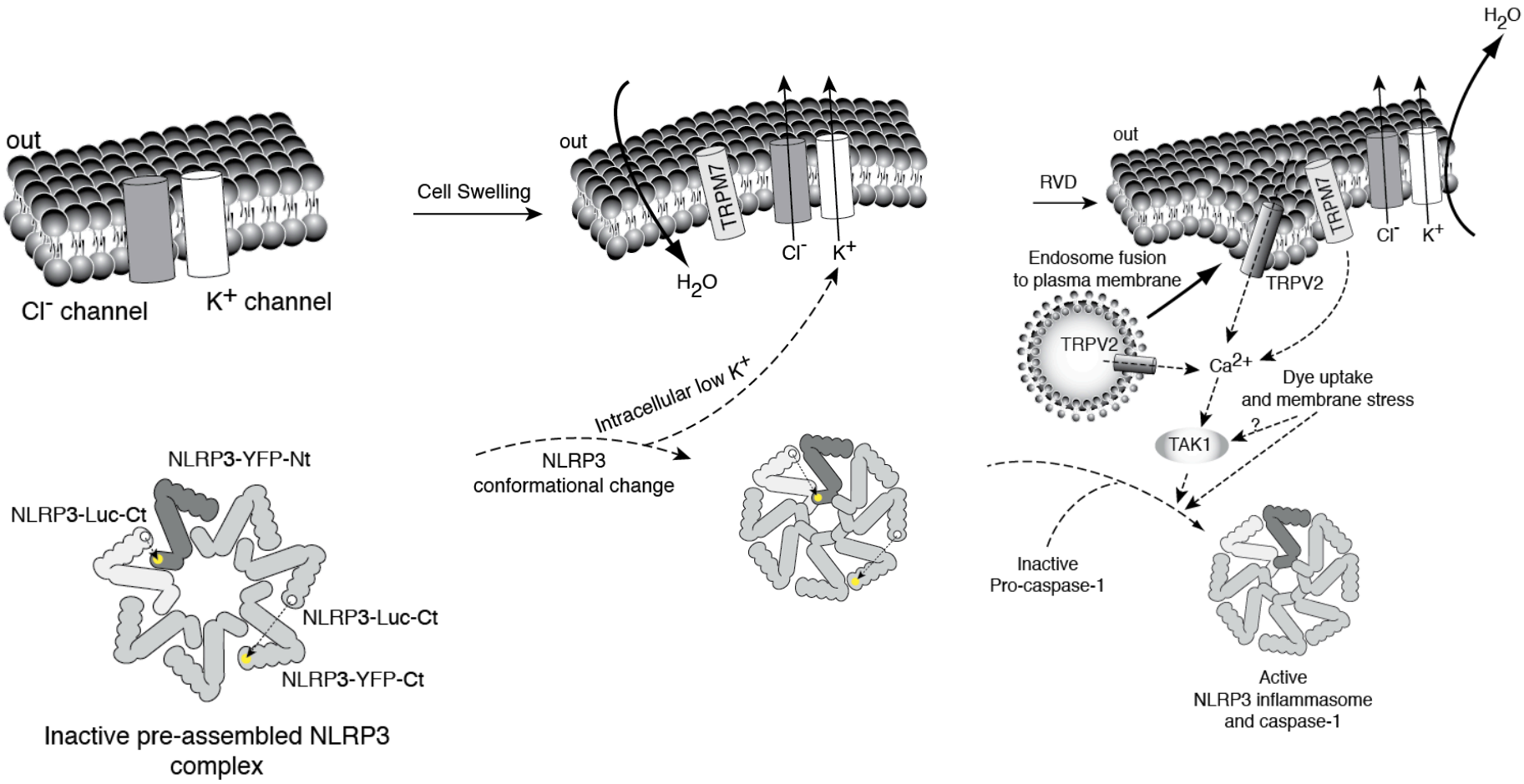




Compan et al., 2012, Immunity

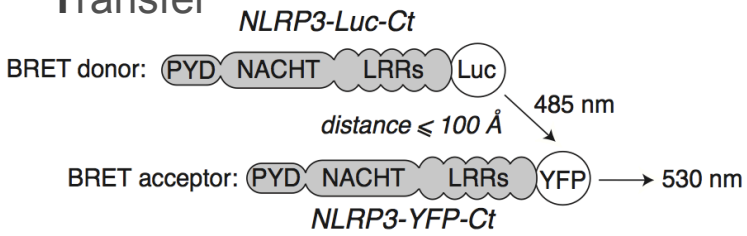
model for NLRP3 activation

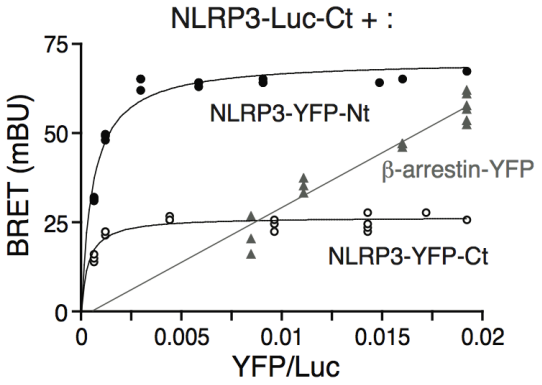
in response to hypotonicity

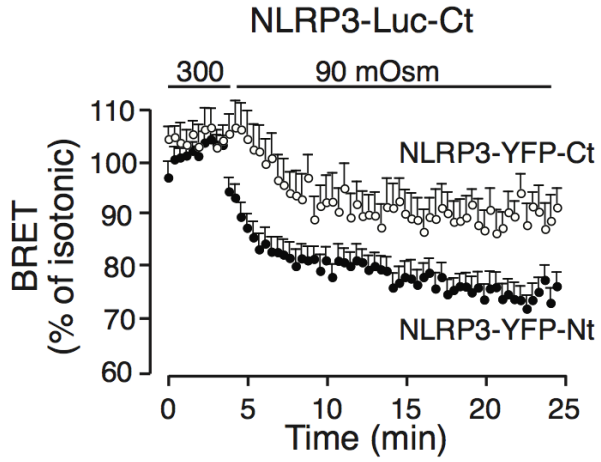


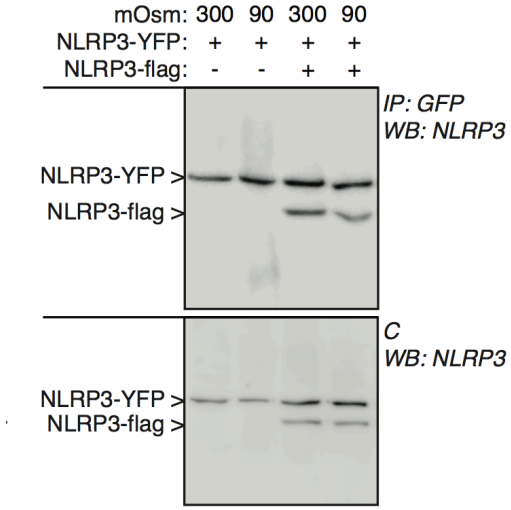
study NLRP3 inflammasome by BRET

Bioluminescence
Resonance
Energy
Transfer





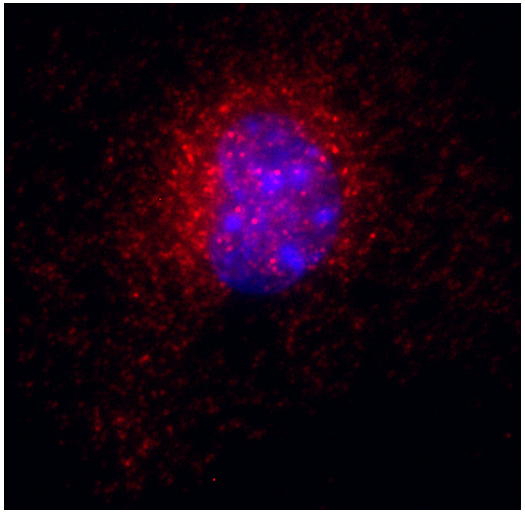




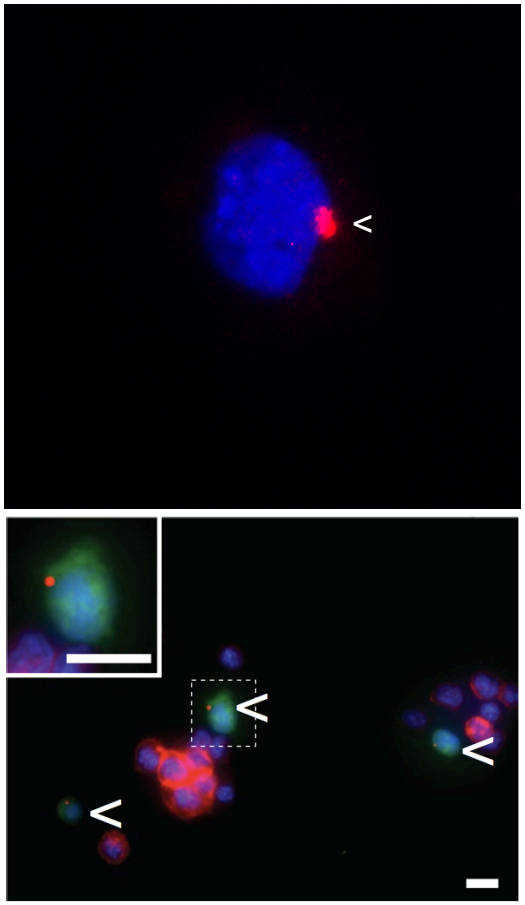
Compan et al., 2012, Immunity

hypotonicity induces formation of ASC focus

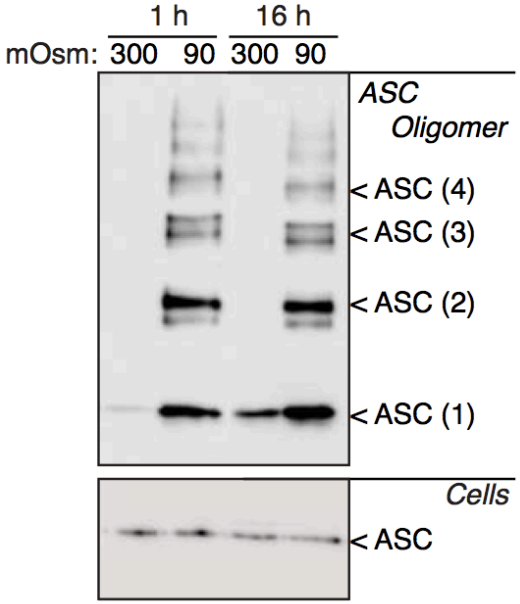
ASC - isotonic



ASC - hypotonic

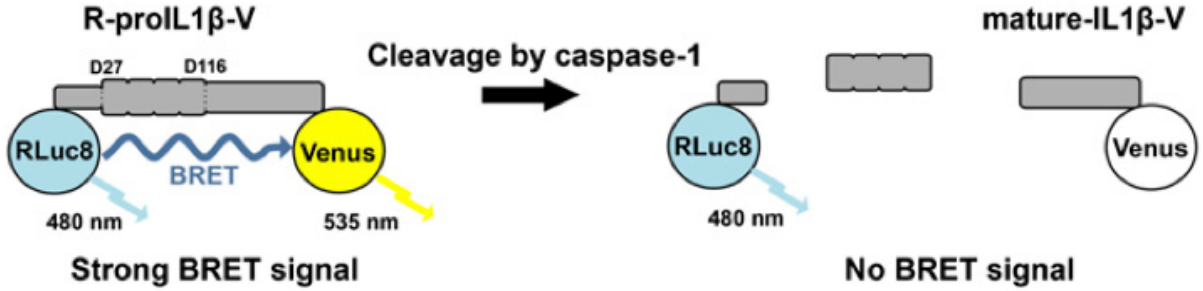


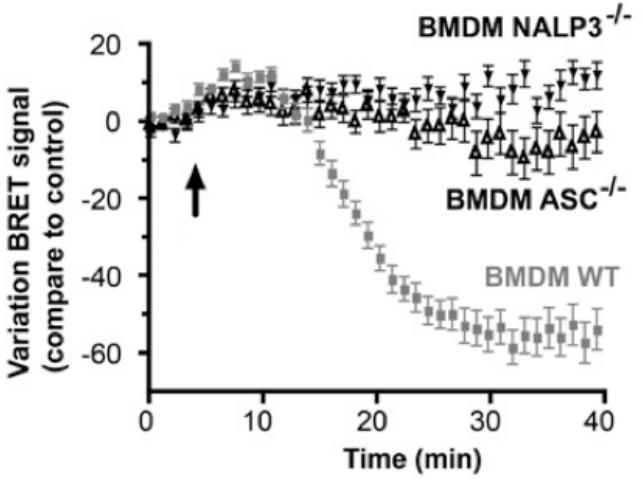
FLICA: active casp-1

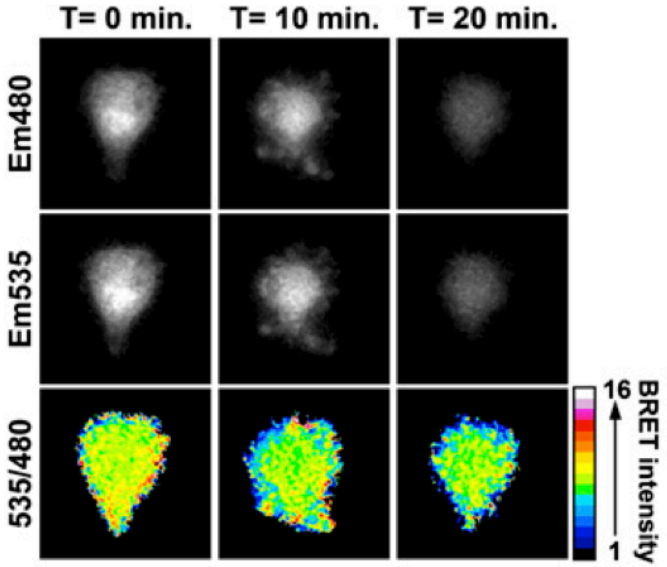


Compan et al., unpublished

ASC focus is NOT
the main IL-1β processing site

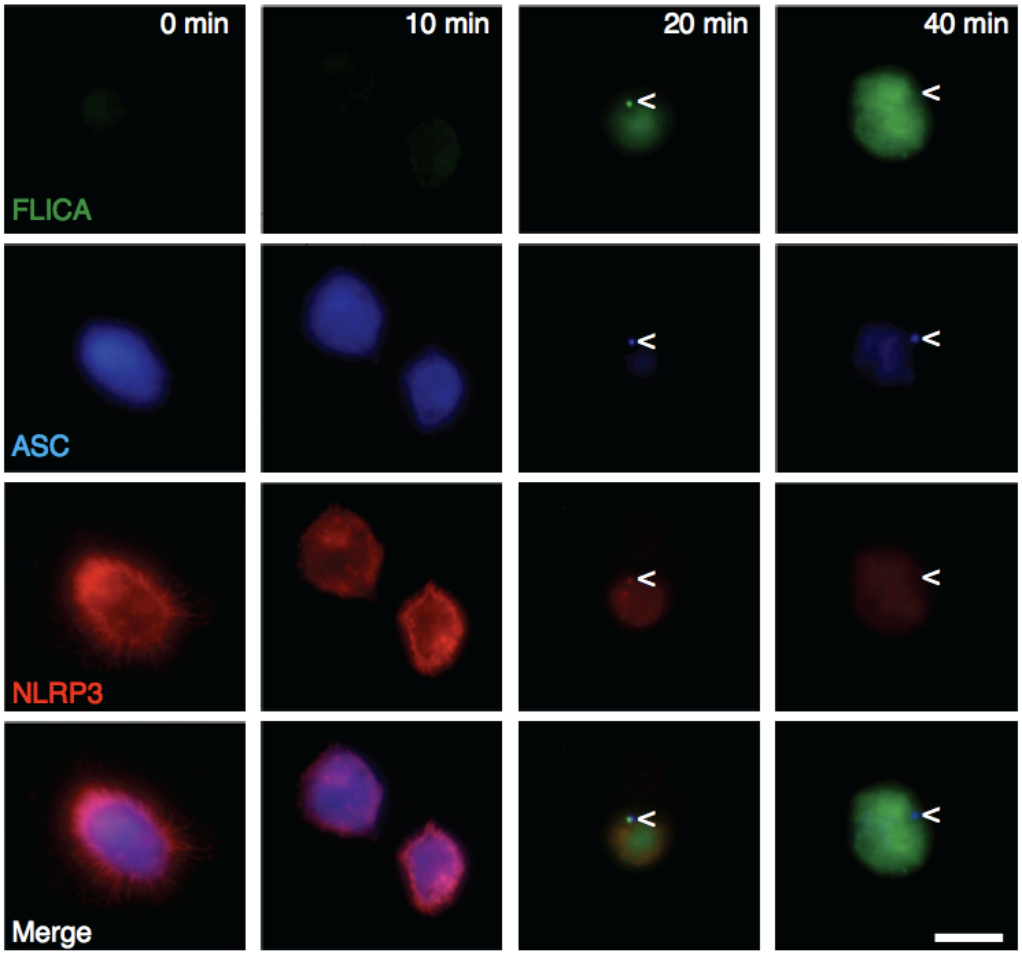


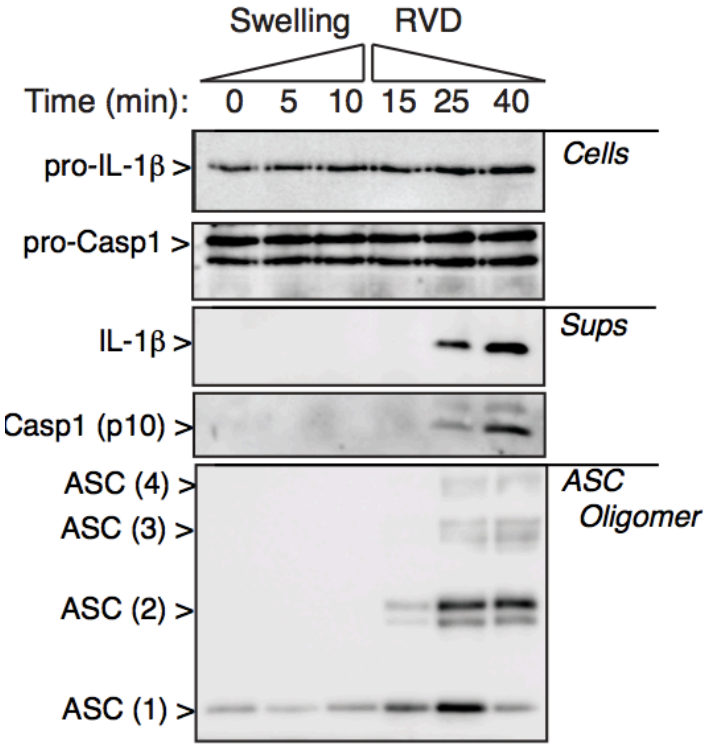




Compan et al., 2012, J. Immunol

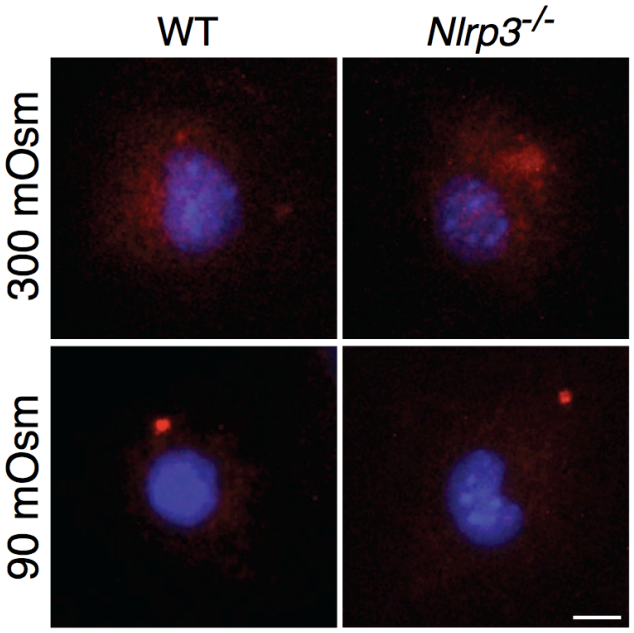
ASC focus is the initial platform to activate caspase-1

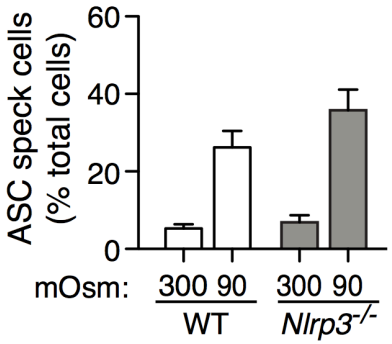


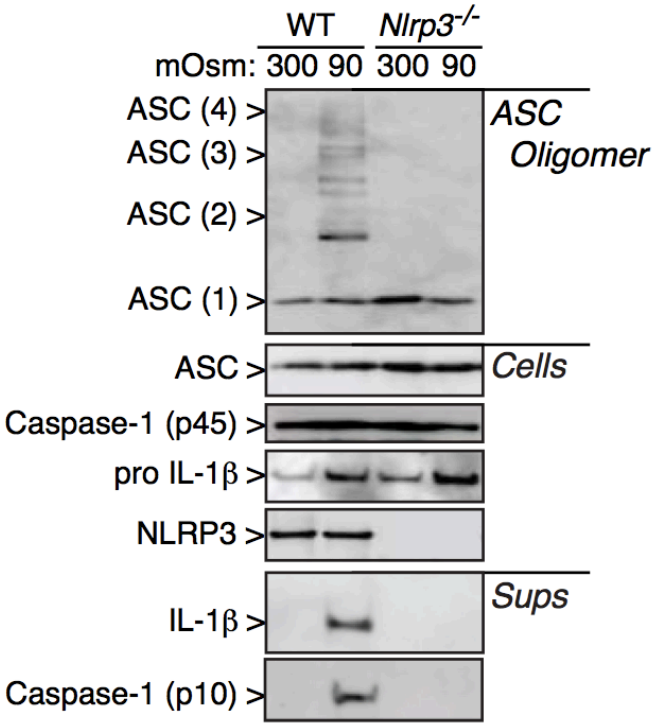


Compan et al., unpublished

ASC focus is independent on NLRP3







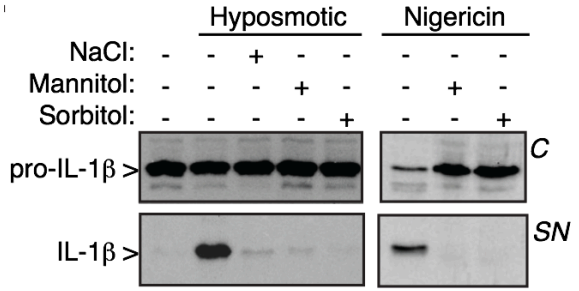
ASC oligomers detected by cross-linking is not the same structure than the ASC speck

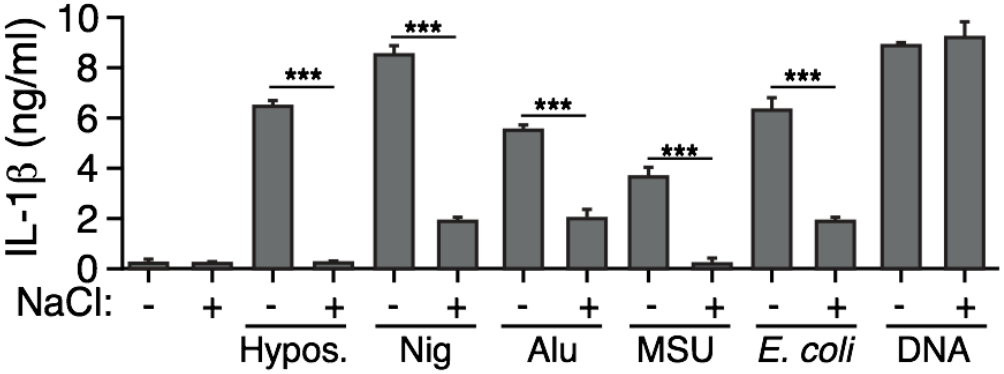
Compan et al., unpublished

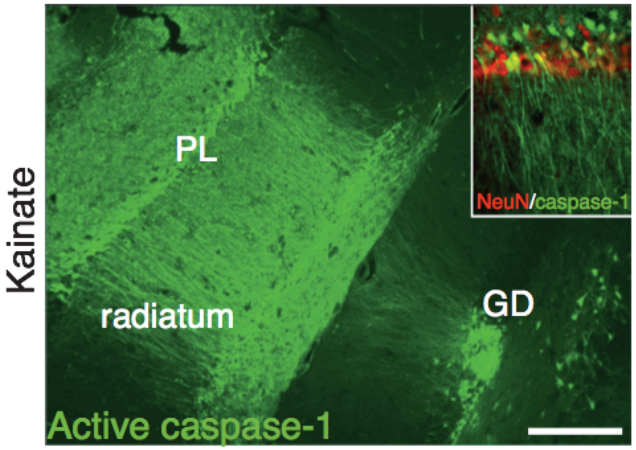
in vivo significance

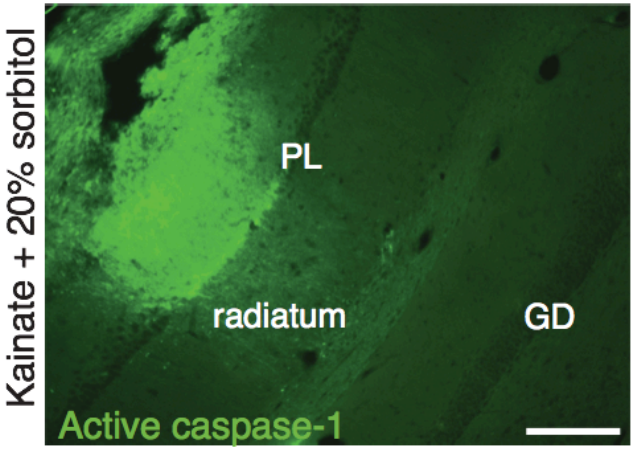
of cell swelling & inflammation

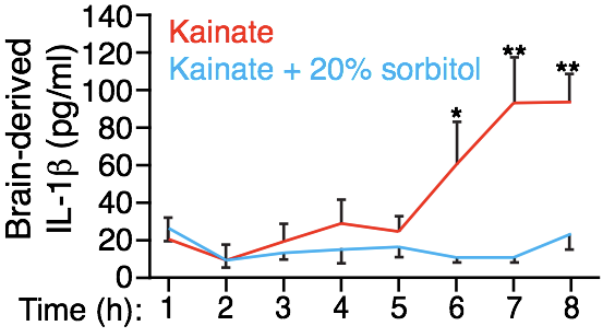
HYPERTONICITY INHIBITS CASPASE-1 ACTIVATION











Compan et al., 2012, Immunity

FINAL REMARKS FOR THE SCIENTIFIC CHALLENGE

“discovering pharmacological targets

- TRP channels
- « Easy » to target as they are plasma membrane receptors
- TRPV2 and TRPM7 are under Biothech drug discovery screening programmes
- Hypotonic solutions made with novel solvents: mannitol / sorbitol