

Modulation of inflammatory response by cell specific storage endosomes

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thématiques

Inserm

Institut national
de la santé et de la recherche médicale

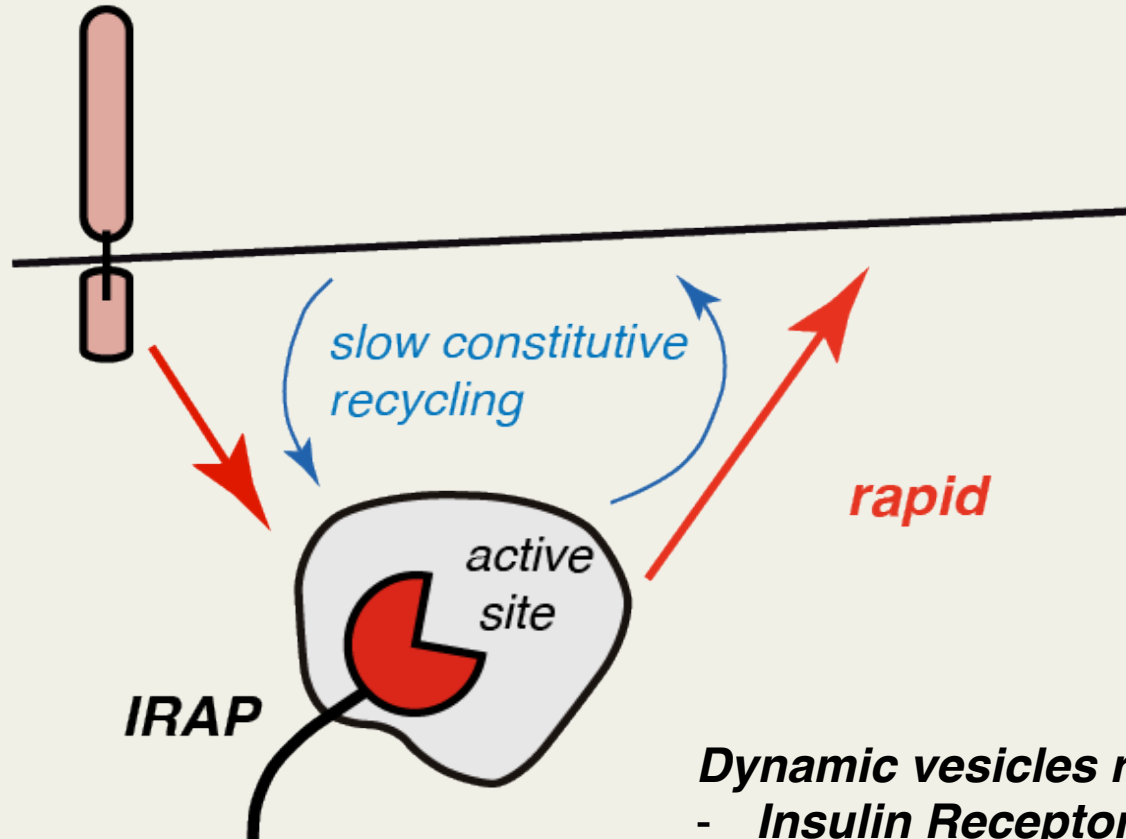


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Storage endosomes are described by IRAP (Insulin Responsive AminoPeptidase)

Cell-specific stimulation



IRAP

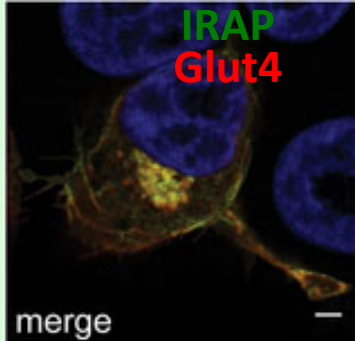
*cytosolic tail
with trafficking motifs*

- Dynamic vesicles regulated by:**
- **Insulin Receptor in adipocytes**
 - **Fc ϵ RI in Mast cells**
 - **Fc γ R in DCs**

Which is the cargo of storage endosomes?

Adipocytes

Glucose transporter GLUT4



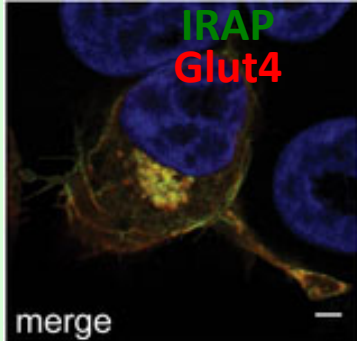
*Regulation of
glucose
level in blood*

Keller et al., JBC 1995

Werno et al, Scientific Reports 2015

Which is the cargo of storage endosomes?

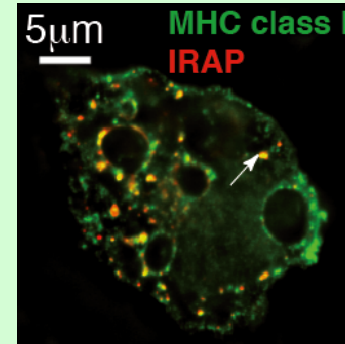
Adipocytes Glucose transporter GLUT4



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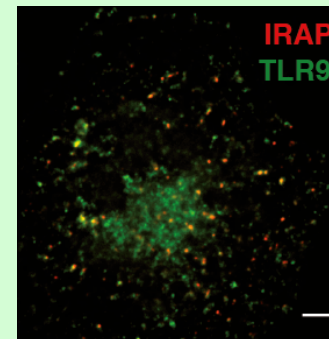
Dendritic cells MHC class I



*Antigen trimming
during MHC-I
cross-presentation*

*Saveanu et al., Science 2009
Weimershaus et al., J. Immunol. 2012*

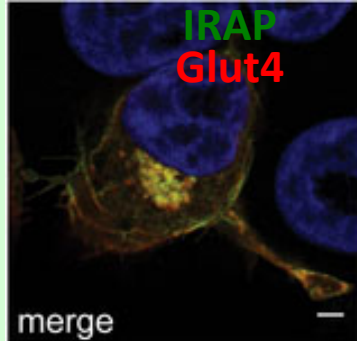
Dendritic cells TLR-9



*Control of TLR9
activation*

Which is the cargo of storage endosomes?

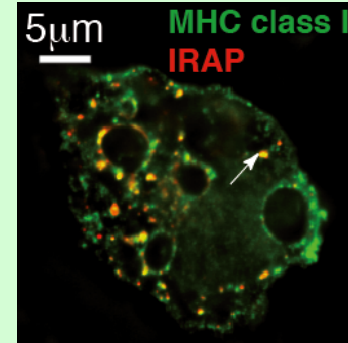
Adipocytes
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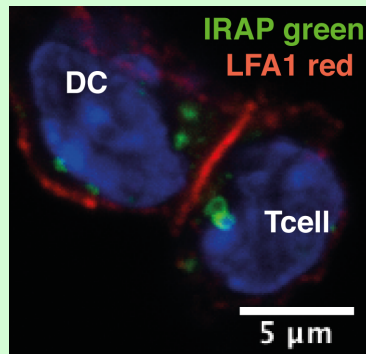
Dendritic cells
MHC class I



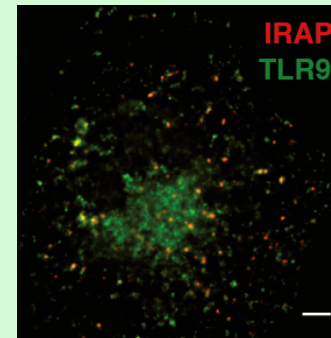
*Antigen trimming
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cross-presentation*

Saveanu et al., Science 2009
Weimershaus et al., J. Immunol. 2012

T cells
...?



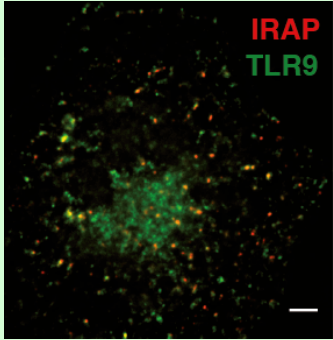
Dendritic cells
TLR-9



*Control of TLR9
activation*

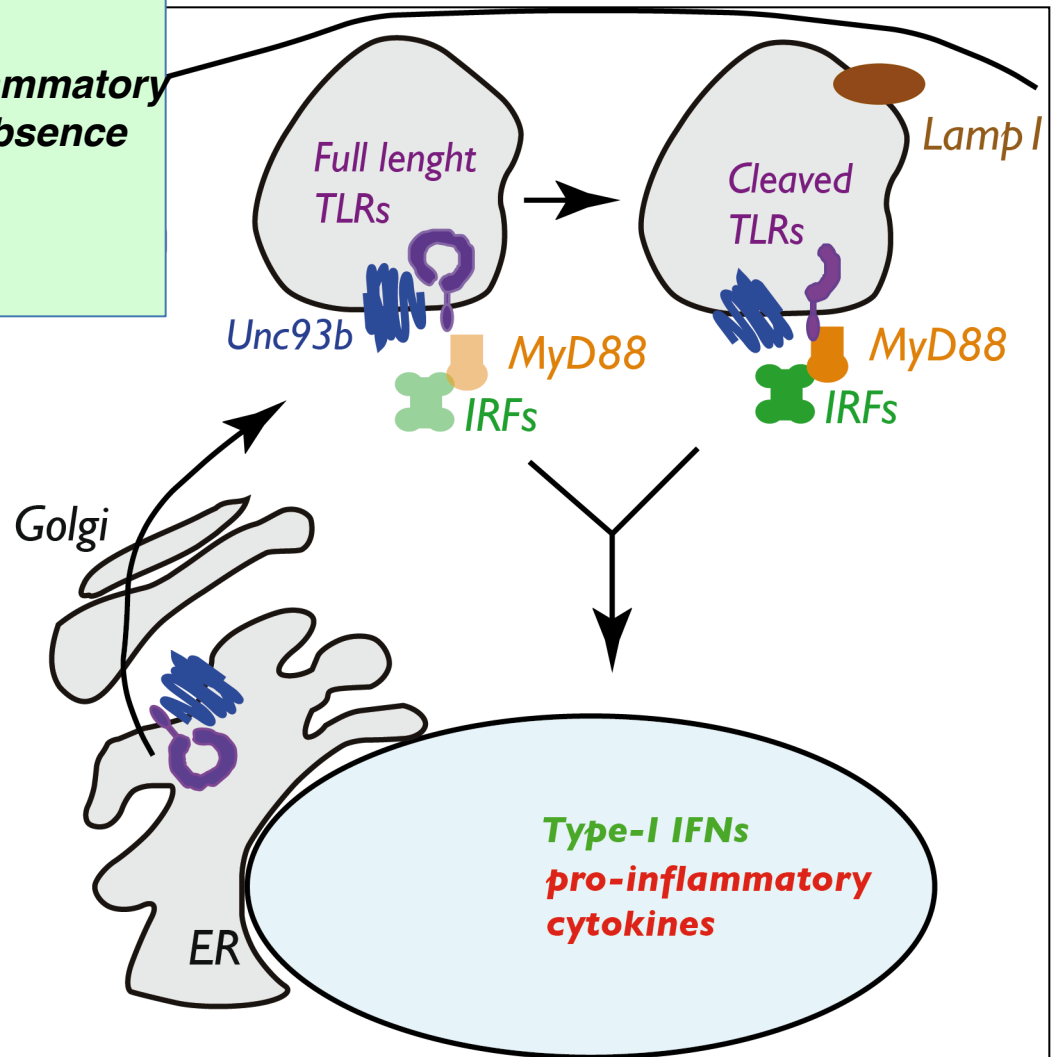
TLR-9

Innate Immunity

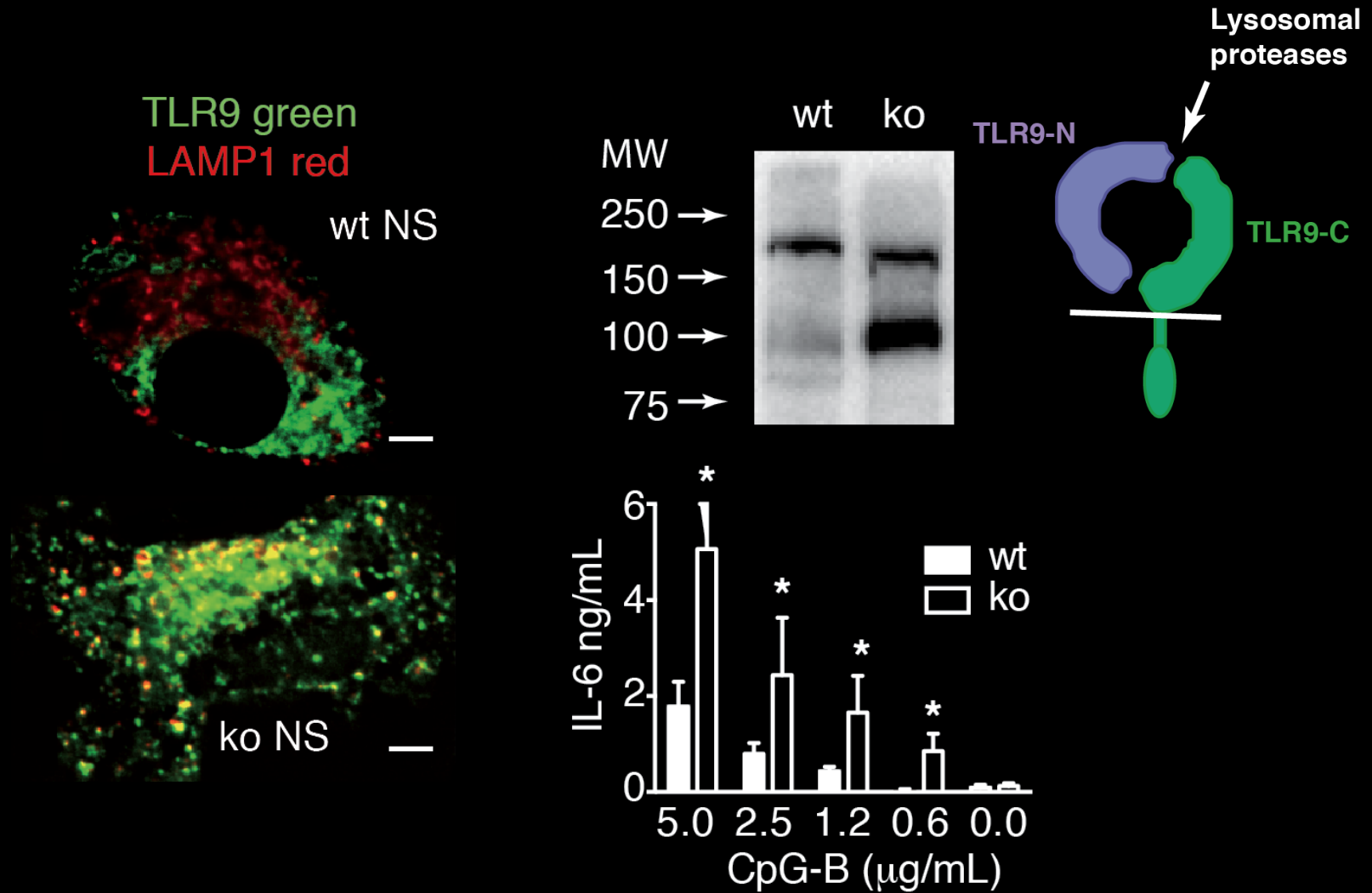


Dendritic cells stimulated with TLR9 ligands

Uncontrolled inflammatory response in the absence of IRAP



IRAP limits endosomal TLRs (7 and 9) signaling

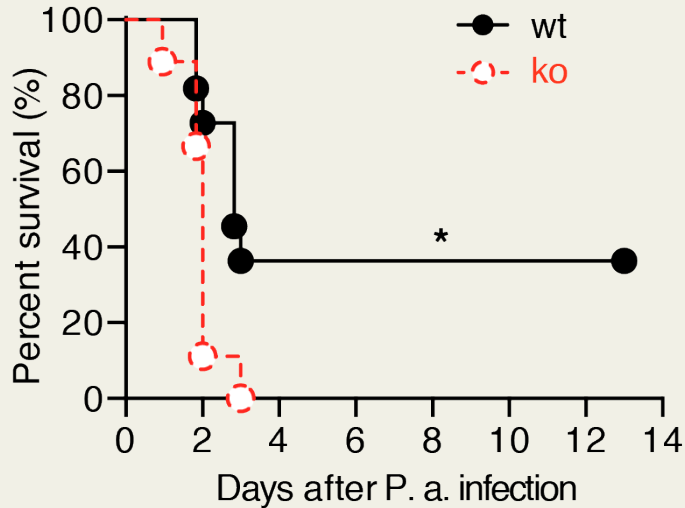


Infectious models of inflammation in IRAPko mice

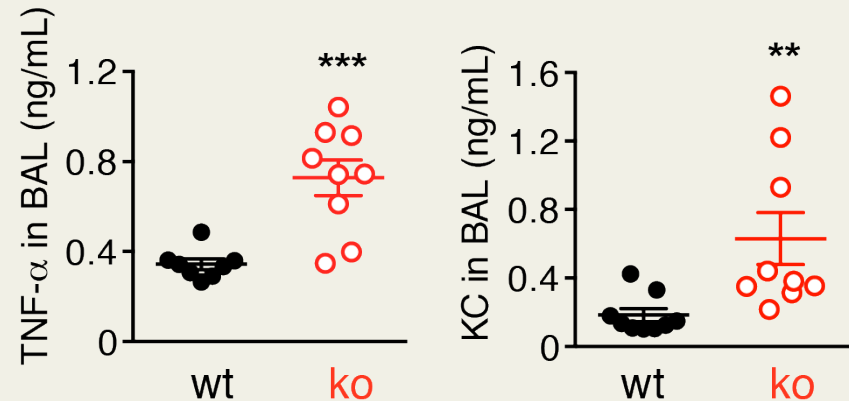
Influenza virus and *P. aeruginosa* pulmonary infections

Collab S. Riffault and D. Descamps U892 INRA –DIM Malinf 2014

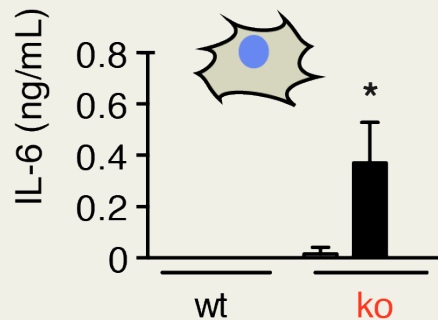
Mice survival



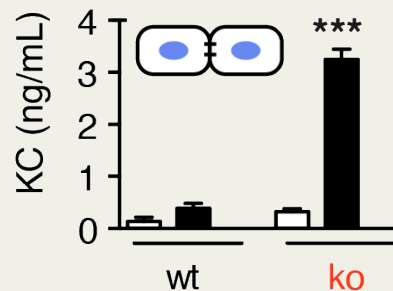
Cytokines in BALs



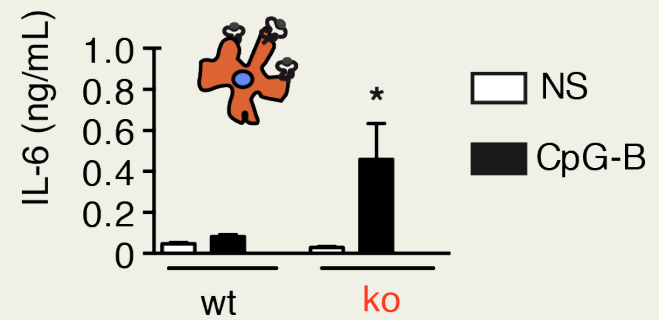
Alveolar MFs



Alveolar epithelial cells

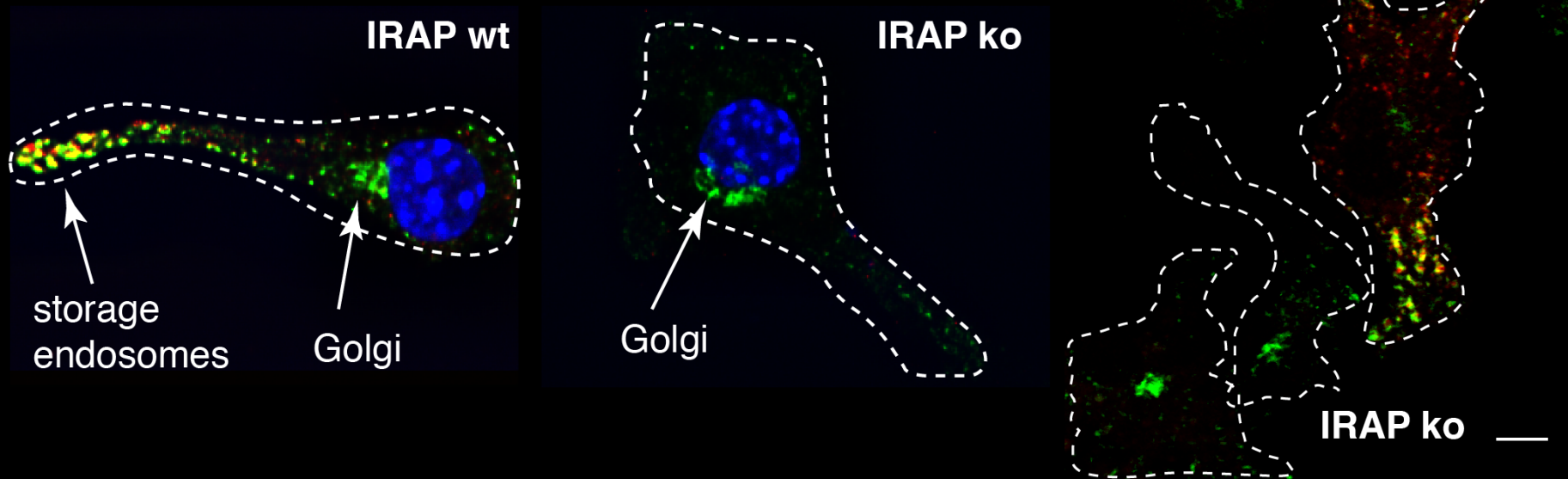


Spleen DCs



IRAP is required for storage endosomes formation or stability

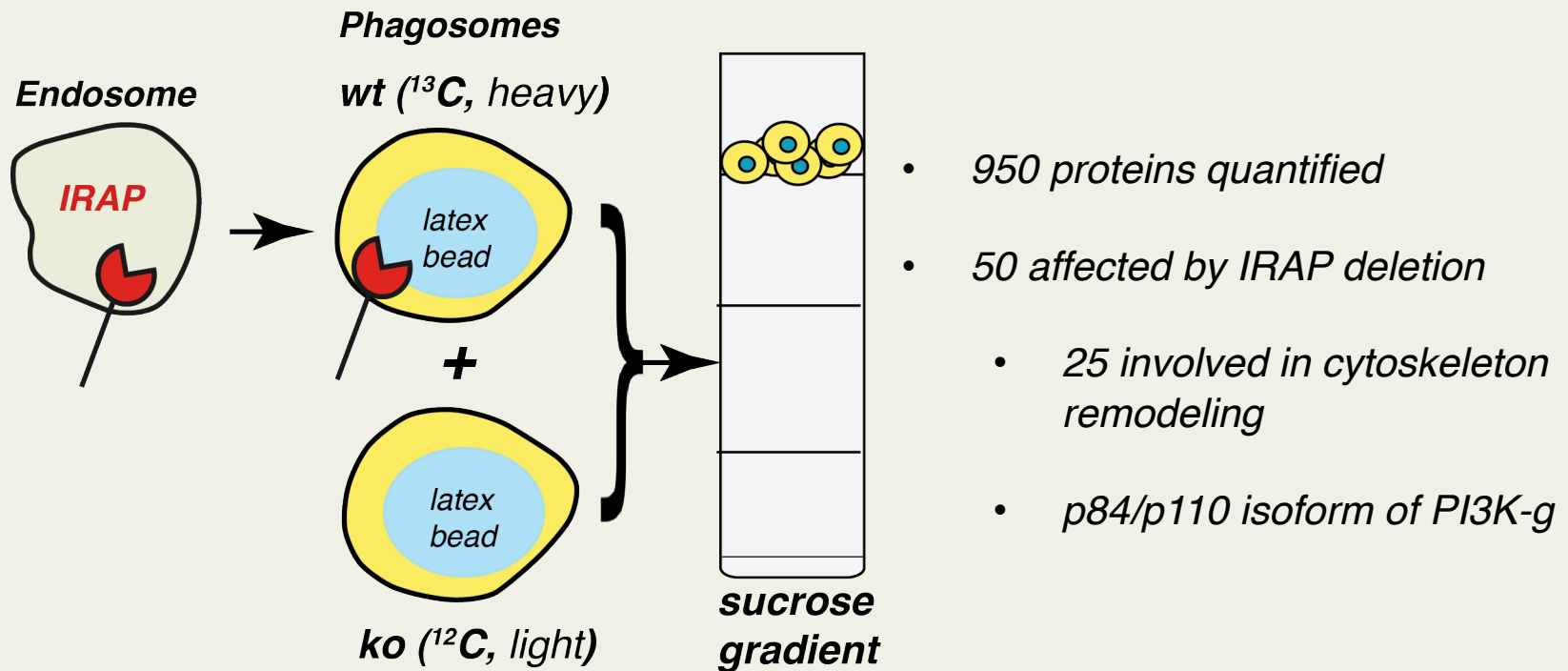
STX6 green IRAP red



Dendritic cells

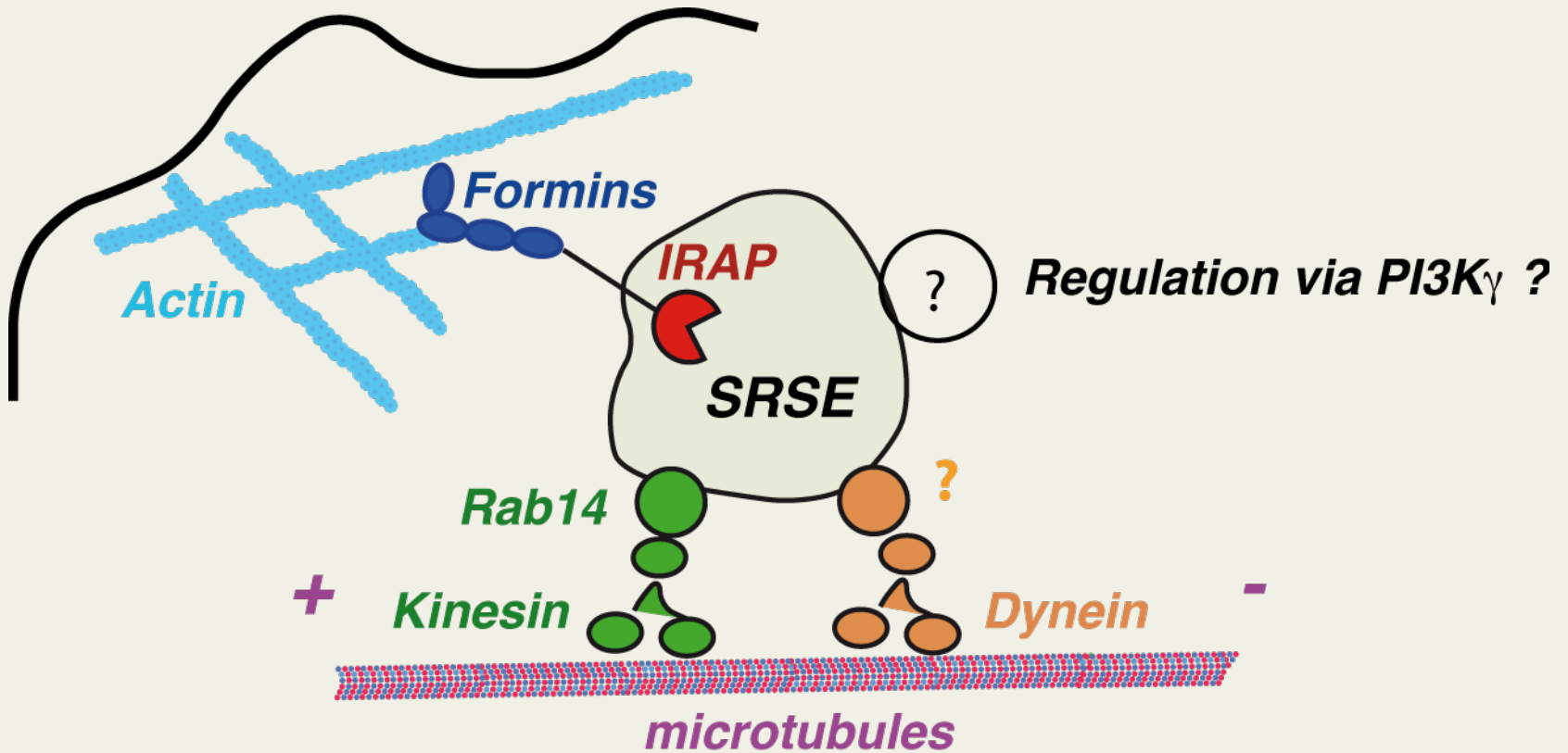
Molecular mechanisms by which IRAP affects the trafficking of storage endosomes

Comparative proteomic analysis of wt and IRAP-deficient phagosomes



SILAC – collaboration with Plateforme 3P5 Univ Paris-Descartes

Storage endosomes trafficking along cytoskeleton

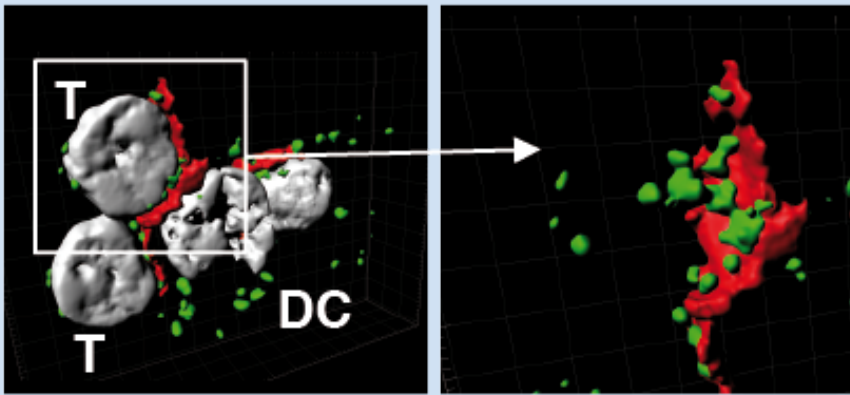


Storage endosomes in T cells

IRAP is expressed in T cells

3D volumes reconstitution

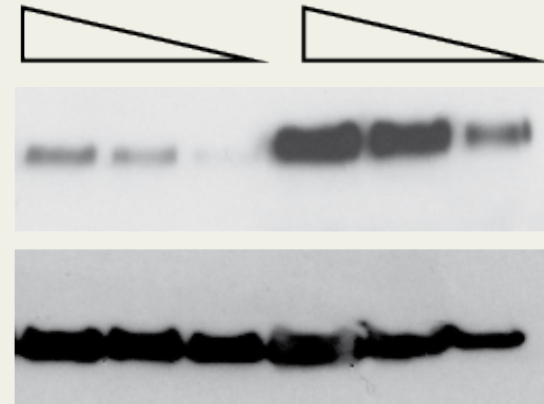
IRAP green, LFA-1 red, DAPI grey



IRAP expression is up-regulated in effector T cells

naive

effect.



Mariacristina De Luca

Collab. with David Gross and Pascal Chappert INSERM U1151 (ANR 2015)

IRAP-cytoskeleton interaction

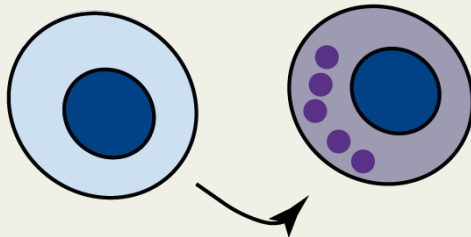


Role of PI3K- γ in storage endosome trafficking



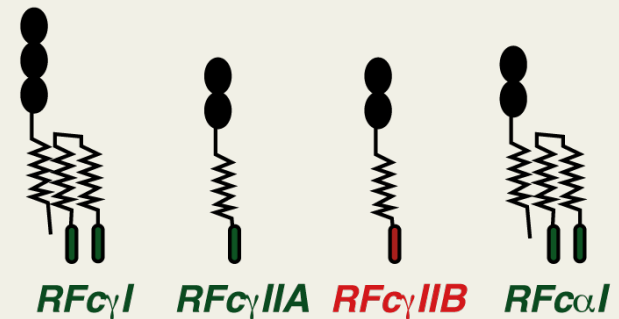
Storage endosomes in T cell activation

Naive T cell Effector T cell



(Collab D.Gross U1151)

Role of Fc Rec in IRAP trafficking?



(Collab R. Monteiro U1149)

In vivo models of infection (Influenza, Pseudomonas)

collab. D.Descamps and S. Riffaut INRA

In vivo models of sterile inflammation (IgAN)

collab. R. Monteiro and L. Berthelot U1149

acknowledgements

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DIM Malinf