RabGDIα is a negative regulator of interferon-γ-inducible GTPase-dependent cell-autonomous immunity to *Toxoplasma gondii*

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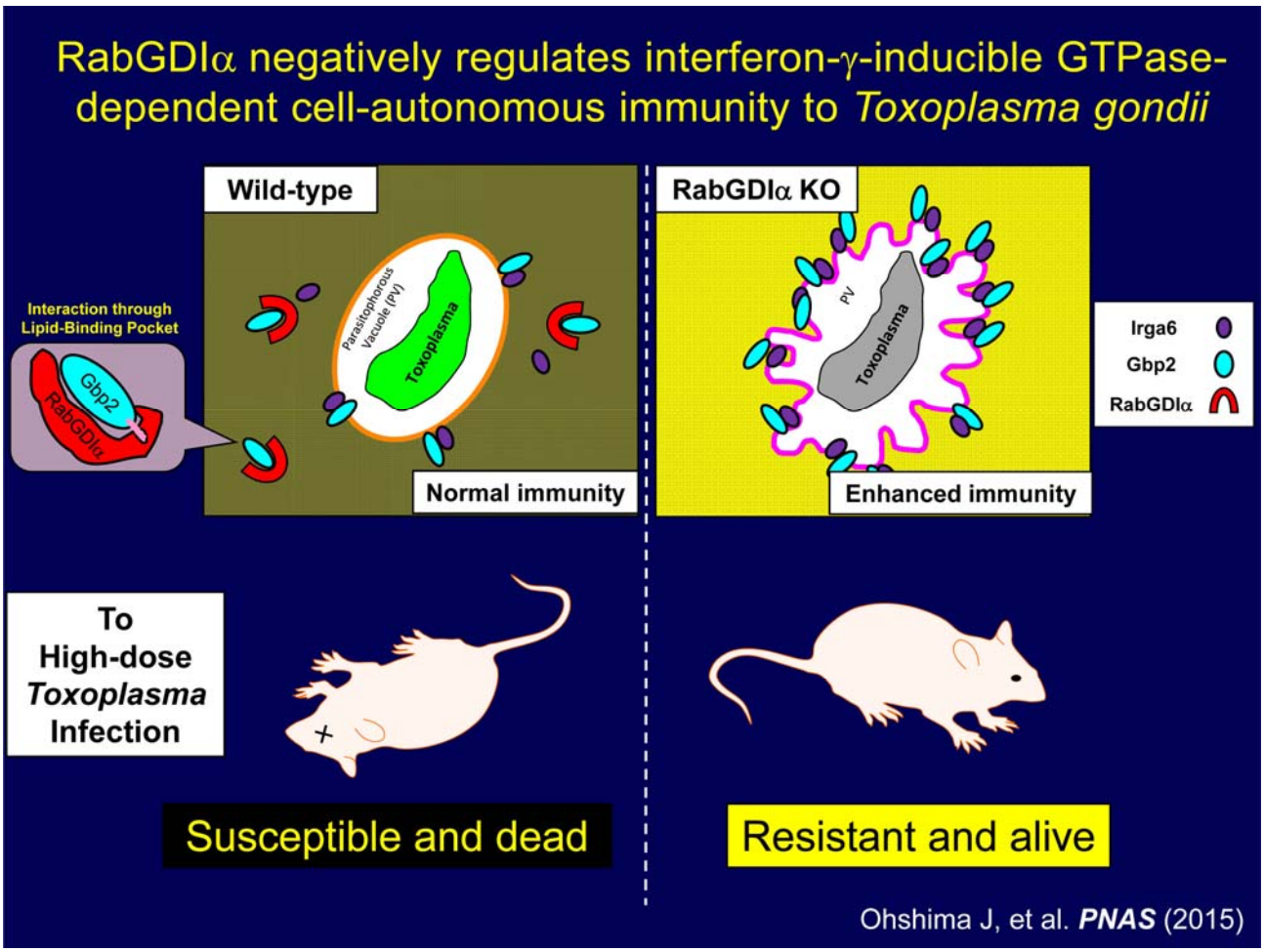
Interferon-γ (IFN-γ) orchestrates cell-autonomous host defense against various intracellular vacuolar pathogens. IFN-γ-inducible GTPases such as p47 immunity-related GTPases (IRGs) and p65 guanylate-binding proteins (GBPs) are recruited to pathogen containing vacuoles, which is important for disruption of the vacuoles, culminating in the cell-autonomous clearance. Although the positive regulation for the proper recruitment of IRGs and GBPs to the vacuoles is being elucidated, the suppressive mechanism is unclear.

Masahiro Yamamoto and his group show that RabGDIα, originally identified as a Rab small GTPase inhibitor, is a negative regulator of IFN-γ-inducible GTPases in cell-autonomous immunity to the intracellular pathogen *Toxoplasma gondii*. Overexpression of RabGDIα, but not of RabGDIβ, impaired IFN-γ-dependent reduction of *T. gondii* numbers. Conversely, RabGDIα deletion in macrophages and fibroblasts enhanced the IFN-γ-induced clearance of *T. gondii*.

Furthermore, upon a high dose of infection by *T. gondii*, RabGDIα-deficient mice exhibited a decreased parasite burden in the brain and increased resistance in the chronic phase than control mice. Among members of IRGs and GBPs important for the parasite clearance, Irga6 and Gbp2 alone were more frequently recruited to *T. gondii*-forming parasitophorous vacuoles in RabGDIα-deficient cells. Notably, Gbp2 positively controlled Irga6 recruitment that was inhibited by direct and specific interactions of RabGDIα with Gbp2 through the lipid binding pocket. Taken together, our results suggest that RabGDIα inhibits host defense against *T. gondii* by negatively regulating the Gbp2-Irga6 axis of IFN-γ-dependent cell-autonomous immunity.


RabGDIα negatively regulates interferon-γ-inducible GTPase-dependent cell-autonomous immunity to *Toxoplasma gondii*
Wild-type
Parasitophorous Vacuole (PV)
Toxoplasma
Normal immunity
Interaction through Lipid-Binding Pocket
Gbp2
RabGDIα
RabGDIα KO
PV
Toxoplasma
Enhanced immunity
Irga6
Gbp2
RabGDIα
To High-dose *Toxoplasma* Infection
Susceptible and dead
Resistant and alive
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