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Role of Peroxisome Proliferator-activated receptor γ (PPAR γ) in Coxiella Burnetii Infection

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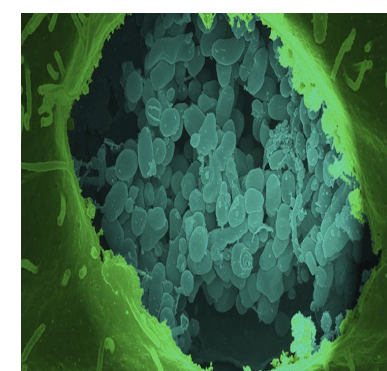
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Introduction

Coxiella burnetii



- Gram negative bacterium
- Causative agent of human Q fever

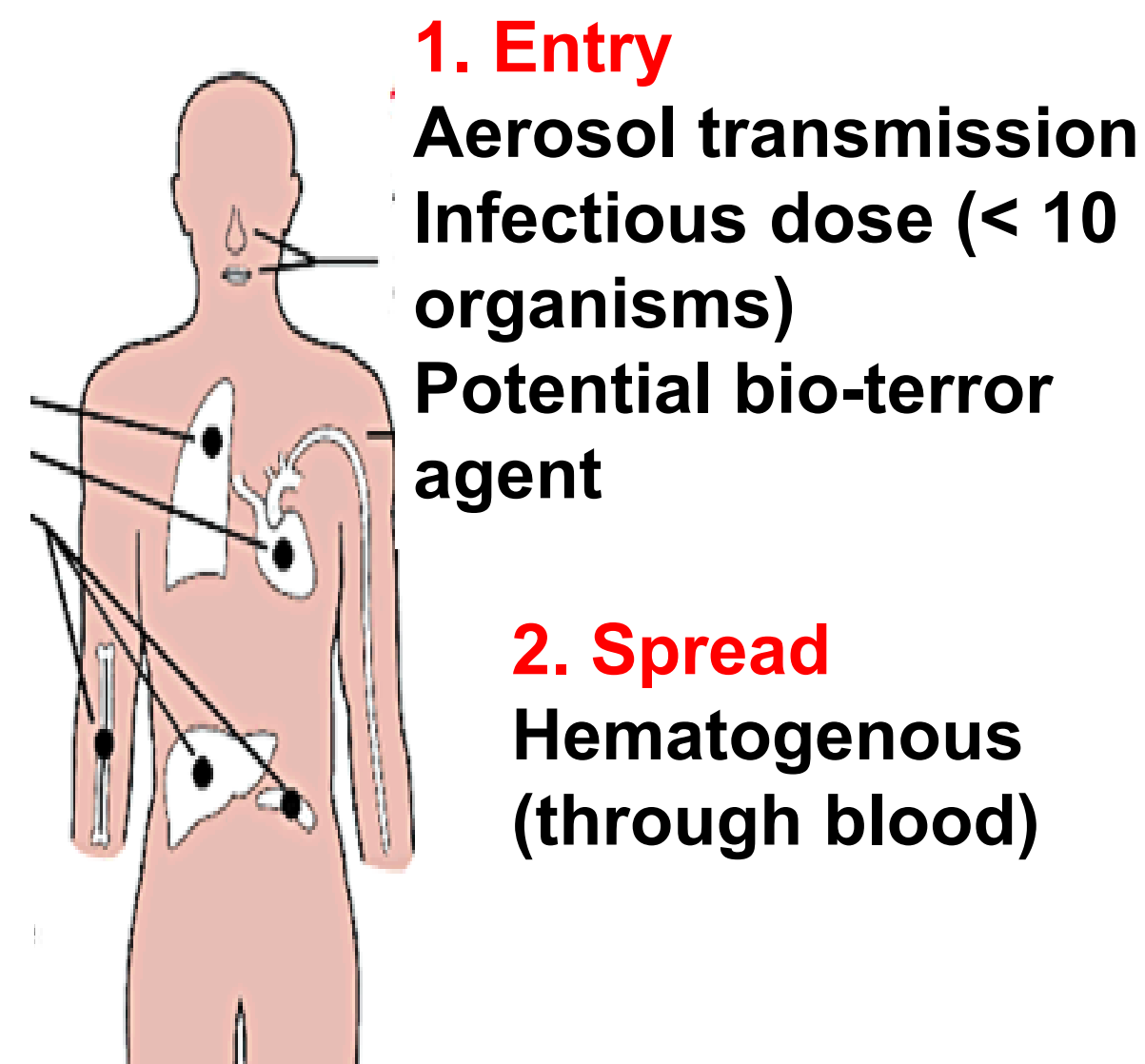
3. Disease

Acute

- Pneumonitis
- Endocarditis
- Granulomas

4. Exit

Usually none in man



Lipid droplets are storage organelles important for cellular metabolism

- Neutral lipid storage organelles
- Store esterified cholesterol and free fatty acids (triacylglycerol)
- Biogenesis from ER
- Functions - Energy homeostasis, membrane trafficking, signaling

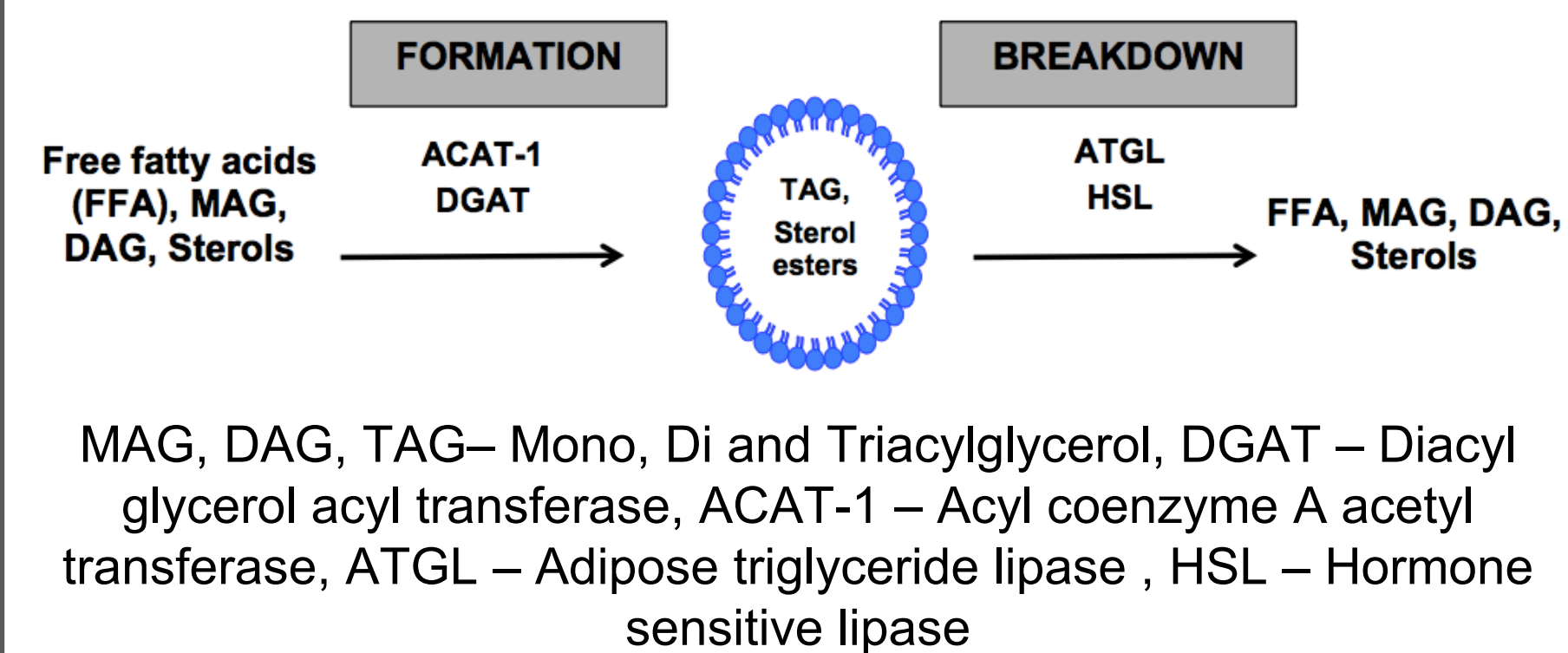
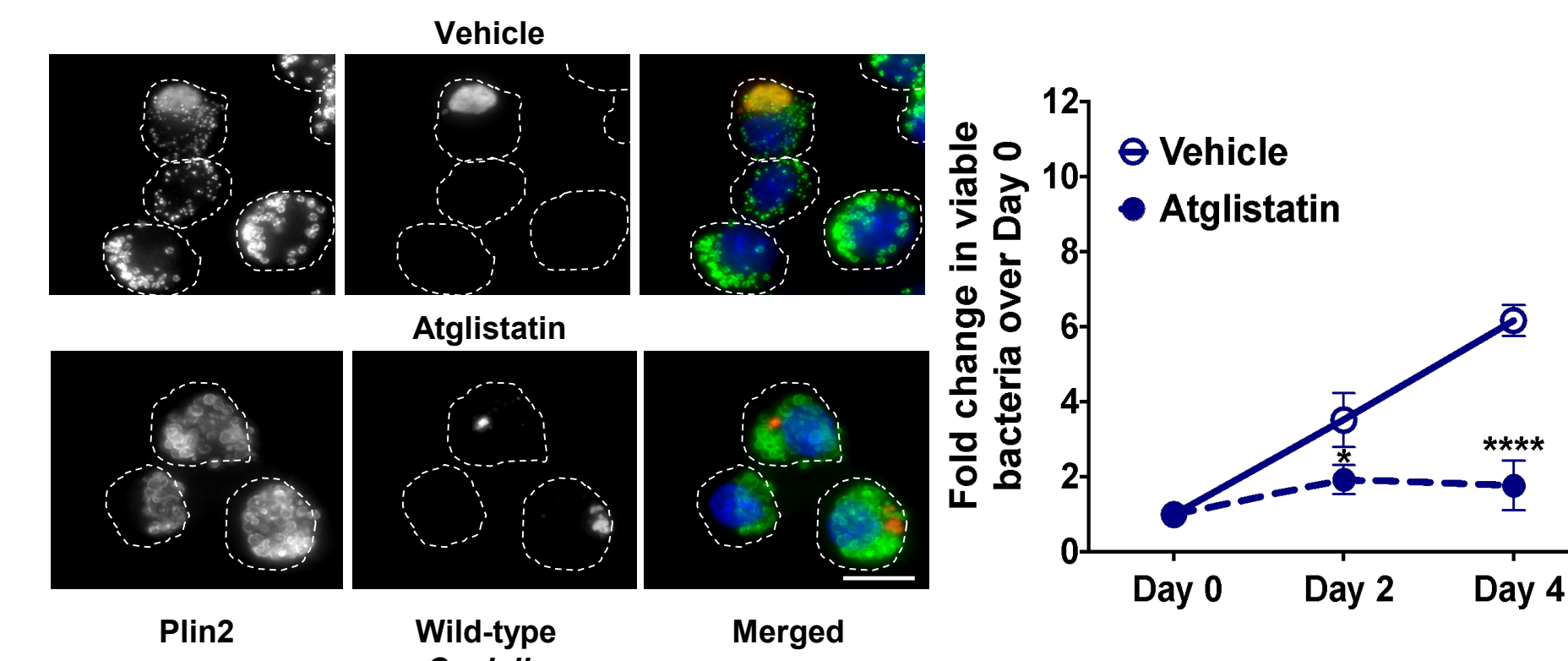


Figure 2: Blocking lipid droplet breakdown results in reduced *Coxiella* growth



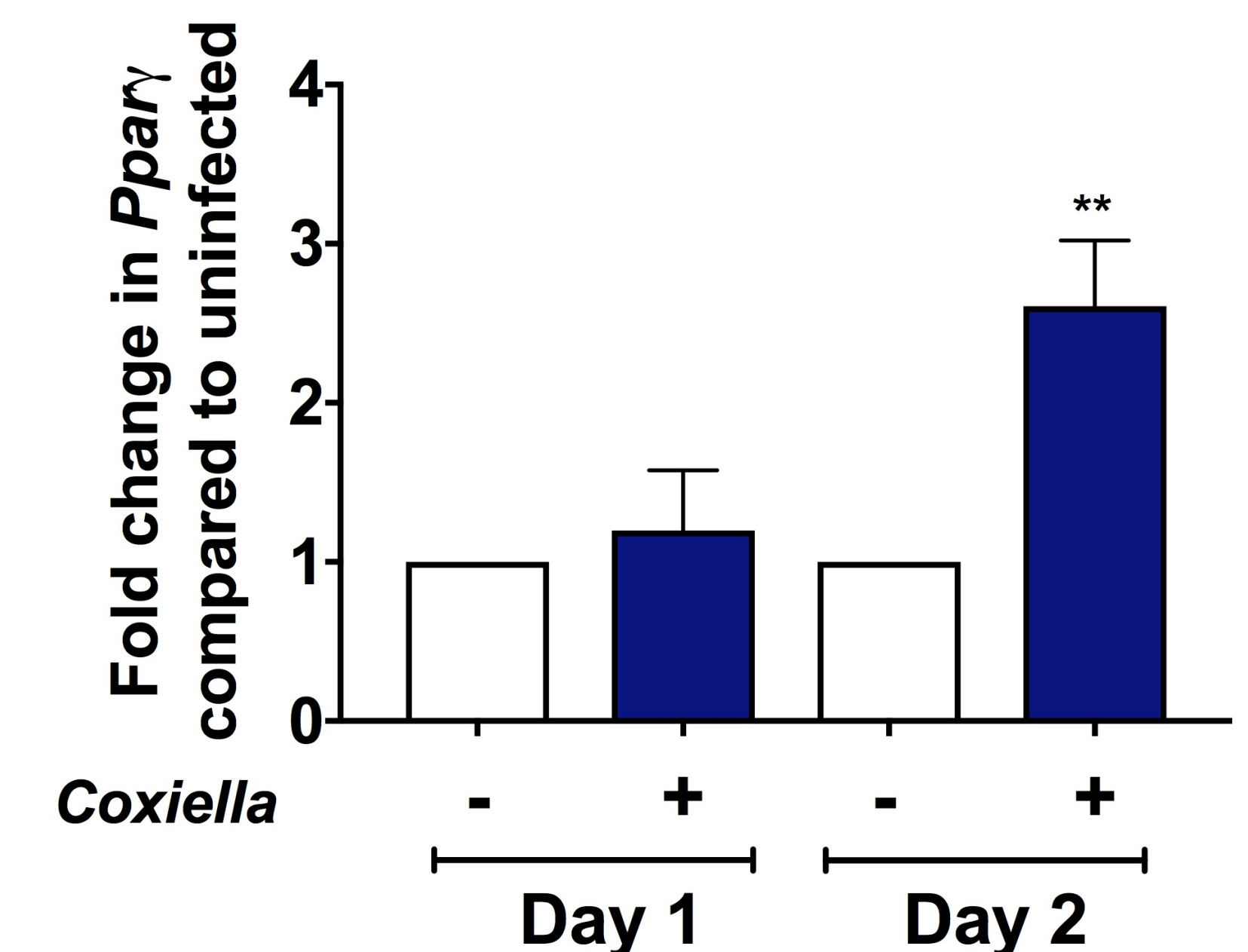
MH-S cells infected with wild-type *Coxiella* were treated with vehicle (DMSO) and 20uM atglisatin. Bacterial growth was determined at day 4 by FFU Assay (n=3) *p<0.05, **** =p<0.0001 compared to vehicle-treated cells two-way ANOVA with Bonferroni post-hoc test. Scale bar = 10 μ m.

Overall Question

Does *Coxiella* infection affect PPAR γ expression and activity to induce anti-inflammatory immune response?

Results

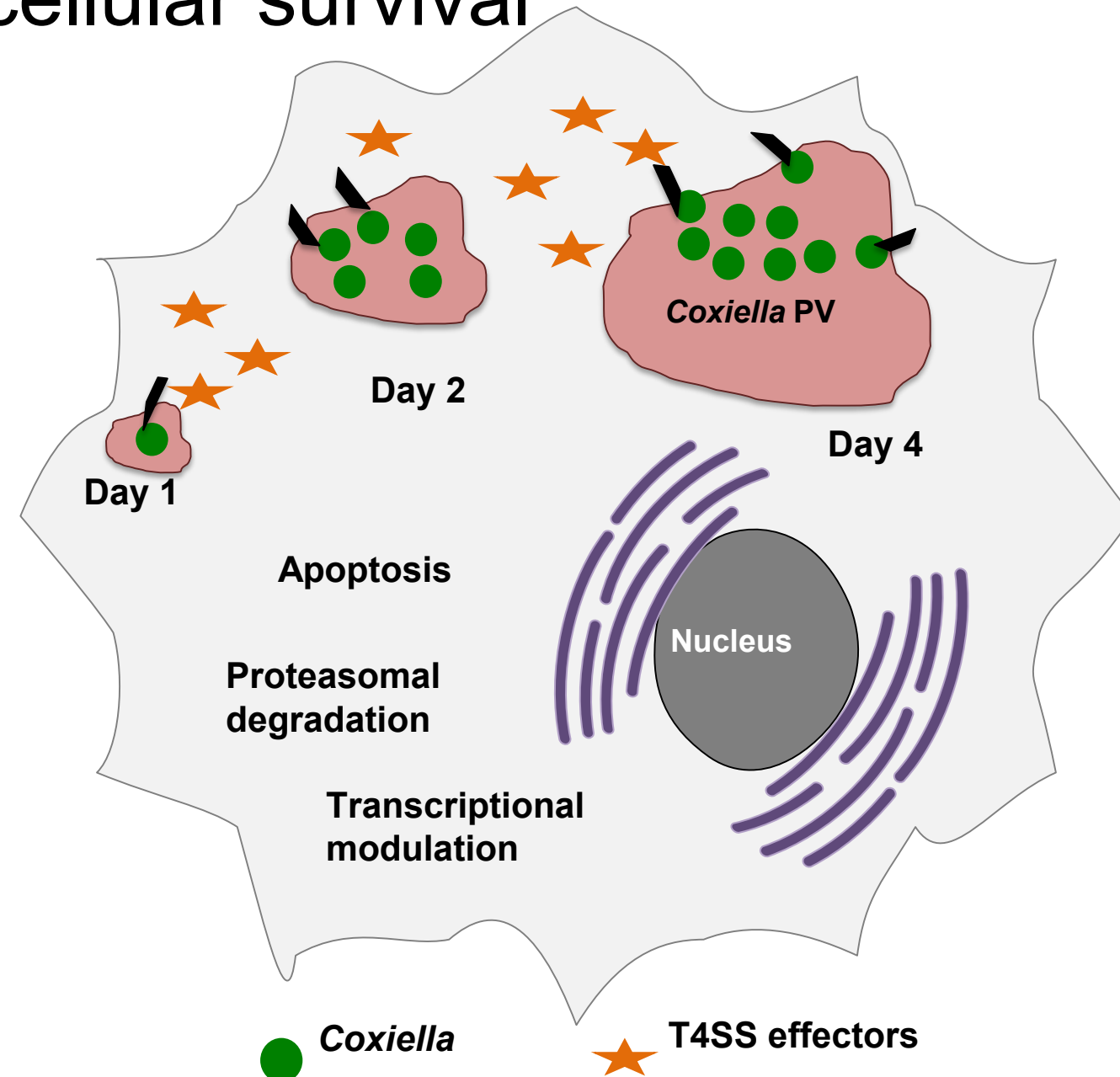
Figure 3: *Coxiella* infection upregulates PPAR γ expression in infected alveolar macrophages



MH-S cells were infected with WT *Coxiella*. RNA was collected Day 1 and 2 post-infection, reverse transcribed to cDNA and gene expression was determined using quantitative Real Time (qRT-PCR). Fold change was calculated compared to uninfected samples using GAPDH expression as housekeeping. **p<0.01 as determined by One-way ANOVA with Tukeys post-hoc test

Pathogenesis of *Coxiella*

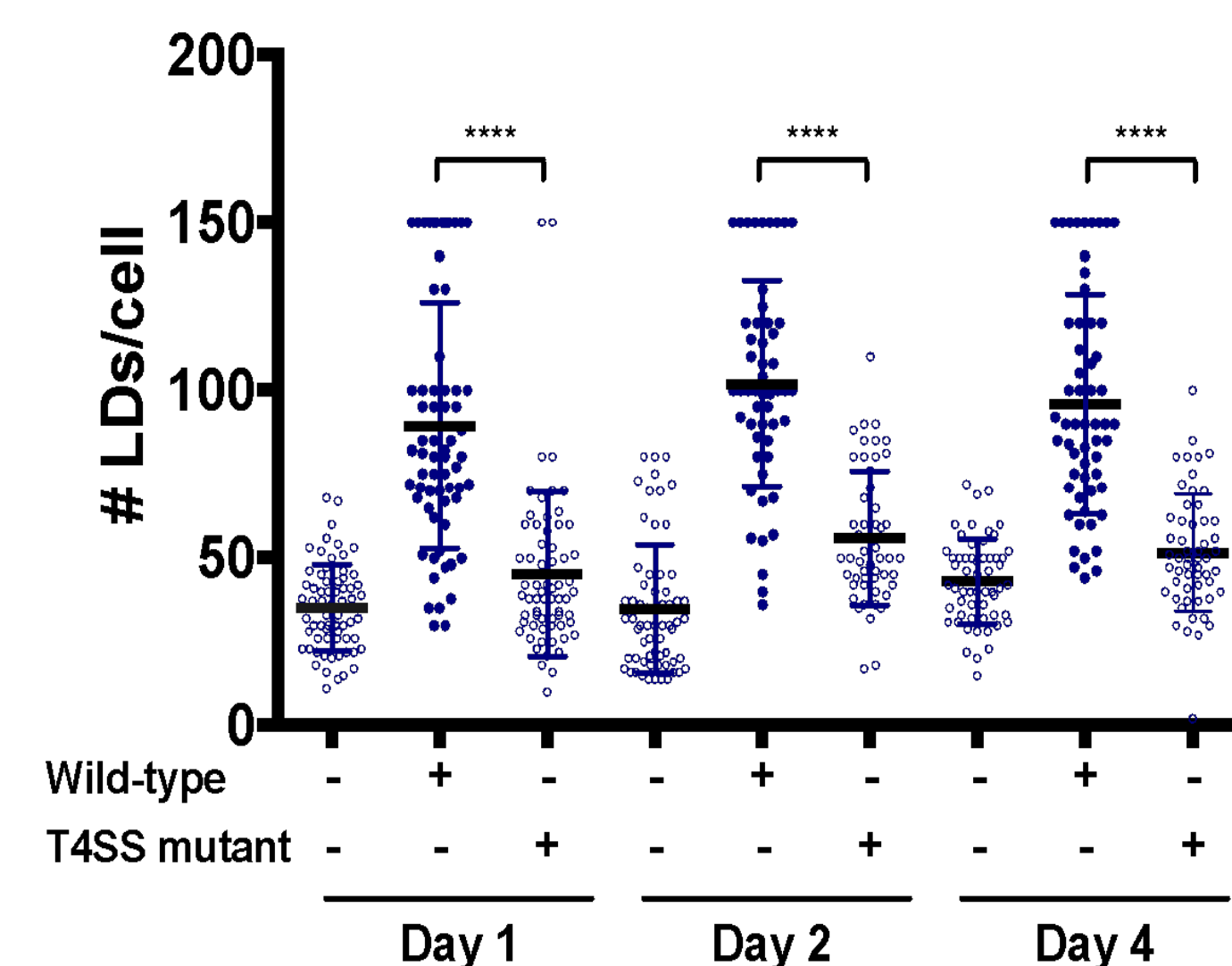
- Preferably infects alveolar macrophages
- Found in lipid droplet-rich foam cells in endocarditis patients
- Parasitophorous vacuole (PV) is essential for bacterial growth
- Uses Type 4 Secretion System (T4SS) to manipulate host cells
- Lipid droplets are important for *Coxiella* intracellular survival



Preliminary Data

Are lipid droplets important for *Coxiella* intracellular pathogenesis?

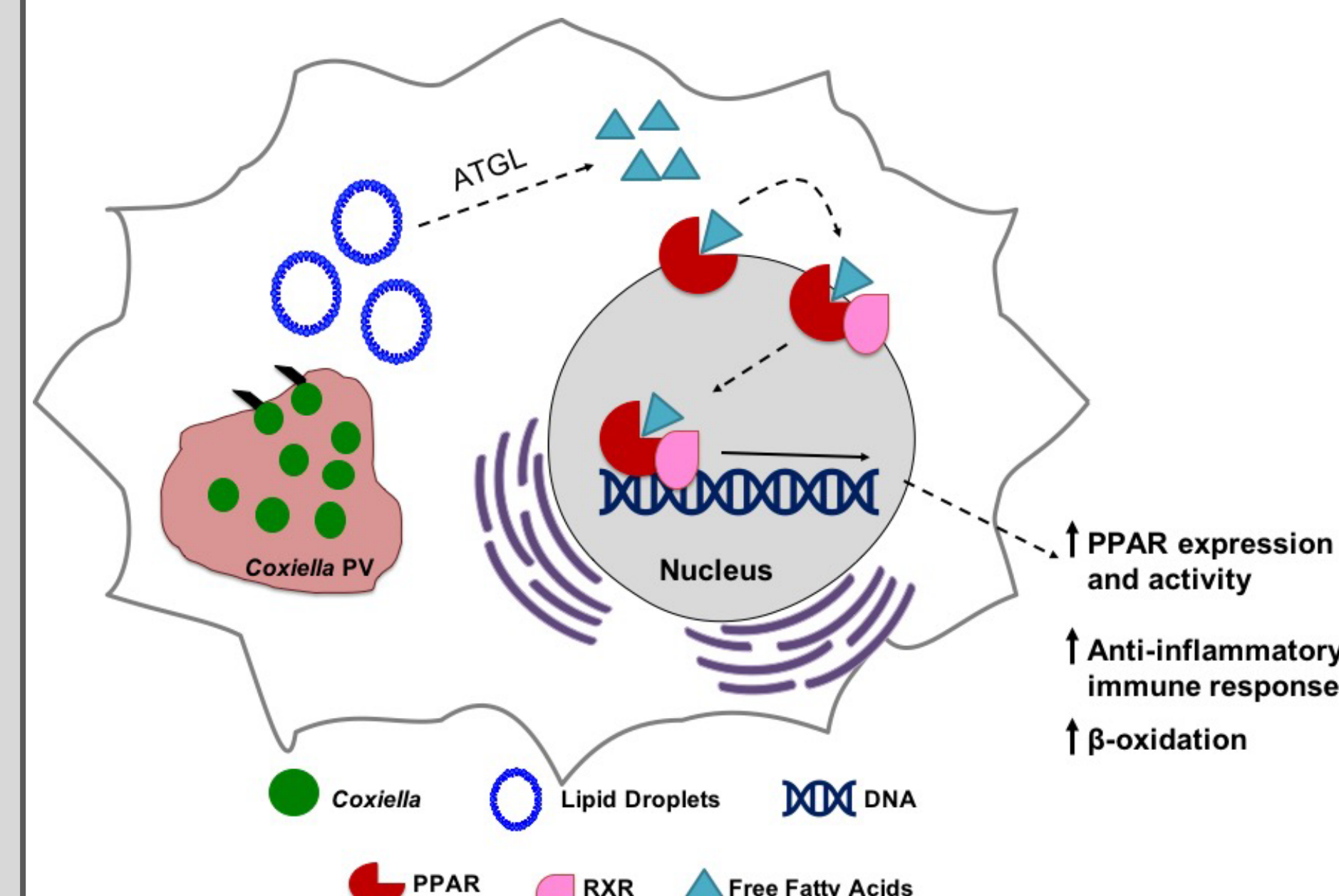
Figure 1: Lipid droplet accumulation is dependent on the *Coxiella* T4SS



Wild-type and T4SS mutant *Coxiella*-infected mouse alveolar macrophages (MH-S) cells were stained for Plin2 and *Coxiella*. Number of lipid droplets were counted by fluorescence microscopy. Graph represents number of lipid droplets/cell in uninfected and infected cells. (n=3) ****=p<0.0001 determined by two-way ANOVA.

Lipid droplets and PPAR γ

- Lipid droplet breakdown releases free fatty acids (FFAs)
- FFAs are PPAR γ agonists
- Activation of PPAR γ induces anti-inflammatory immune response
- Example: *Mycobacterium tuberculosis*, *Mycobacterium leprae*



Coxiella breaks down lipid droplets in presence of the enzyme ATGL to release Free Fatty Acids (FFAs) which act as PPAR γ agonists. The activated PPAR γ receptor then heterodimerizes with Retinoid X Receptor (RXR) and translocates to the nucleus, binds to PPAR response elements (PPRE) and regulates expression of several genes influencing cellular β -oxidation, host immune response etc.

Conclusions

Coxiella infection upregulates PPAR γ gene expression in alveolar macrophages

- suggests *Coxiella* might manipulate PPAR γ expression and activity to induce an anti-inflammatory immune response to promote intracellular survival.