

Role of Nod2 in virus-plus-susceptibility gene interaction

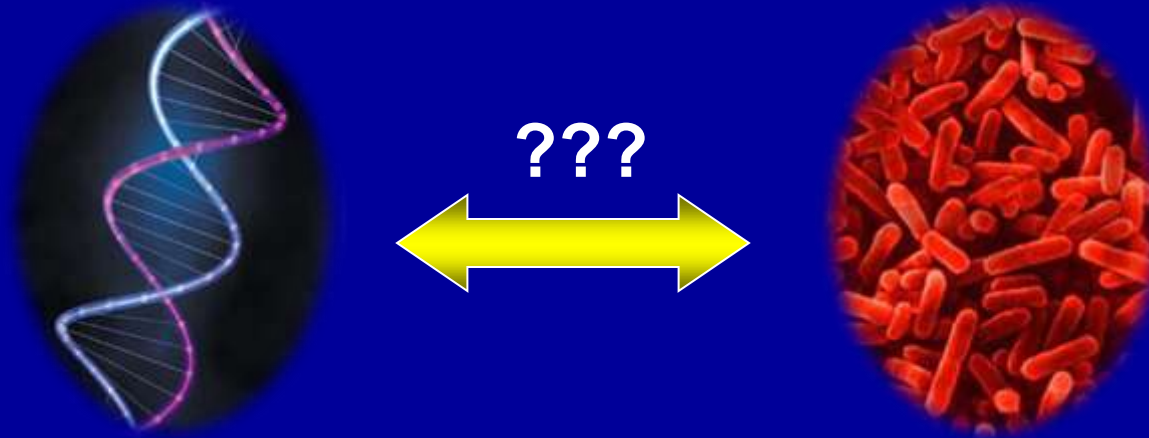
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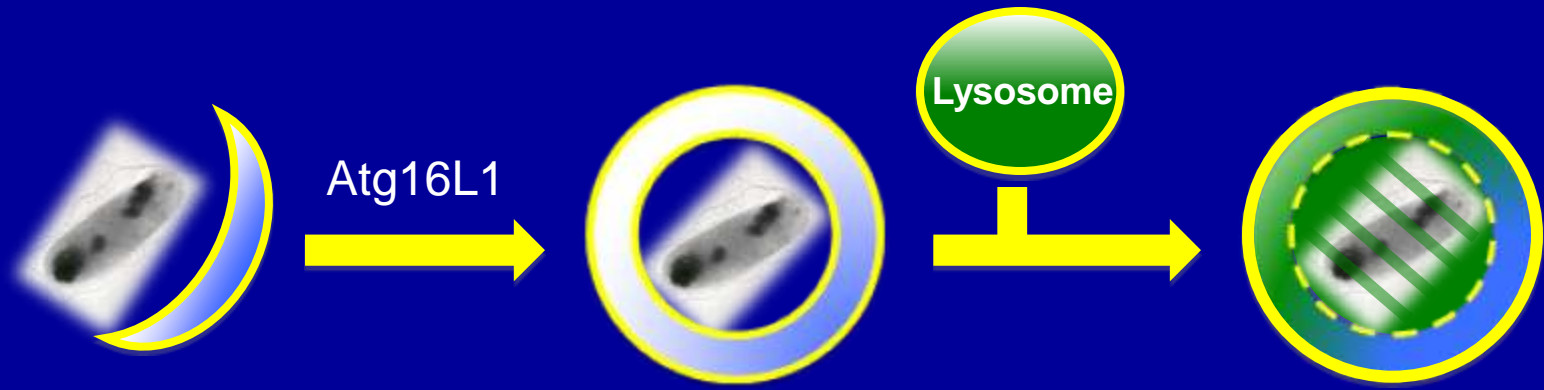
**²Department of Pathology and Immunology,
Washington University School of Medicine**

Genes, environment, and commensal bacteria in Crohn's disease

71 genetic loci associated with increased susceptibility.
Franke et al, *Nat Genetics*. 2010



Susceptibility and autophagy gene *Atg16L1*



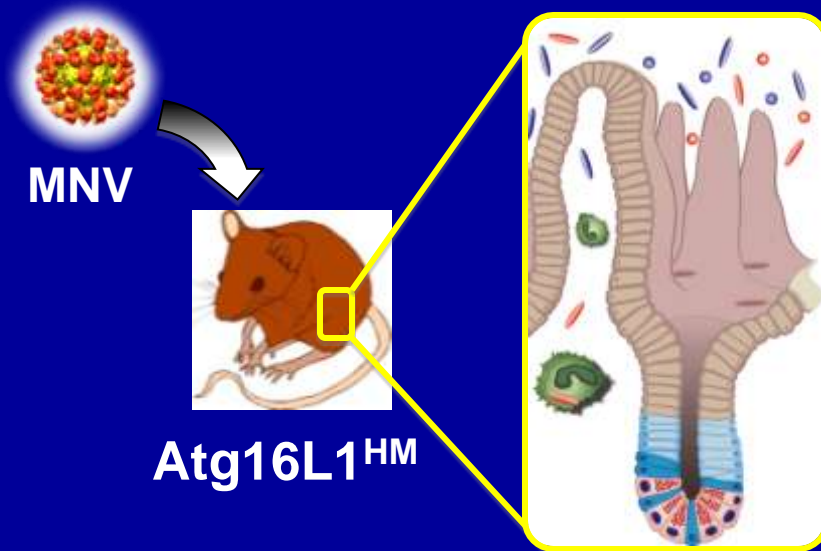
Gene trap
mutagenesis



- *Atg16L1* protein expression
- Autophagy

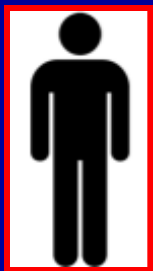
Atg16L1^{HM} mice (HM = hypomorph)

Atg16L1 mutation leads to abnormal Paneth cells in mice and Crohn's disease patients



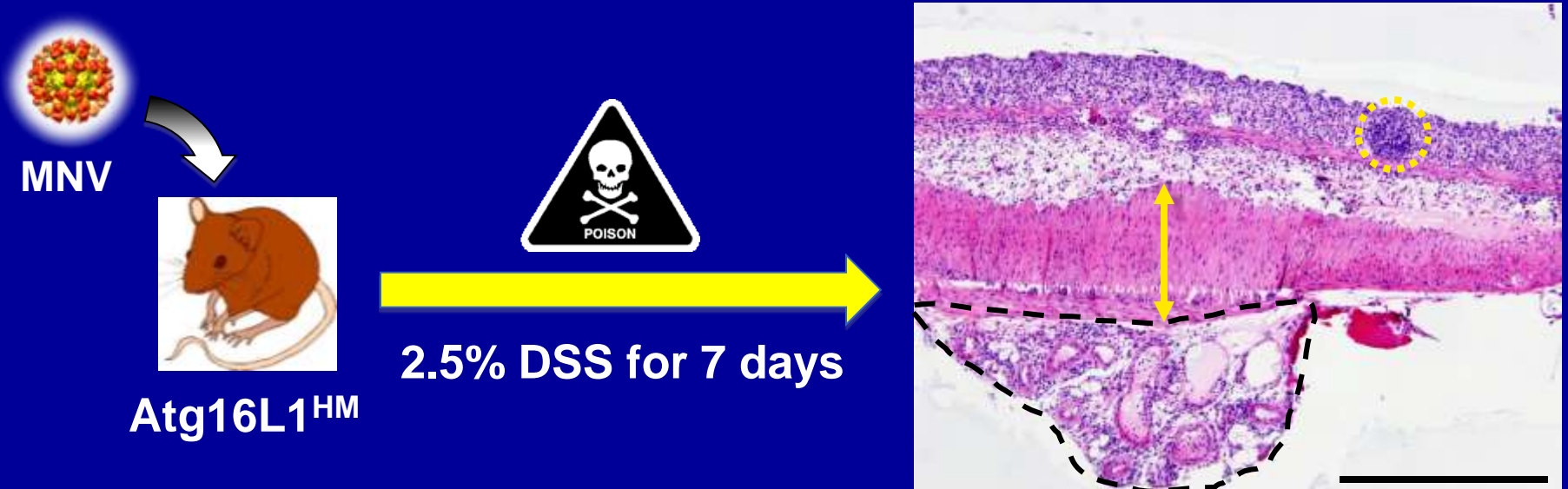
Abnormal Paneth cells

- Aberrant morphology
- Altered gene expression
- Defective granule packaging and secretion

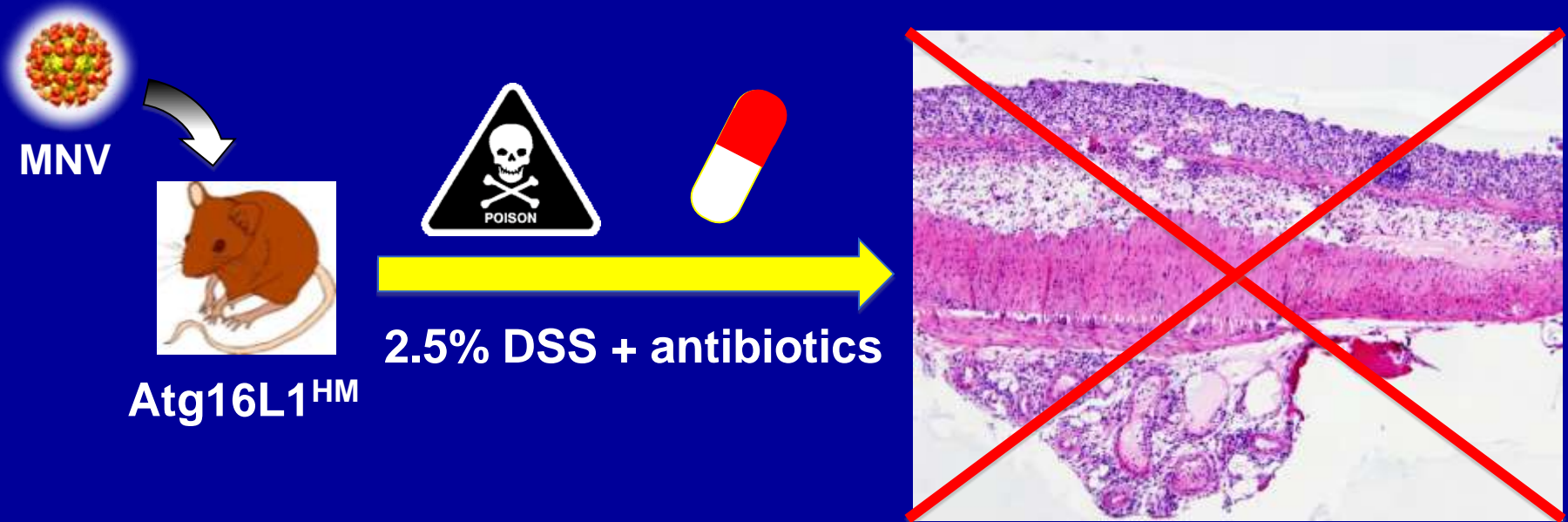


Similar Paneth cell defects in patients homozygous for the risk allele of *Atg16L1*.

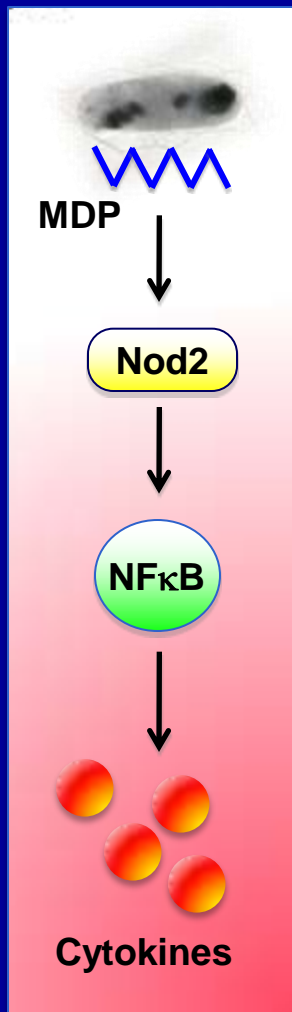
Virus + susceptibility gene interaction



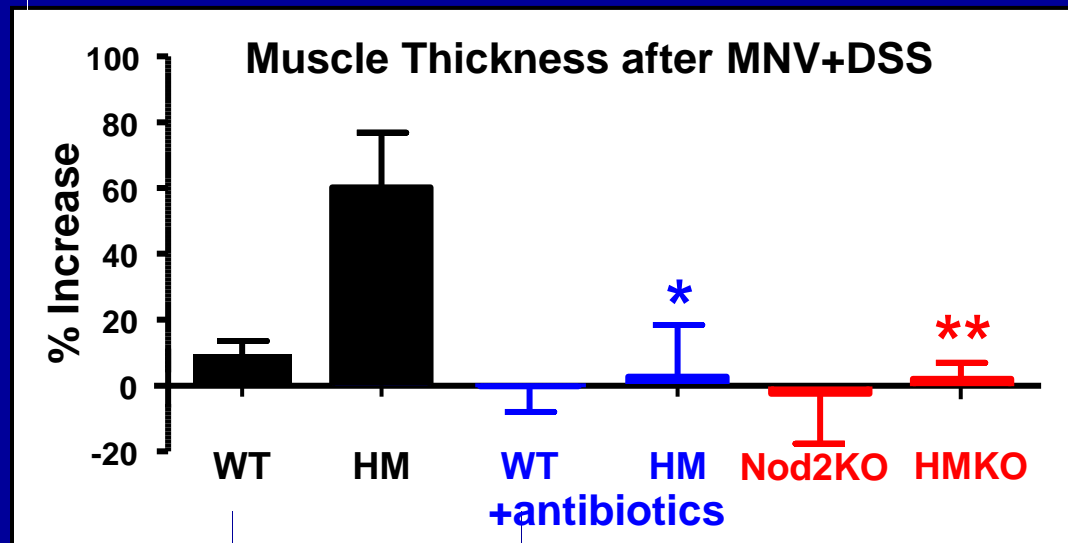
Commensal Bacteria are required for virus + susceptibility gene interaction



Nod2 is essential for virus-plus-susceptibility gene interaction



HMKO = Atg16L1^{HM} x Nod2KO



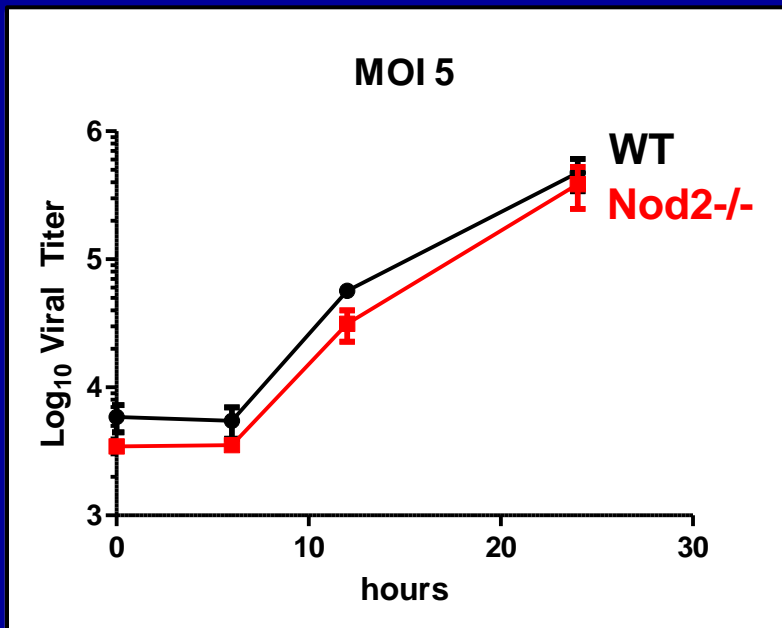
Nod2 does not directly recognize MNV

In addition to the bacterial cell wall, Nod2 recognizes –ssRNA viruses and activates an IFN β transcription.

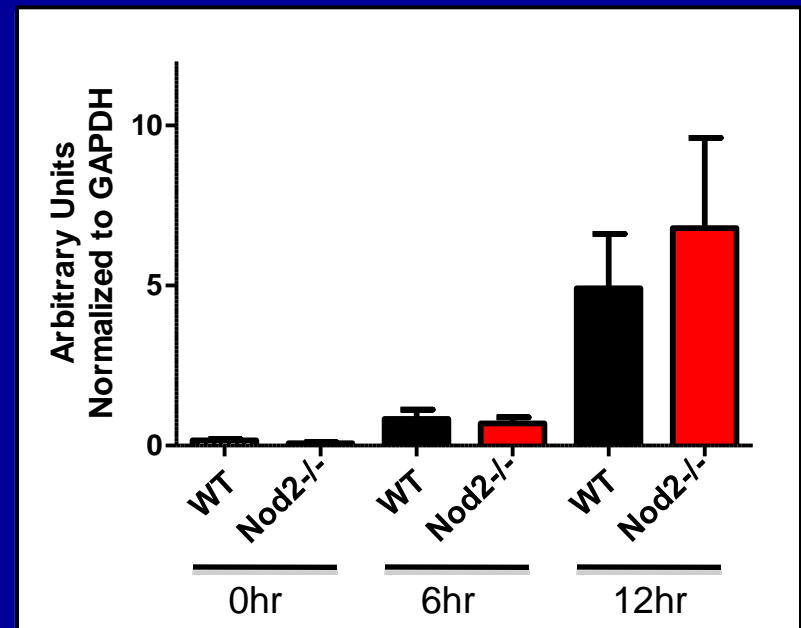
-Sabbah et al., *Nature Immunology*. 2009

Bone marrow derived macrophages

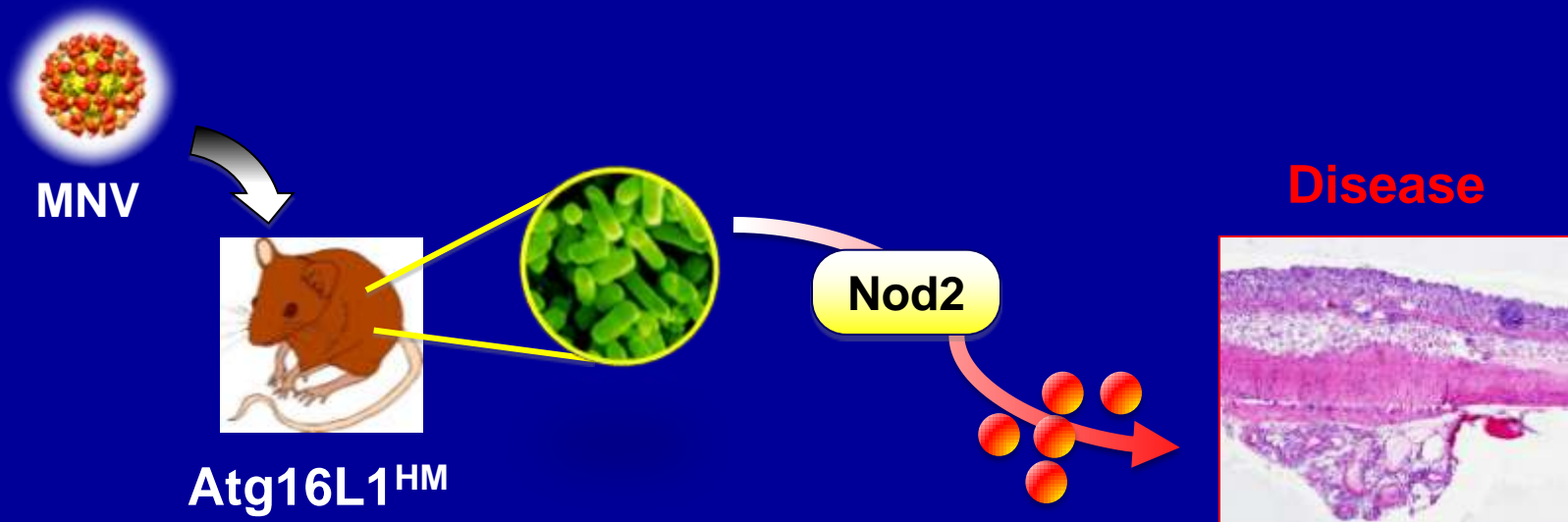
MNV replication



Induction of IFN β



Model by which Nod2 mediates virus-plus-susceptibility gene interaction



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