

Literature Report

Reporter: 段承恩

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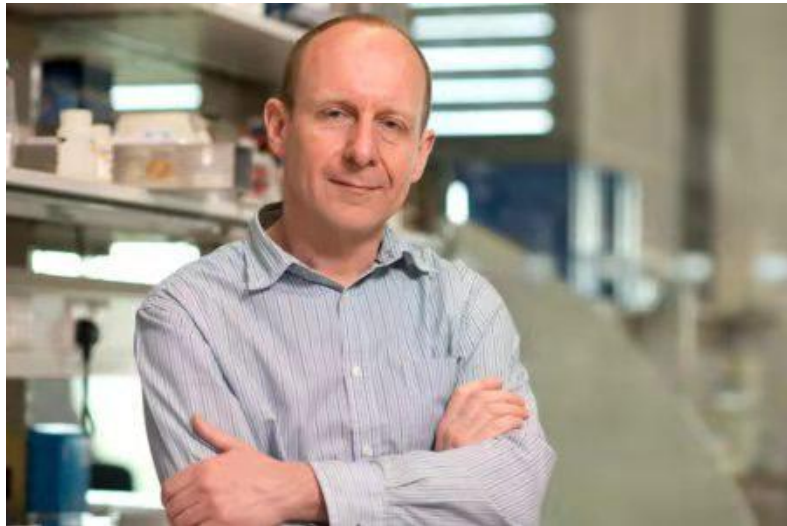
Ubiquitylation of lipopolysaccharide by RNF213 during bacterial infection

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Felix is originally from Germany. He obtained his PhD from Humboldt University Berlin before moving to Boston where he was a post-doc with Brian Seed at Harvard Medical School. In 2003, Felix became Group Leader at LMB.

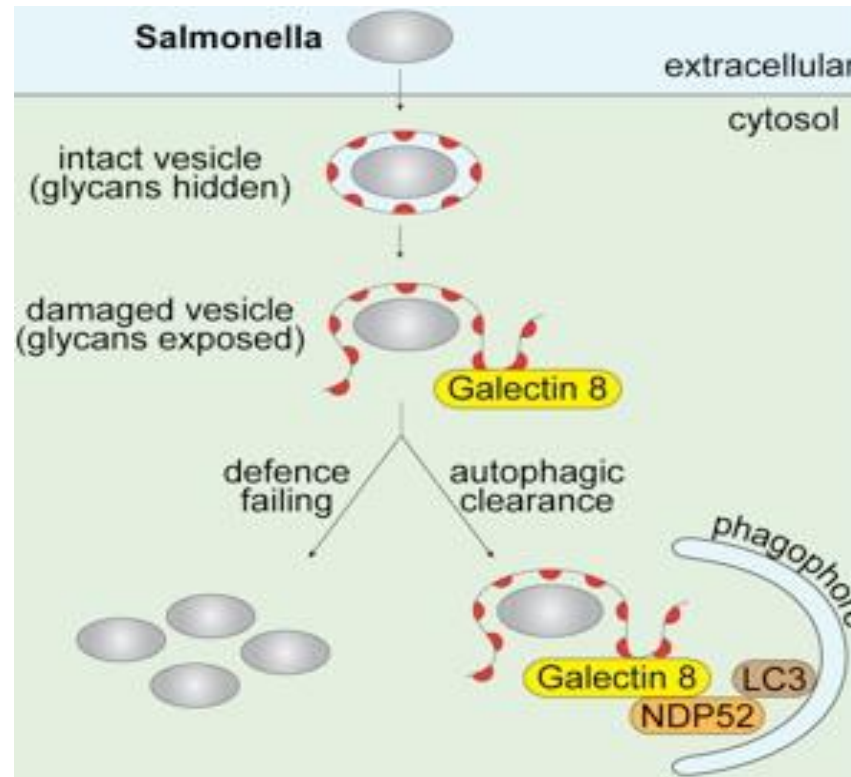
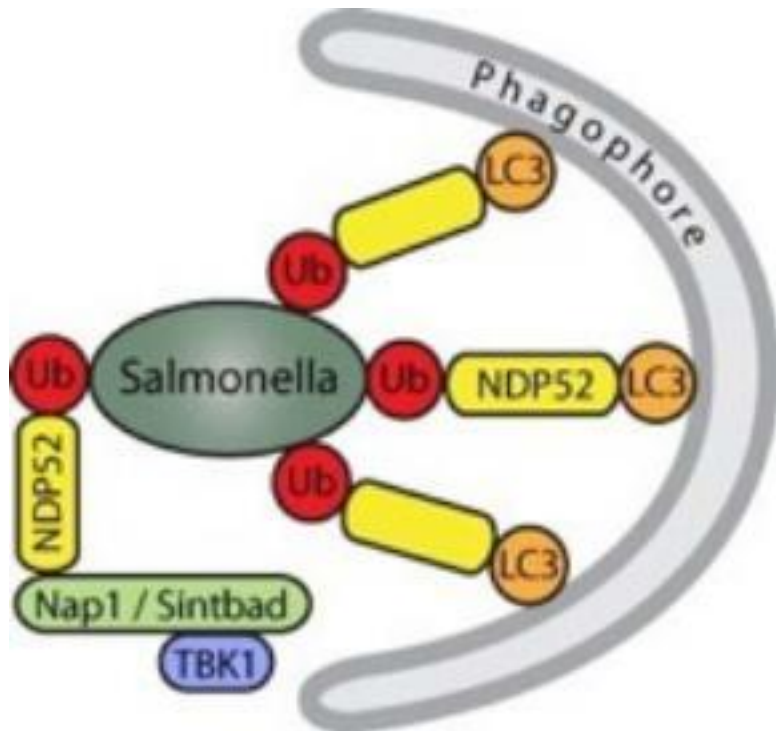
Introduction



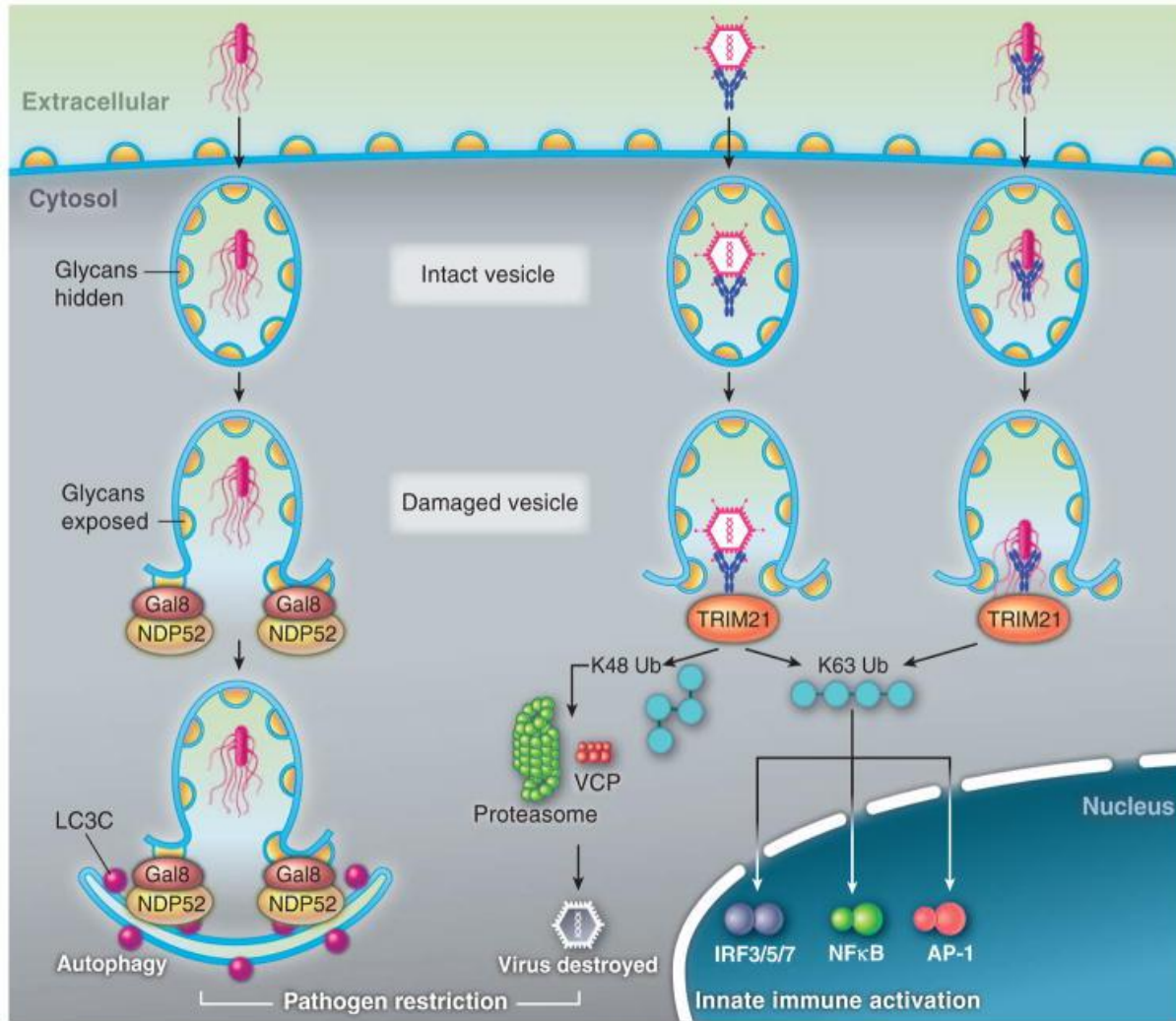
Research: interested in cell autonomous innate immunity, i.e. in the ability of individual cells to defend themselves against infection.

The mammalian cytosol is rich in nutrients but can be colonized by specialized bacteria only. We therefore wish to understand i) how cells succeed in defending their cytosol against most invasion attempts and ii) how professional cytosol dwelling bacteria outwit cellular defences. We are particularly interested in danger receptors that detect breaches in cellular integrity, and in the ubiquitin system that marks invading bacteria as cargo for autophagy receptors.

Cytosolic defense against bacterial invasion

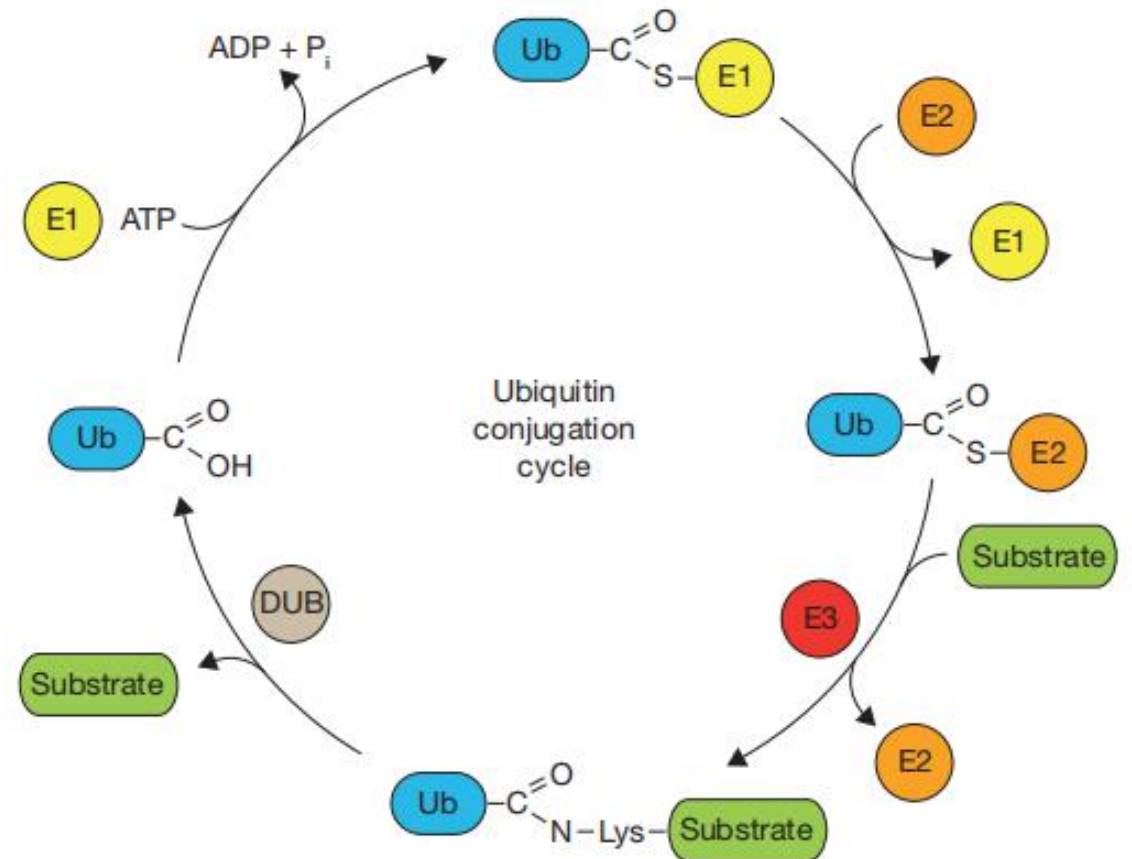


Introduction



细胞自主免疫如何抵御病原体

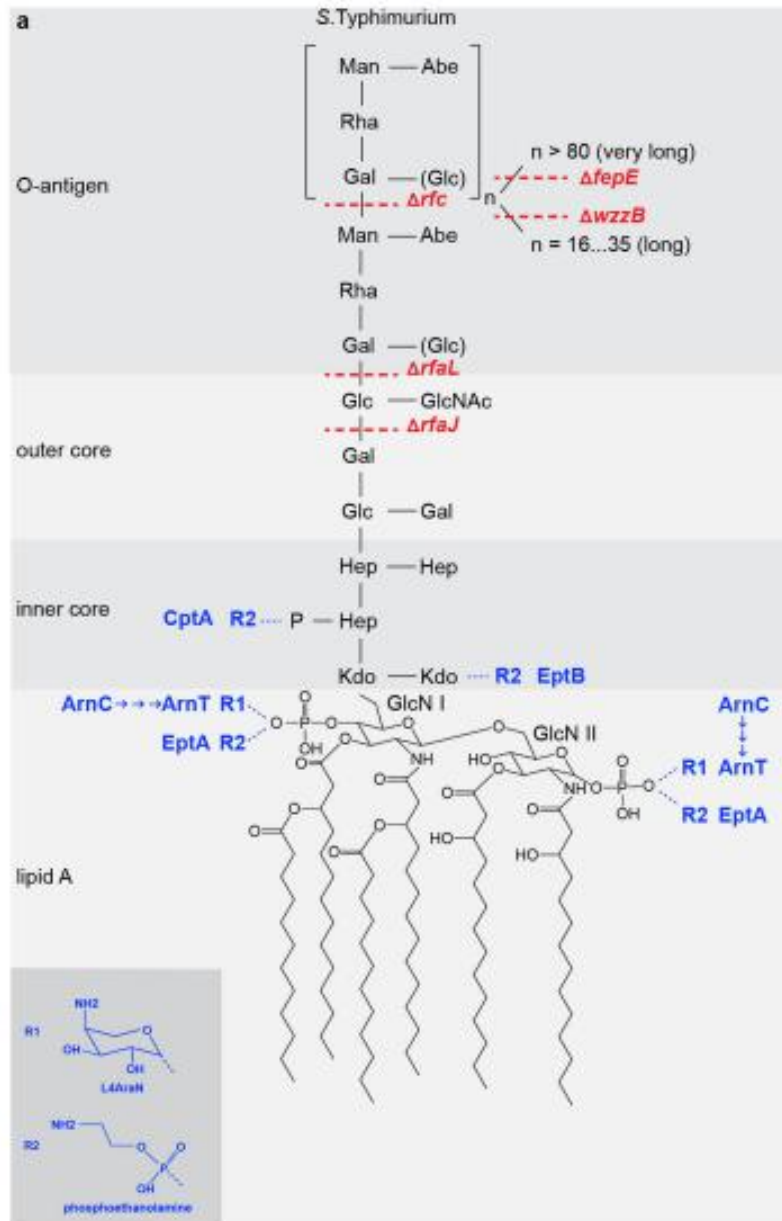
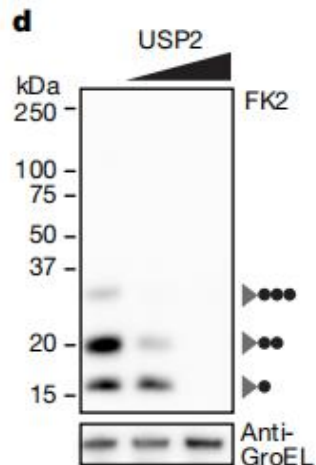
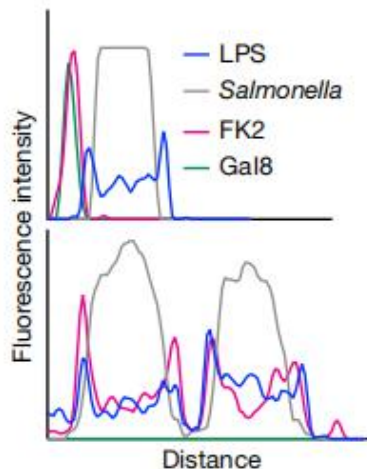
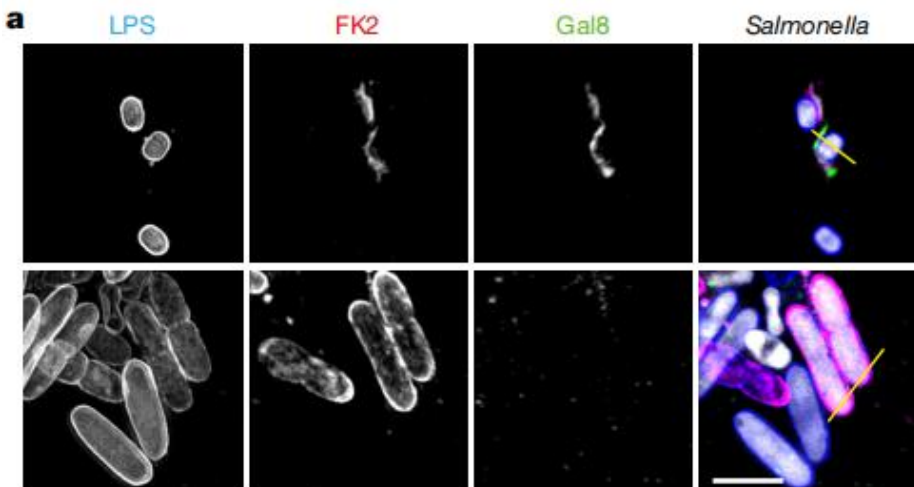
Science .2013 May 10;340(6133):701-6.



泛素化过程：E1活化酶、E2结合酶、E3连接酶

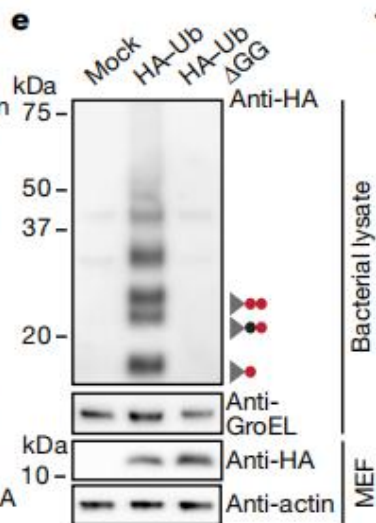
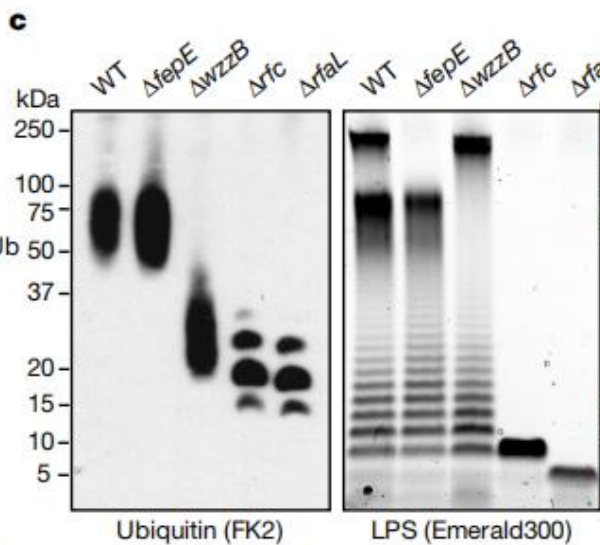
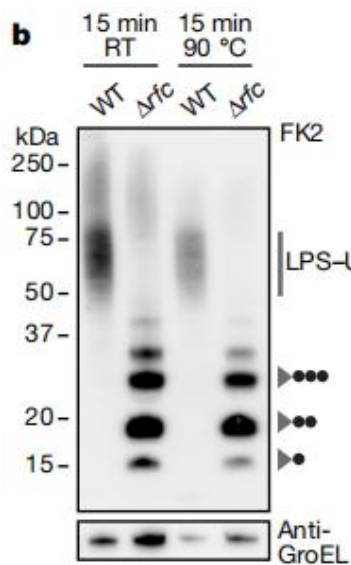
Nat Cell Biol. 2009 May;11(5):527-34

1. Ubiquitylation of LPS



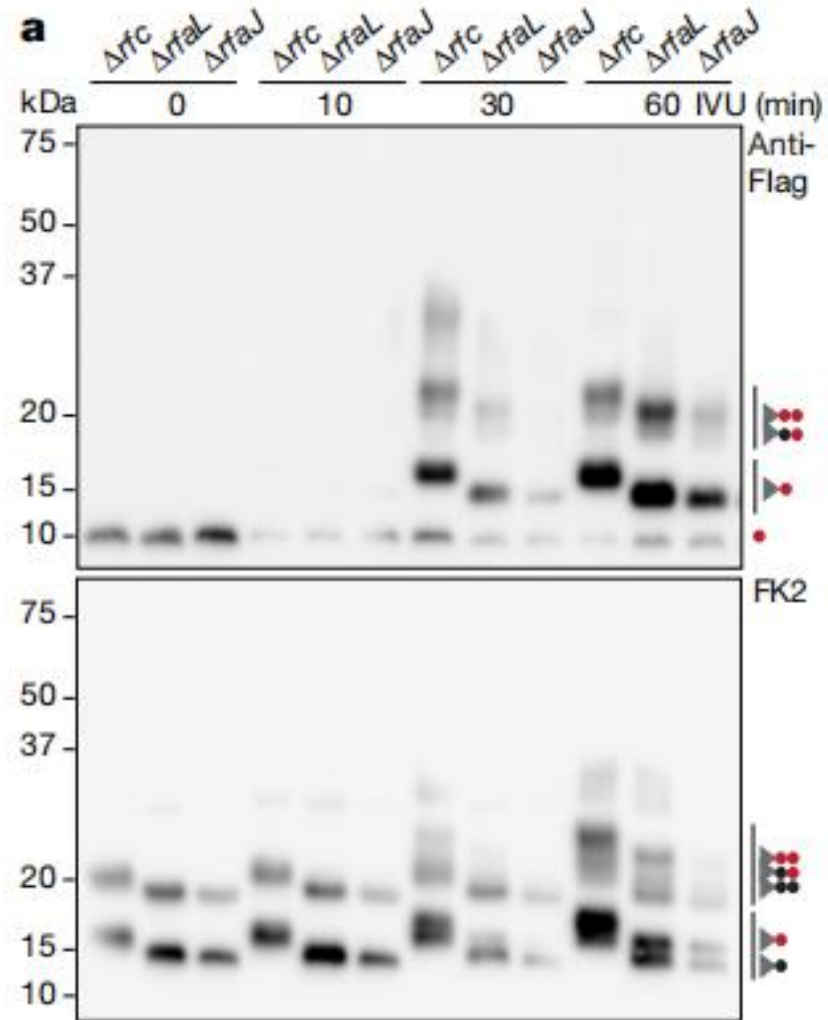
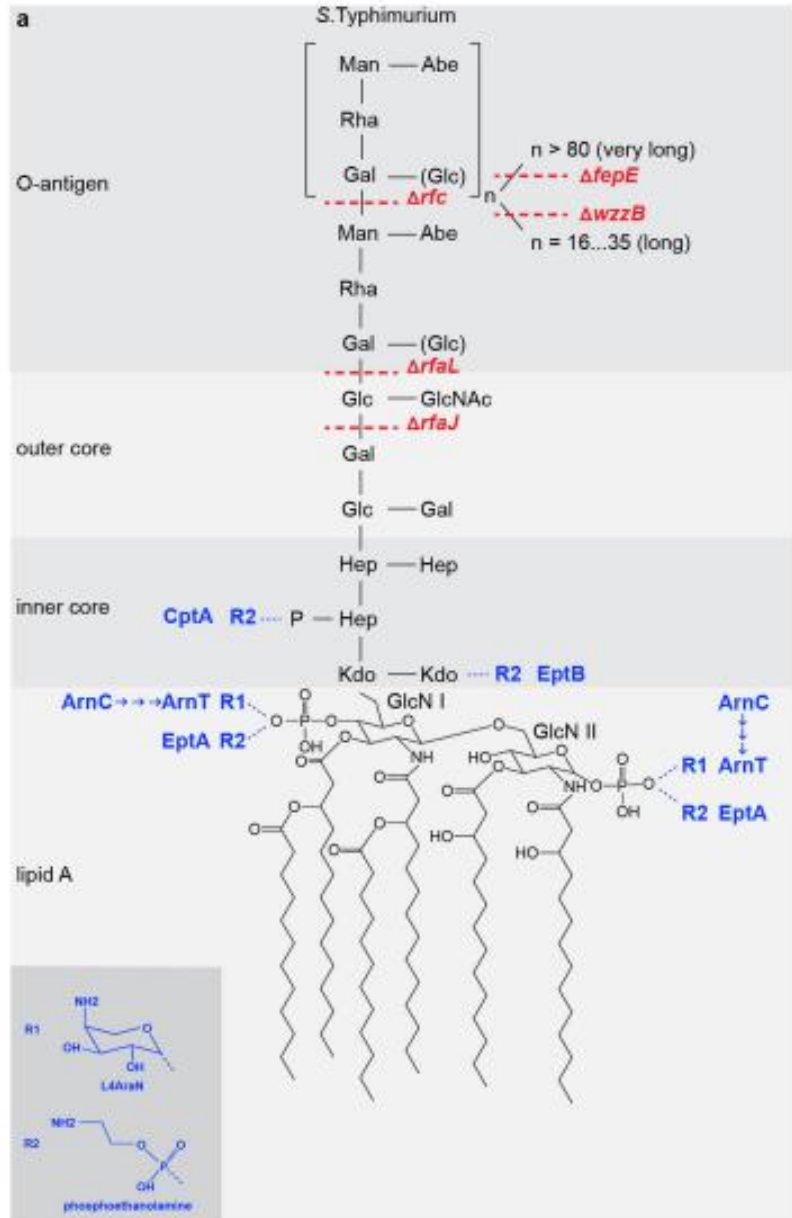
LPS: 脂多糖
FK2: 泛素
Gal8: 半乳糖凝集素8

灰色三角形:
Δrfc LPS
黑点: 泛素
红点: HA-泛素



综上所述，研究结果证明了LPS在入侵细胞质细菌的泛素化，这一发现将泛素化范围从翻译后蛋白质修饰扩展到一个完全不同的生物分子（非蛋白质底物）。

2.RNF213 is required for ubiquitylation of LPS

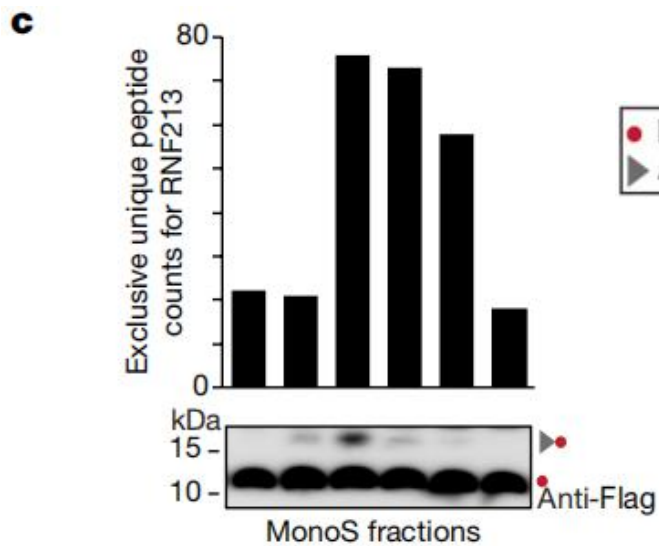
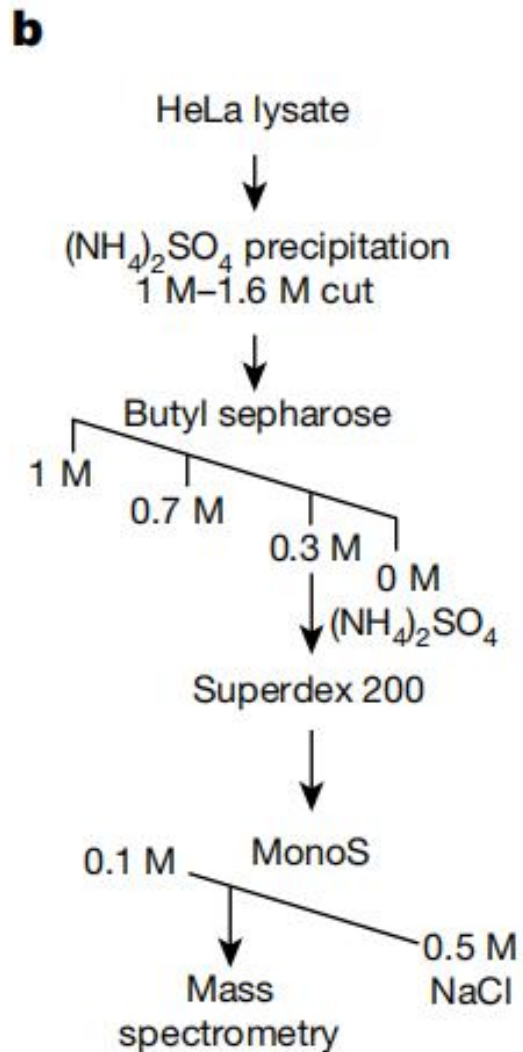


体外重建LPS泛素化作用

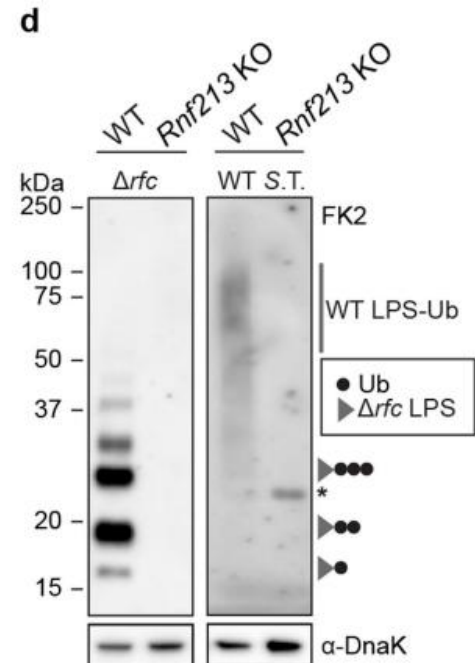
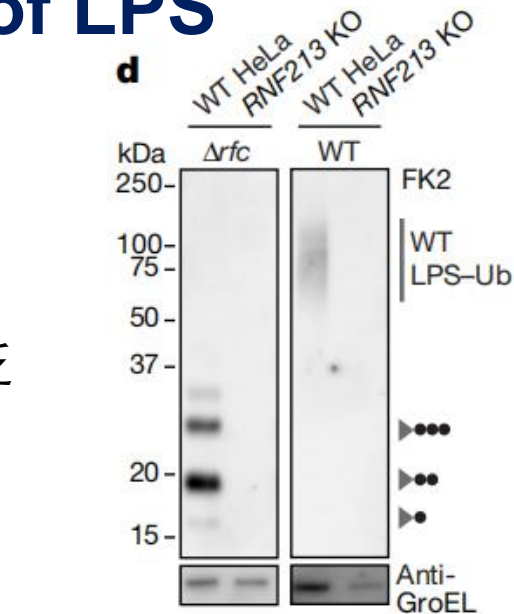
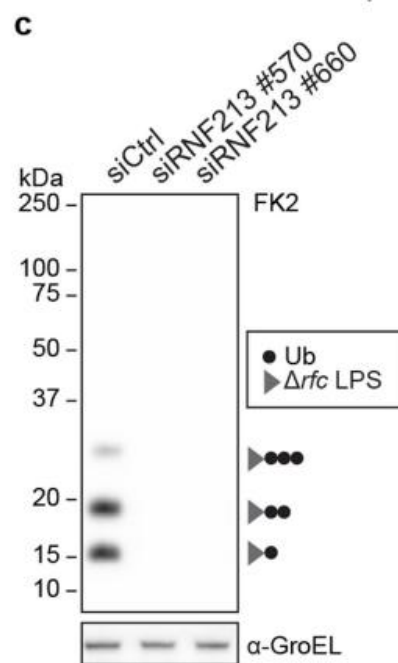
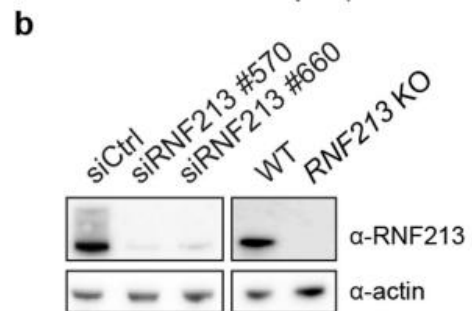
灰色三角形: LPS
黑点: 泛素
红点: FFlag-泛素



2. RNF213 is required for ubiquitylation of LPS



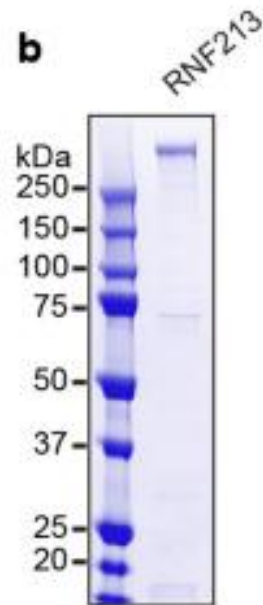
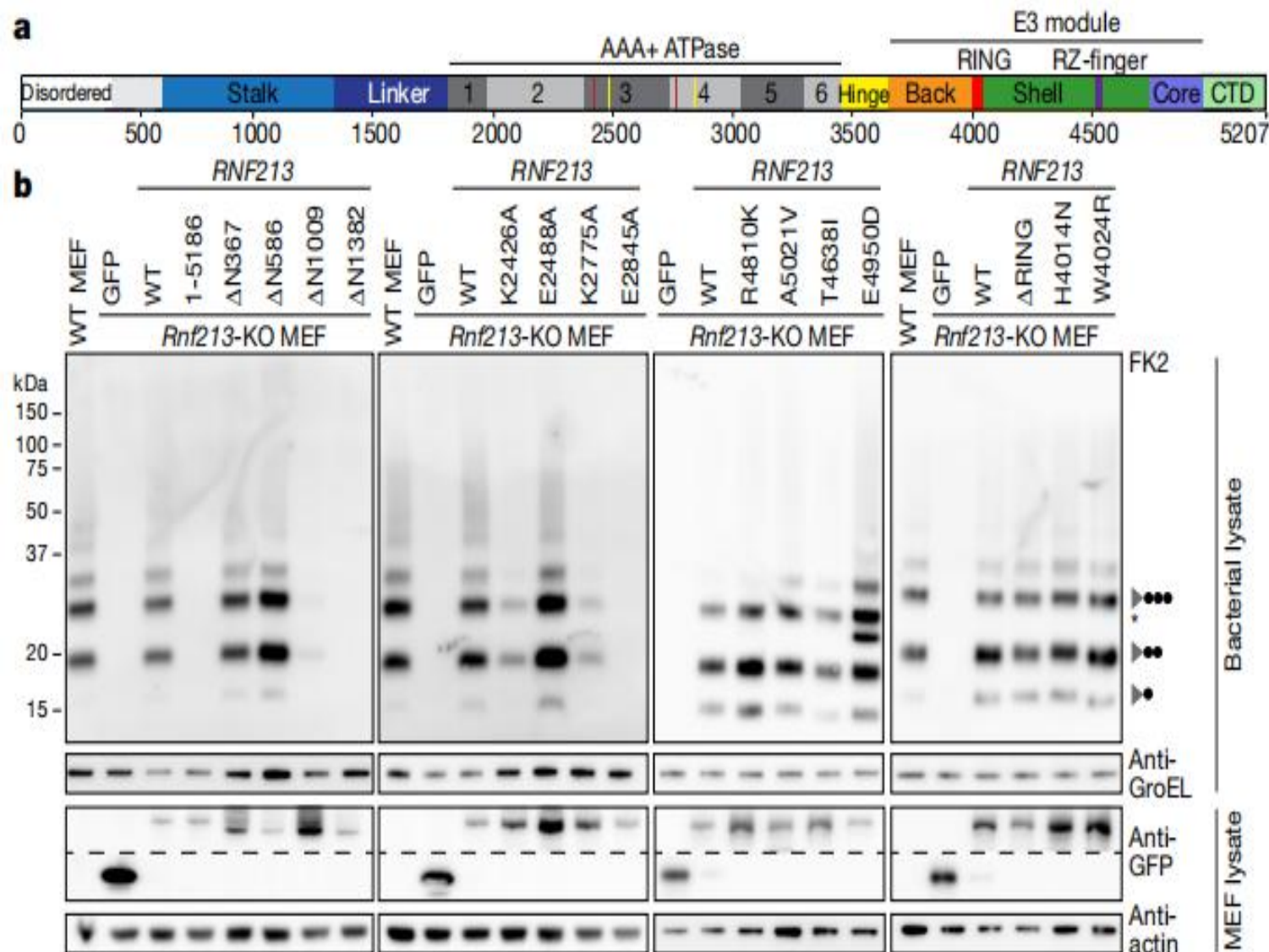
鉴定产生LPS泛素化的酶是RNF213



揭示了RNF213在入侵细胞质细菌上泛素化LPS的重要作用。



3. Ubiquitylation of LPS by RNF213 is a RING-independent, RZ-finger-mediated reaction



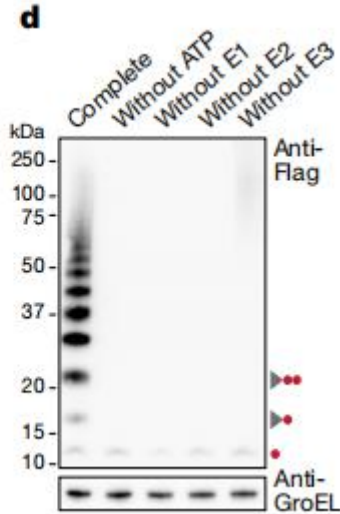
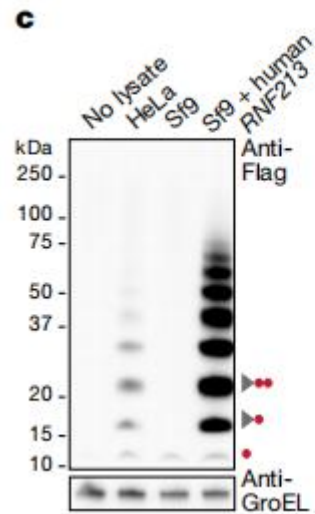
RNF213是导致人类烟雾病的主要易感基因，烟雾病是一种脑血管疾病，由RNF213定位于RING周围结构域错义突变引起的，RNF213能够参与细胞死亡和脂滴形成和信号转导。

灰色三角形：
Δrfc LPS
黑点：泛素

结果显示：RNF213介导的LPS在细胞质鼠伤寒杆菌上的泛素化需要具有催化活性的动力蛋白样核心模块，但不依赖于RING结构域，与之前RNF213非RING自泛素化报道一致。

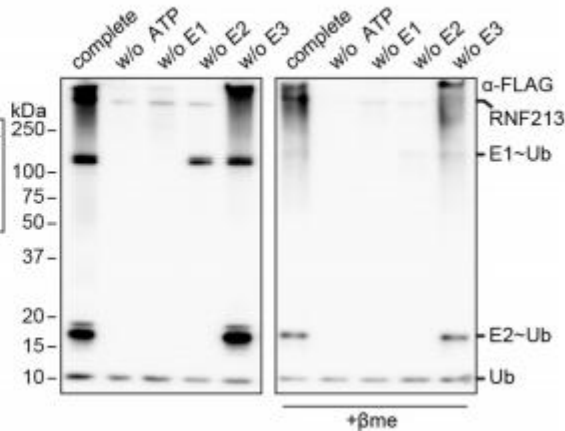
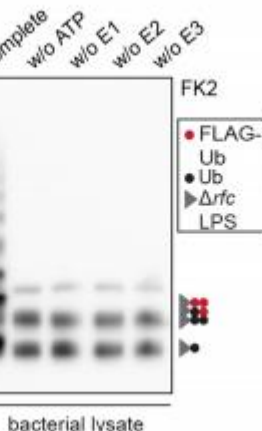
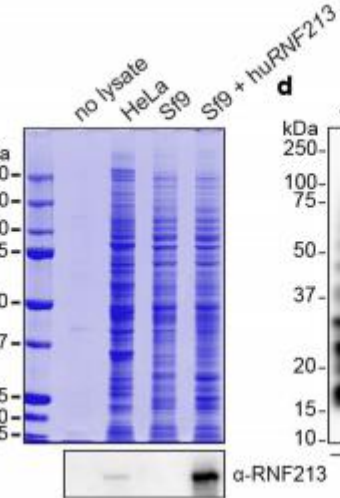
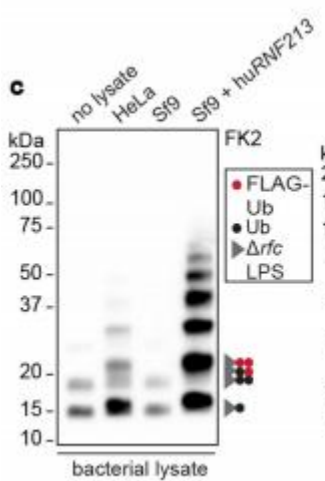
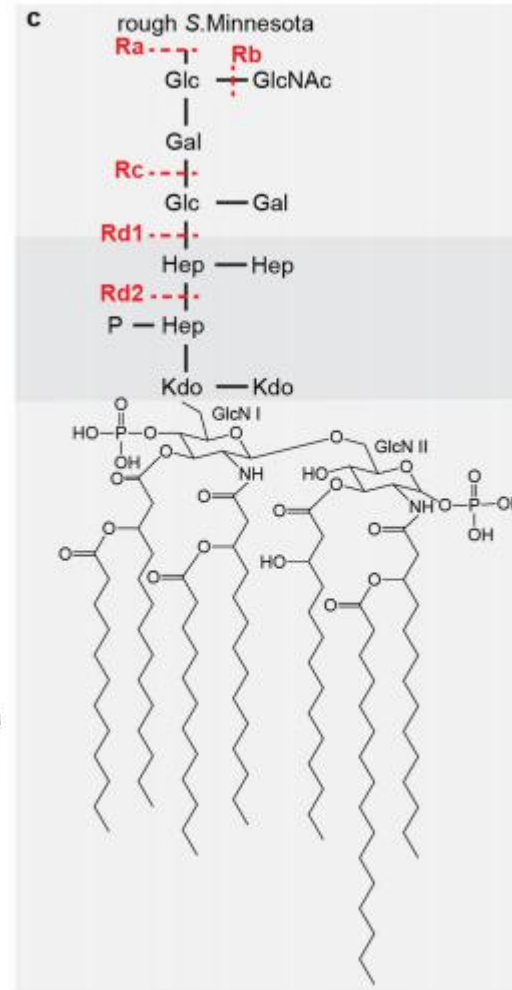
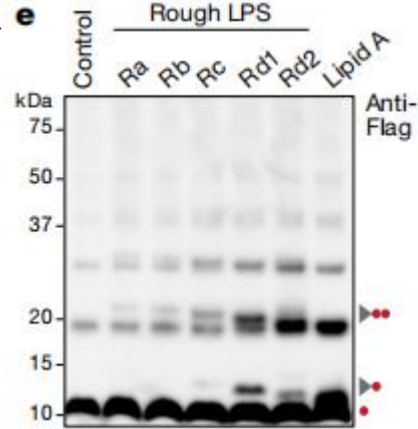


3. Ubiquitylation of LPS by RNF213 is a RING-independent, RZ-finger-mediated reaction



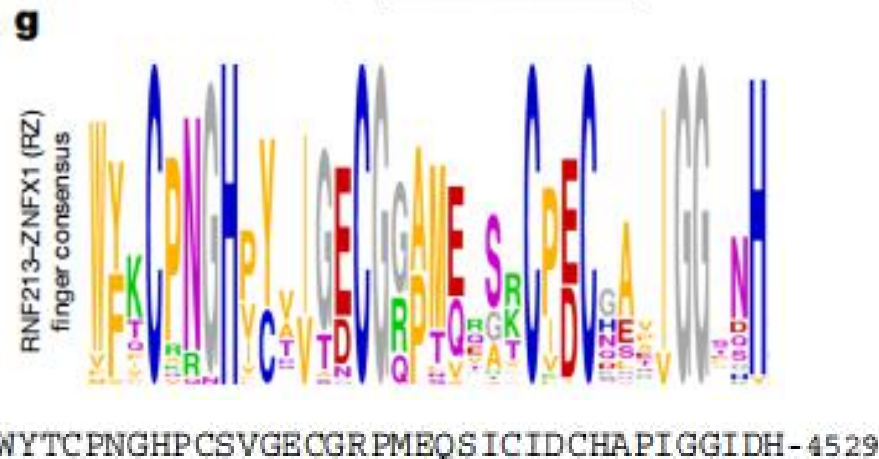
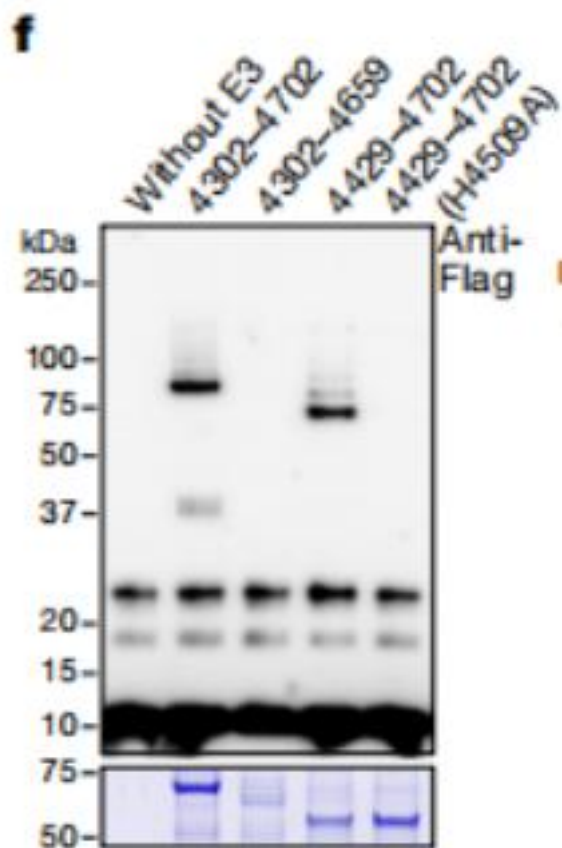
体外重建RNF213介导的LPS泛素化作用

灰色三角形：
(c, d) Δrfc LPS
(e) LPS和脂质A
红点：HA-泛素

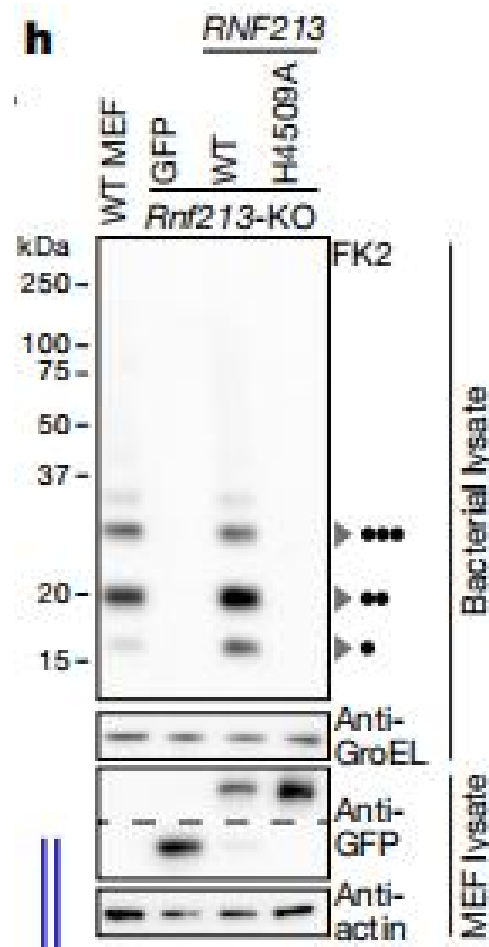


综上所述：脂多糖脂质A部分的泛素化是由RNF213的RING独立的E3连接酶活性介导的

3. Ubiquitylation of LPS by RNF213 is a RING-independent, RZ-finger-mediated reaction



E3模块中4502-4529这27个氨基酸与ZNFX1含锌指蛋白序列相似，这是一种干扰素诱导的RNA解旋酶，具有抗病毒功能，因此这一段命名为RNF213-ZNFX1指（RZ指）。

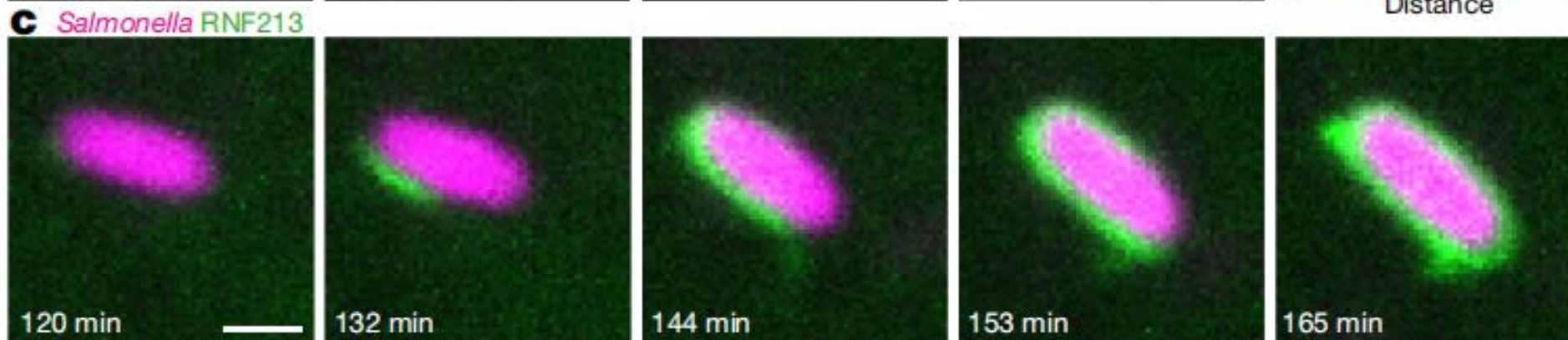
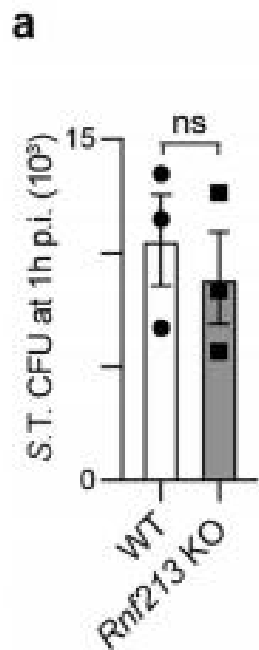
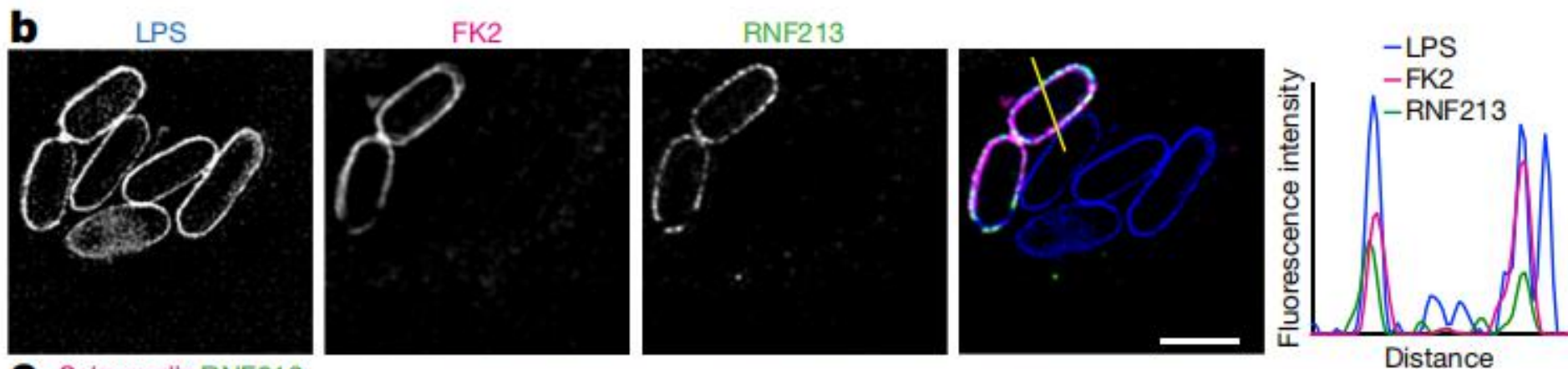
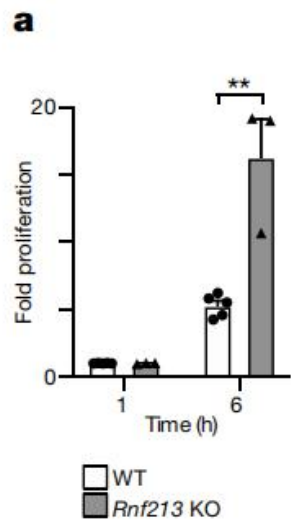


上述结论是RNF213对LPS泛素化是一种独立于RING的RZ指介导的反应。

4. RNF213 provides cell-autonomous immunity

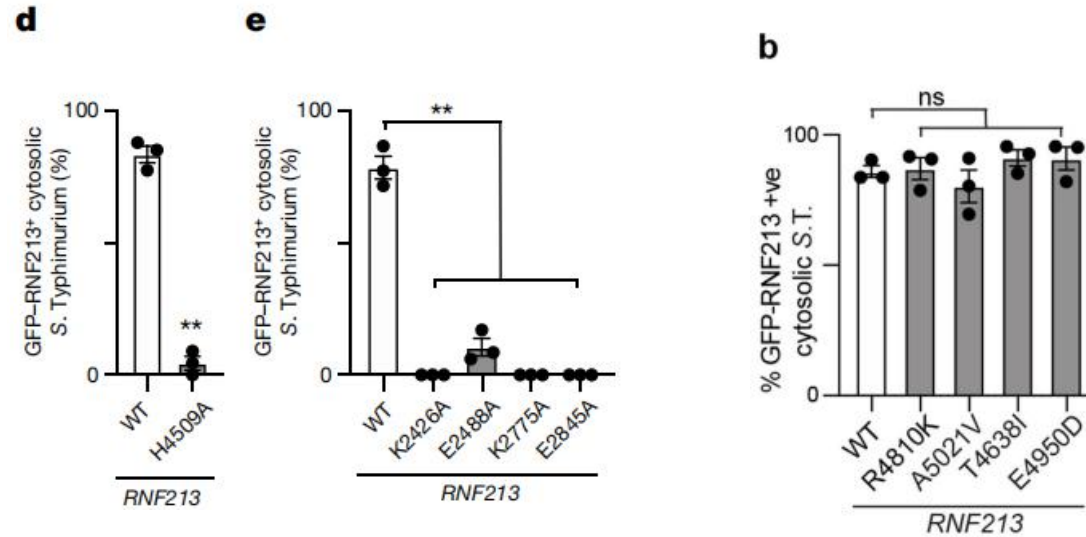


验证单细胞活体检测RNF213对细胞自主免疫的功能重要性

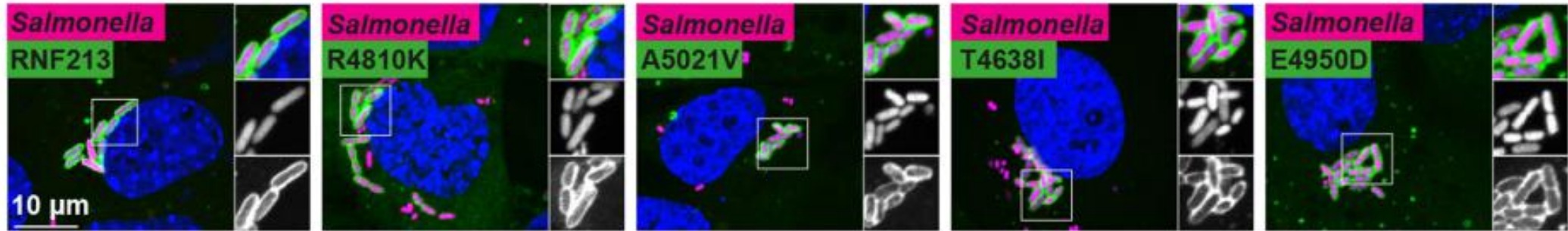




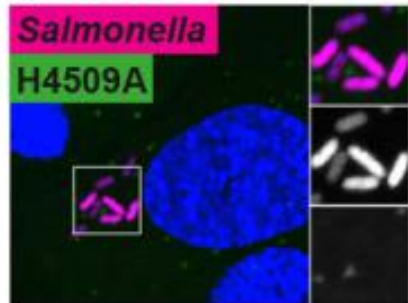
4. RNF213 provides cell-autonomous immunity



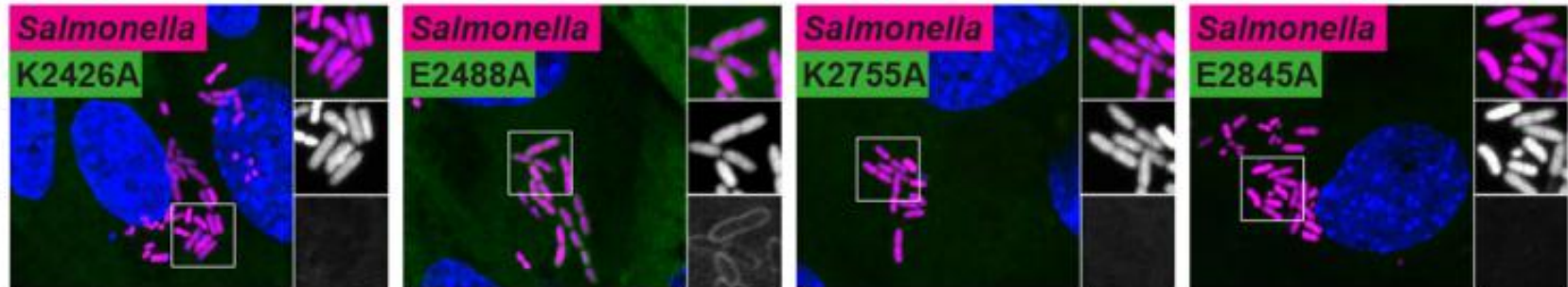
c



d

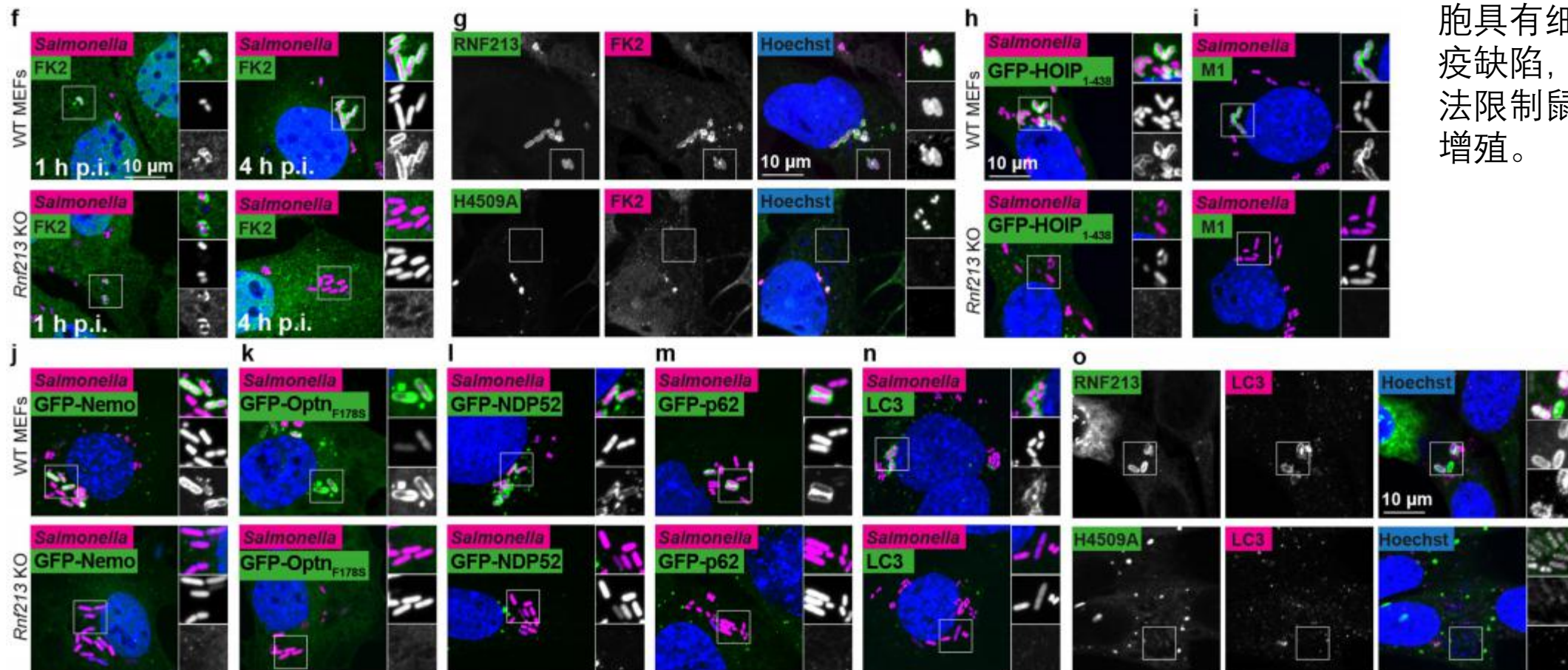
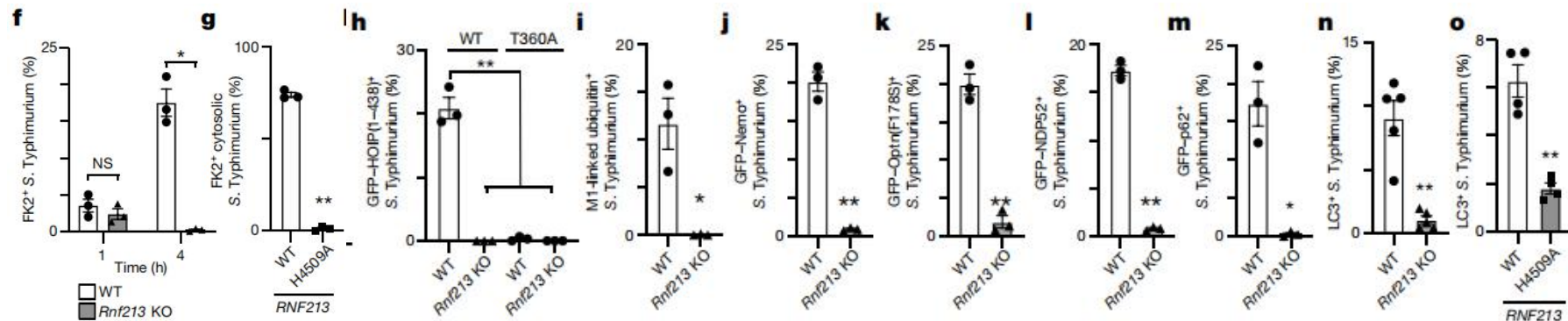


e





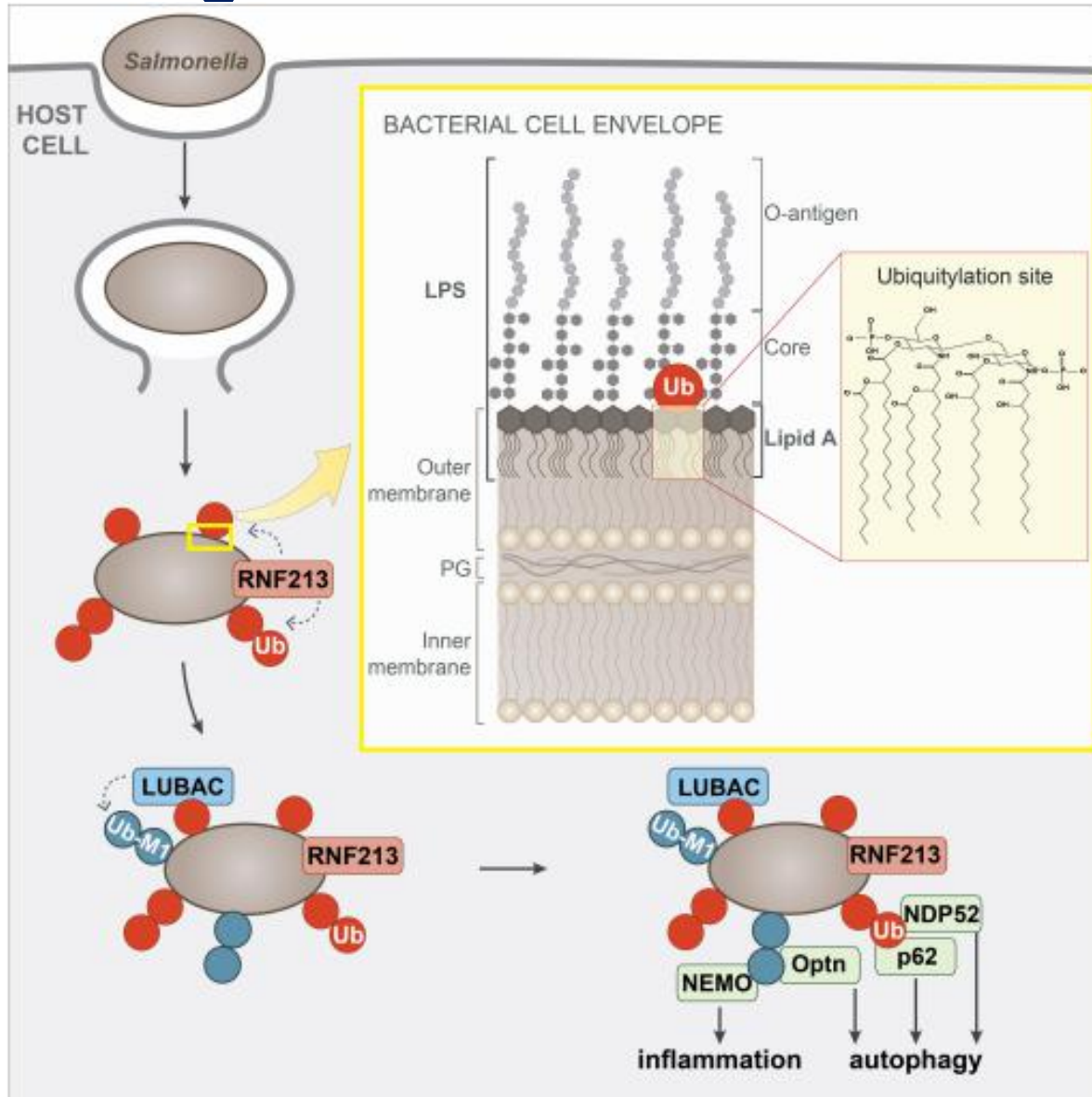
4. RNF213 provides cell-autonomous immunity



上述结论是RNF213对细菌泛素外壳生成至关重要，而缺乏RNF213存在的细胞具有细胞自主免疫缺陷，表现为无法限制鼠伤寒杆菌增殖。



5. Model of RNF213-mediated ubiquitylation of LPS during bacterial infection



细菌感染宿主细胞过程中RNF213直接或者间接介导的LPS泛素化模型，是对本篇文章所诉内容的总结示意图。

本文中发现的LPS泛素化的范围扩大了泛素化的范围，超出了翻译后蛋白修饰的范围。进一步表明非蛋白质泛素化底物可能存在于细胞质入侵病原体 and 宿主细胞。