

BACTERIAL MENINGITIS

Basic Science review of Host-Pathogen interactions

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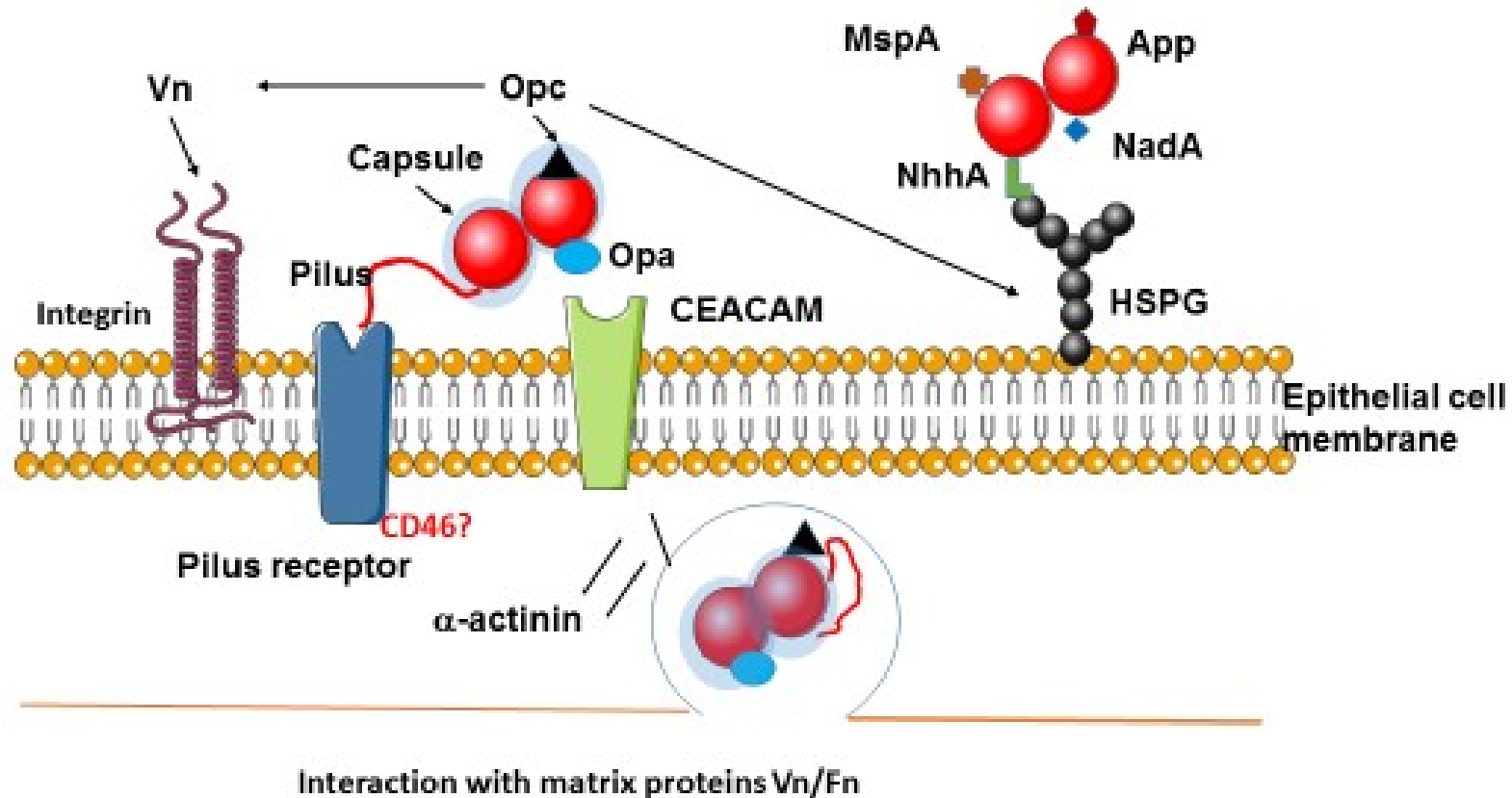
A brief introduction to bacterial meningitis

1. Bacterial meningitis is a serious health threat worldwide with a case fatality rates ranging from 10% to 50% and reaching 100% if left untreated.
2. *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Hemophilus influenzae*, Group B. *streptococcus* and *Listeria monocytogenes* account for 85% of meningitis cases in infants and adults.
3. Other bacteria that cause meningitis include *Escherichia coli* K1, *Salmonella*, *Klebsiella* spp., *Staphylococcus aureus*, and a zoonotic pathogen *Streptococcus suis*.
4. *Mycobacterium tuberculosis* (Mtb) also cause meningitis in 1% of all TB cases. Mtb-meningitis affects all age groups, but very common in young children and in people with untreated HIV-infection.
5. Despite treatment with effective antibiotics and required supportive care, 50% of survivors suffer neurological complications such as mental retardation, hearing loss, and learning deficits.

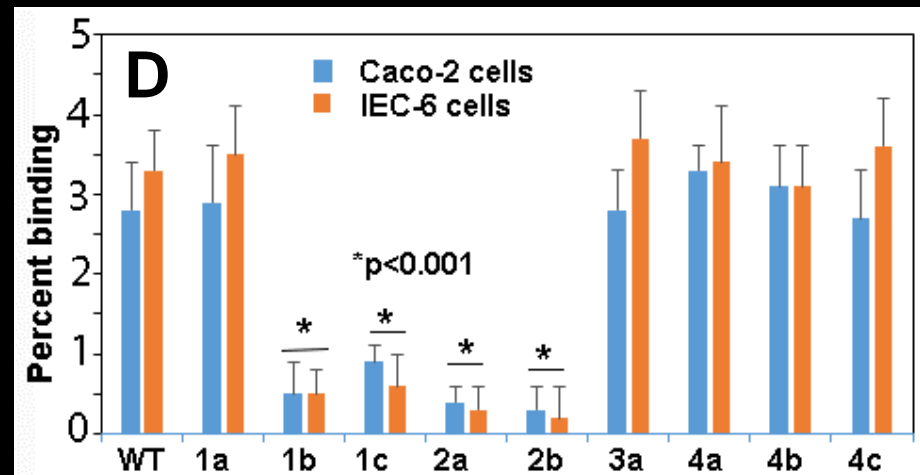
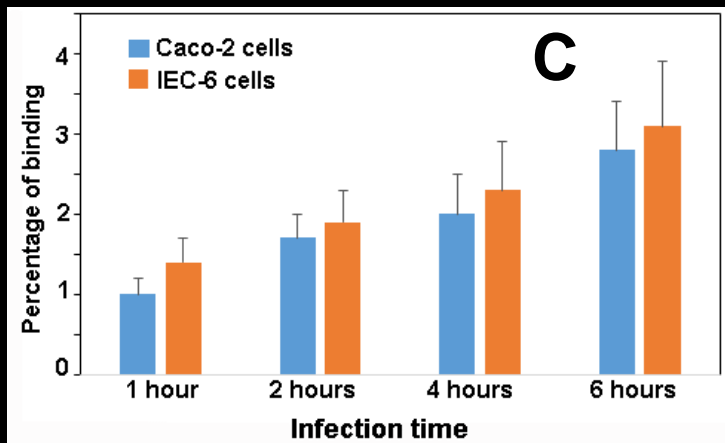
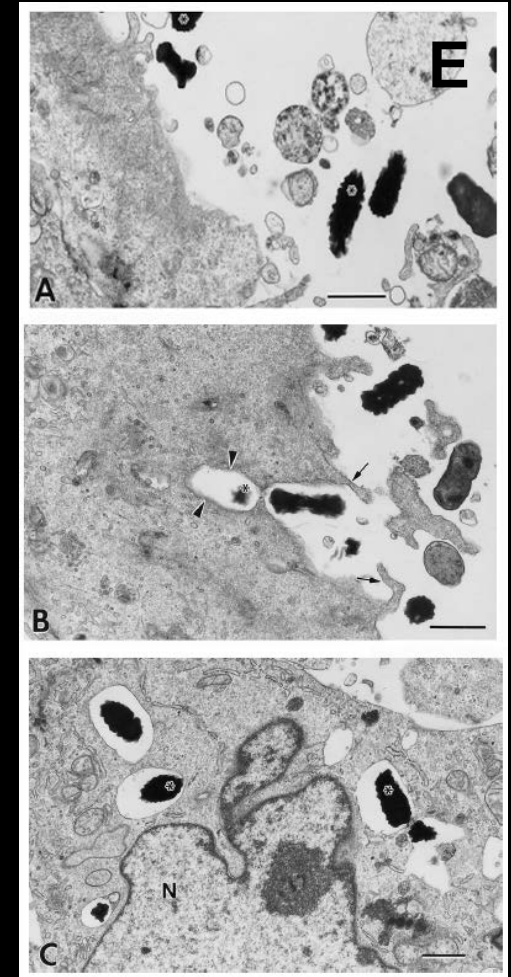
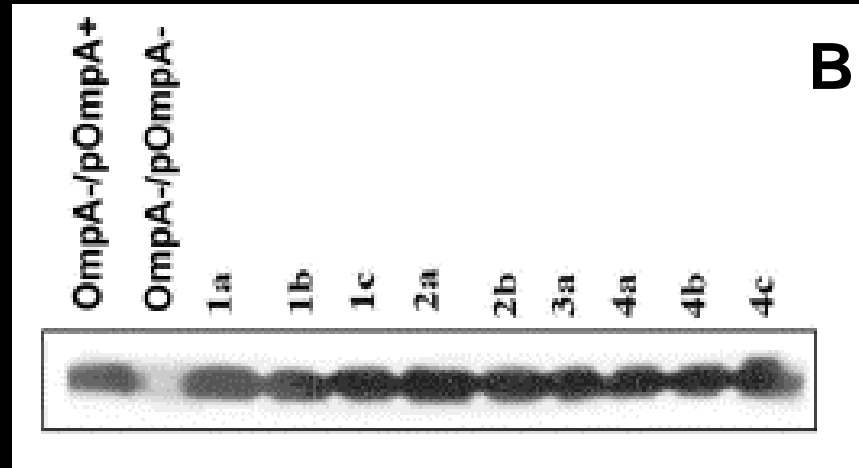
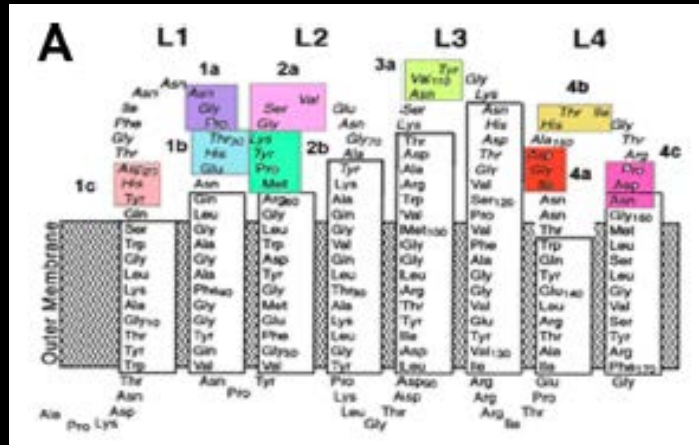
Major steps and mechanisms involved in the pathogenesis of meningitis

	NM	SP	GBS	EC	Mtb
Colonization	Nasopharynx	Nasopharynx	Hematogenous Nasopharynx	Hematogenous Nasopharynx/GIT	Lung Hematogenous?
	Common inhabitant	Common inhabitant	Colonizer of female genital tract	Nosocomial infections/environmental	Inhalation
	Capsule, Pili, Outer membrane proteins	Capsule, cell-wall proteins, cytolysin	Cell-wall anchored proteins, capsule, LTA, pili, cytolysin.	OmpA, Capsule, CNF-1, Fimbriae, IbeA	HABA
Survival in blood	Complement inhibition, PMN-killing	Complement inhibition	Complement Inhibition, intracellular survival	Compl. inhibition, PMN & MΦ intracellular survival	Compl. Inhibition?, PMN & MΦ intracellular survival
CNS entry	B-CSFB Pili, Opa proteins	BBB B-CSFB P-choline pneumolysin	BBB Pili, LTA, other adhesins	BBB Fimbriae, Omps, CNF-1	BBB Several genes are required for entry

NM interaction with epithelial cells of nasopharynx



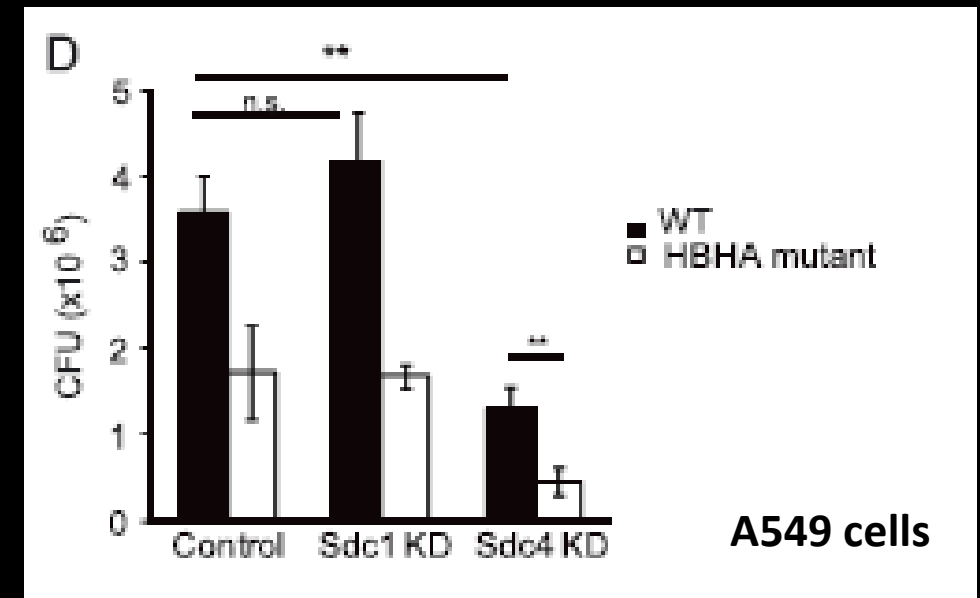
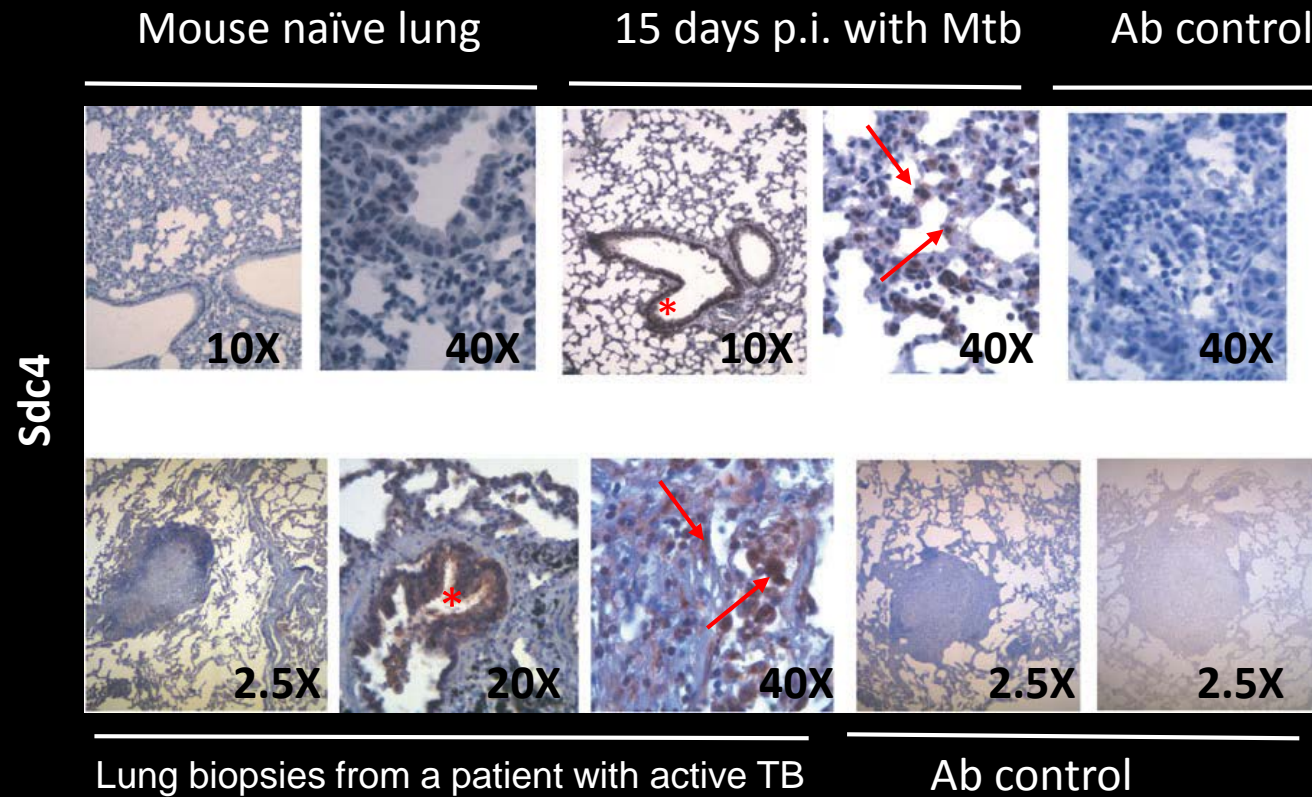
E. coli K1 interaction with epithelial cells



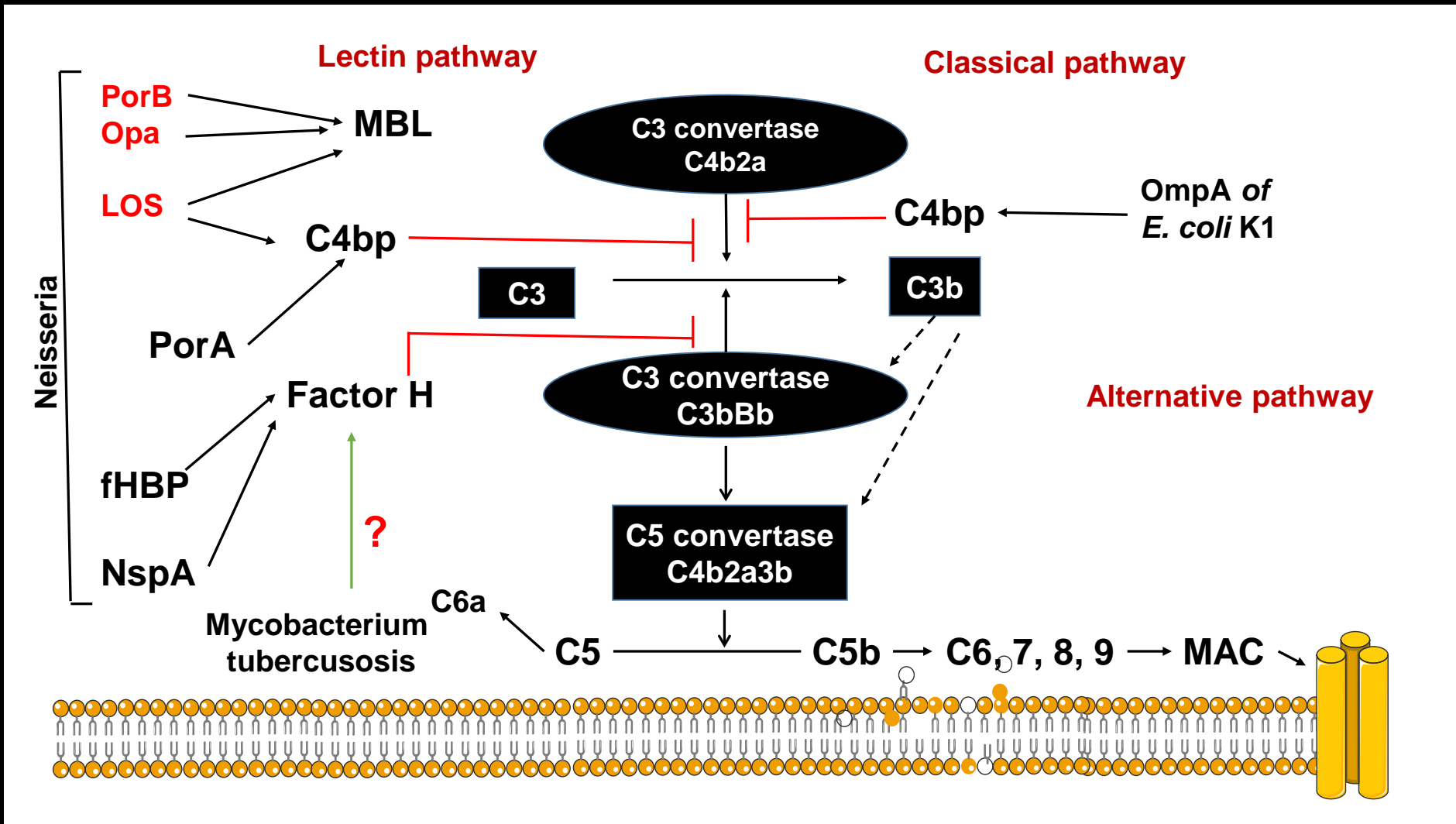
EC: Mittal et al., J. Biol. Chem. 286, 2183-93, 2011 and unpublished results

Figure B, reused from Burns et al., Pediatrics Research, 49, 30-37, 2001, (Copy Right permission obtained)

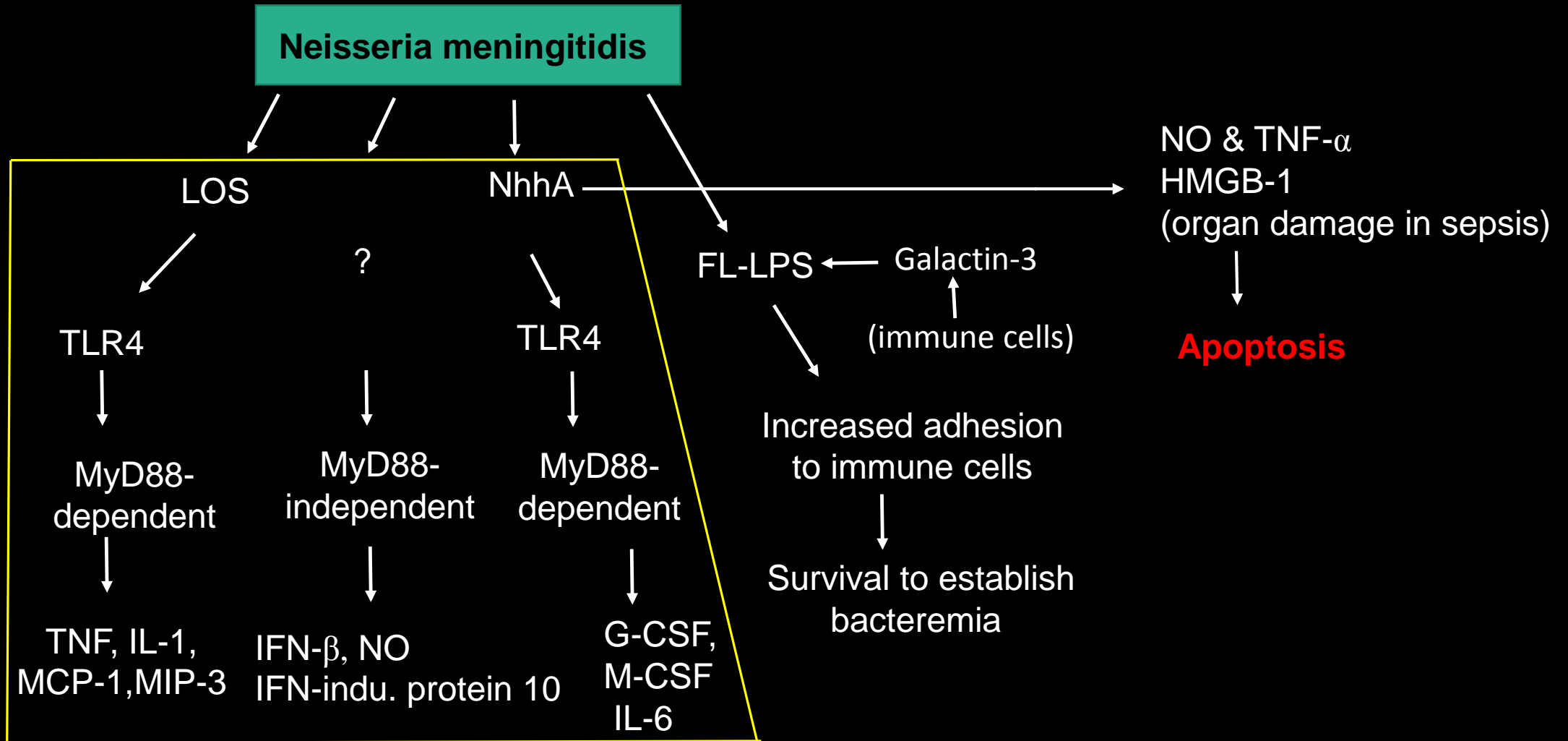
Syndecans are involved in Mtb attachment to lung epithelial cells



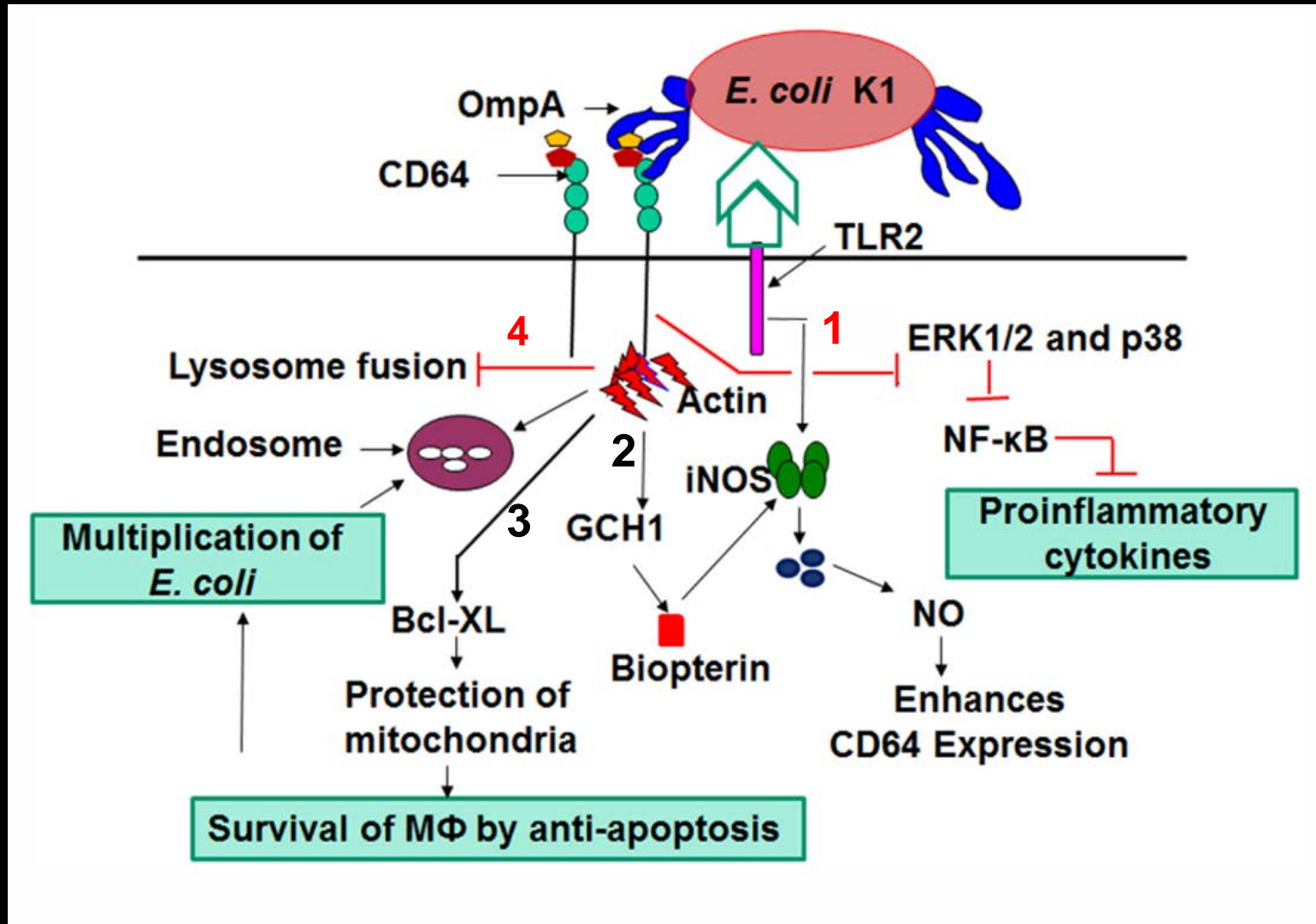
Complement evasion strategies of meningitis-causing bacteria



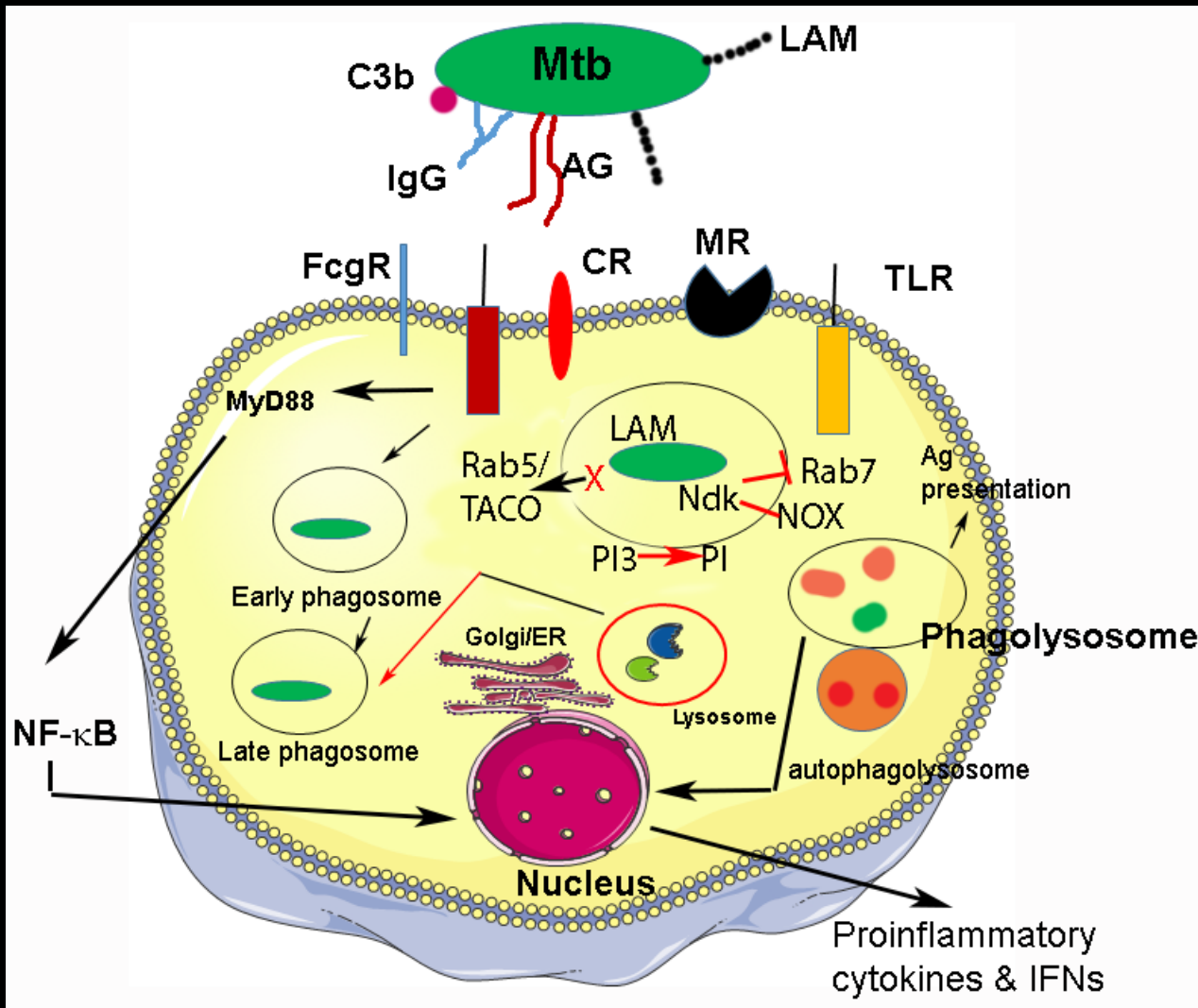
NM survival in monocytes and macrophages



E. coli K1 entry and survival mechanisms in macrophages



Mechanisms of Mtb entry and survival in macrophages



TLR2: LAM, LM, 38- and 19-kDa (LpqH) mycobacterial glycoproteins, PIM, triacylated (TLR2/TLR1), or di-acylated (TLR2/TLR6) lipoproteins, chaperon proteins

TLR4: Tetra-acylated LM, HSP65, 50S ribosomal protein

TLR9: CpG DNA

MR: Mannose (LAM and manLAM)

Fc γ R: Fc-gamma receptors

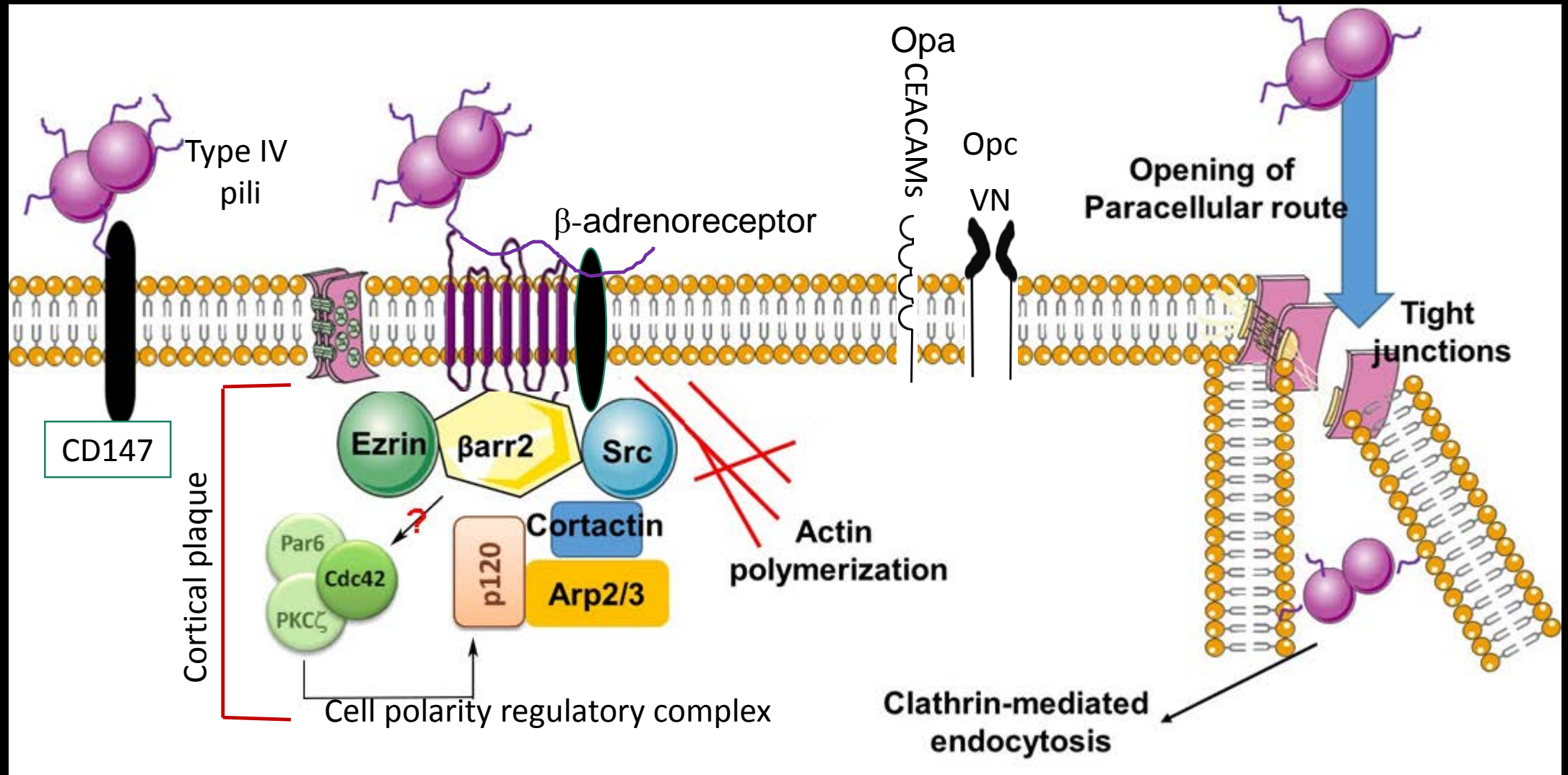
CR: Complement receptors

Autophagy is another mechanism by which macrophages recognize Mtb antigens on cell surface.

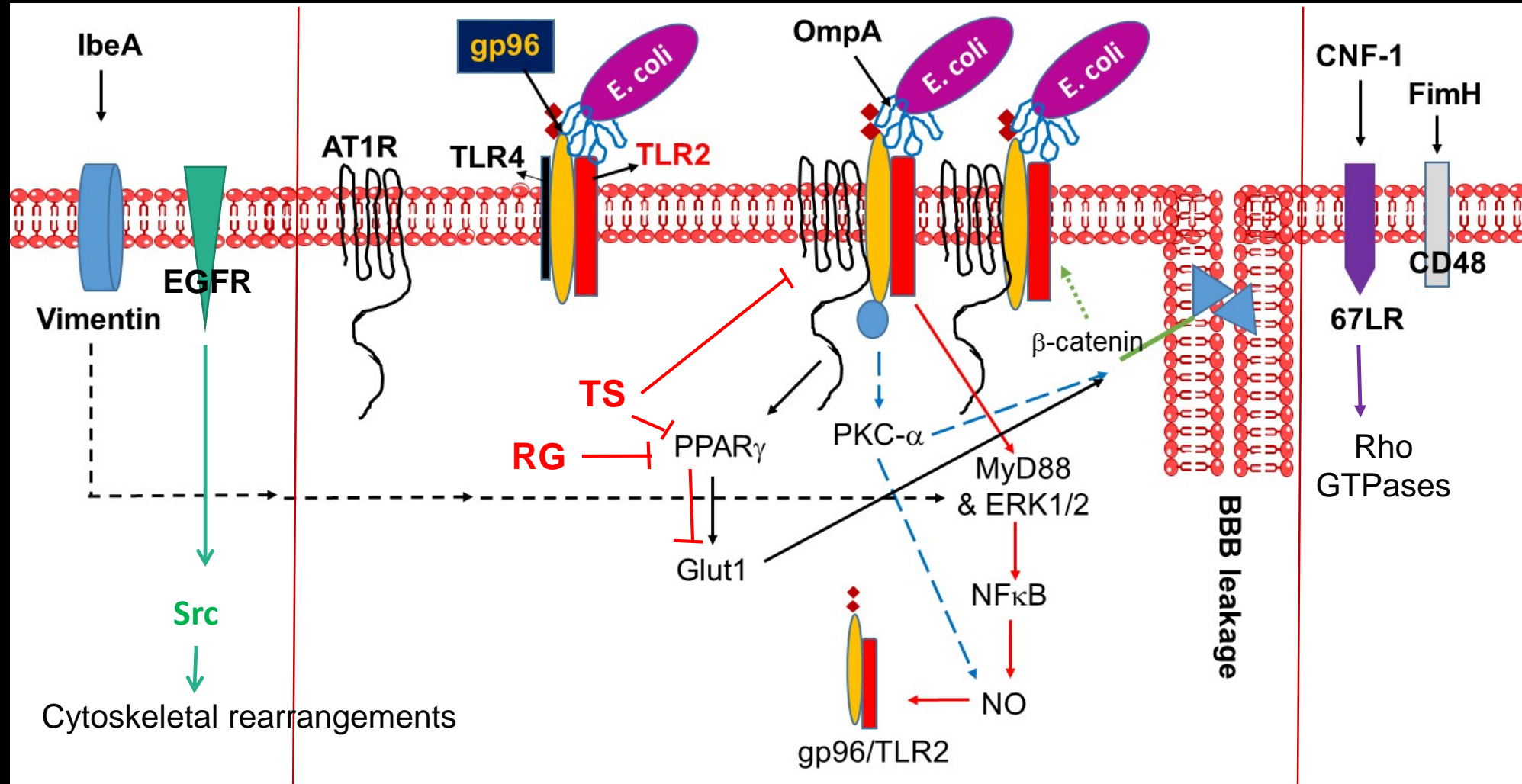
Mechanisms of Mtb inhibition of phagosome maturation include:

1. Prevention of Rab5 recruitment
2. Deactivation of PI3K
3. Ndk (Mtb nucleoside diphosphate kinase) interact with Rac1 and blocks NOX2 assembly (mechanism is not clear).
4. Ndk also blocks the fusion of Rab7.

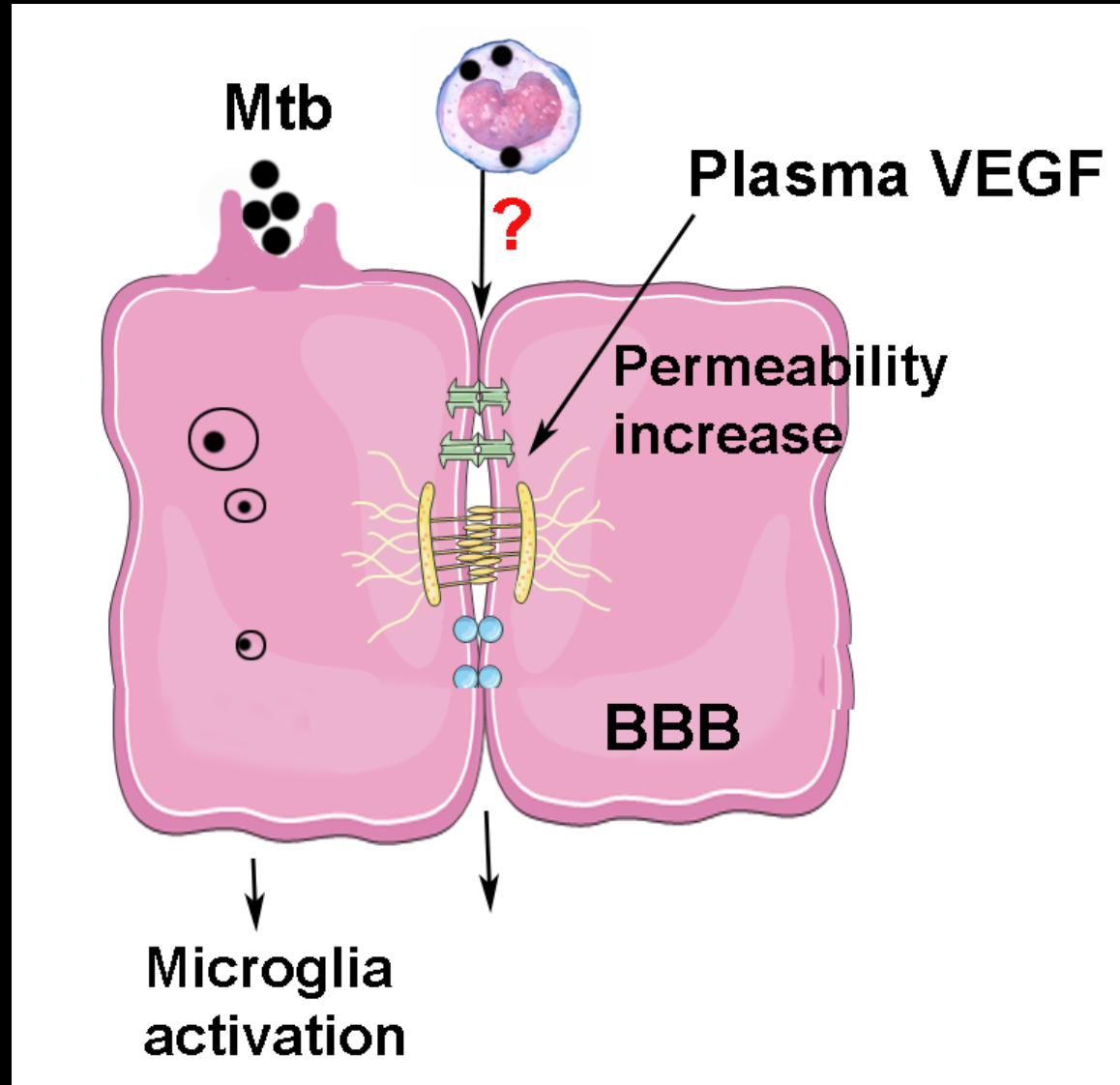
NM binding to and invasion of brain endothelial cells



Invasion mechanisms involved in *E. coli* K1 crossing of the BBB



Mtb invasion of brain endothelial cells



Summary of overview of bacterial meningitis

	Infection stage	Bacterial pathogens	<i>Mycobacterium tuberculosis</i>
1.	Entry into the host	Asymptomatic colonizers of nasopharynx, female genital tract or GIT	Inhalation of droplets containing Mtb
2.	Colonization	Mucosal epithelial cells	Lung epithelial cells
3.	Complement evasion	Binding to C4bp or FH	Mechanism unclear (C4bp?)
4.	Immune cell interaction	Binding to receptors to avoid killing by different immune cells by altering their function.	Prevents phagosome maturation
5.	Interaction with the BBB	Several bacterial ligand-interactions with BMEC receptors. Cytoskeletal rearrangements required	Bacterial ligands and their cognitive receptors are not known. Cytoskeletal rearrangements required

THANK YOU FOR YOUR ATTENTION