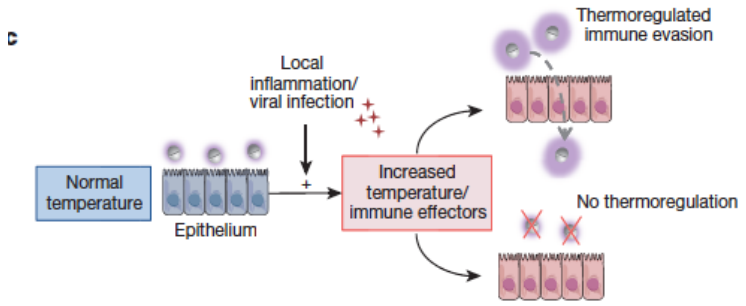
Temperature triggers immune evasion by *Neisseria meningitidis*

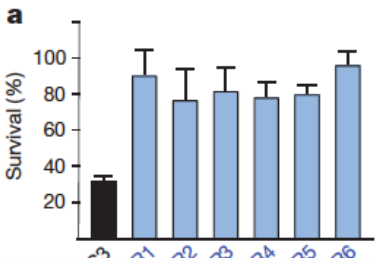
Loh et al., Nature 502:237-40, 2013

How does a commensal pathogen survive when another pathogen activates the immune response ?



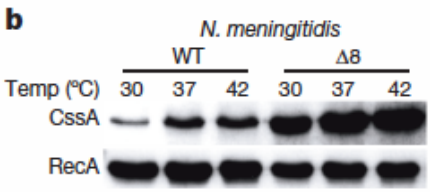
Neisseria meningitidis is a **commensal pathogen** present in the nose or throat of approximately 15% of the population. This pathogen can cause, in rare cases, sever septicemia with *purpura fulminans* and meningitis. One of the major virulence factors is the **production of a capsule**, which allows escape of the immune response by avoiding complement activity. Several capsular serotypes exist. In Switzerland the predominant serotype is type C, against which a vaccine exists. Meningococcal meningitis is most frequent in periods preceded by flu outbreaks or in conditions with reduced resistance, amongst children younger than 5 years and in young adults. Other virulence facors are actor H binding protein and sialylated LPS.

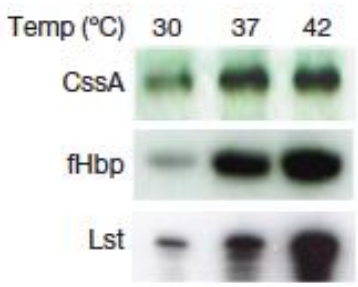
Factor H down-regulates the alternate pathway of complement activation by binding to the host cells, thereby protecting self and leaving the complement available for the anti-pathogen response. By recruiting Factor H through a binding protein fHbp, pathogens like *S. pyogenes*, *H. influenzae* b, etc., they prohibit complement action on themselves.



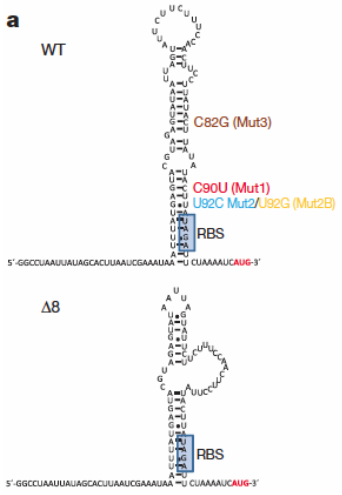
LPS is a powerful endotoxin that activates the innate immune response to clear infections by Gram-negative bacteria. By sialylation of LPS by Lst (lipopolysaccharide sialylation protein), the bacteria will mimic sialylated host tissue and therefore avoid clearing by the innate immune response.

In the paper by Loh et al. a *Meningococcus* was cultivated for several passages in serum to select for resistant strains. Out of 6 isolates, five had a 8bp repeat deletion in the upstream region of a capsule biosynthesis gene causing increased expression of a capsule synthesis protein (Css). The expression of the mutant gene was less dependent on temperature, compared to the wt gene, a situation that could be recapitulated in a heterologous host. A **secondary structure** suggested a **thermosensor** that **sequesters** the **ribosome-binding site** at lower temperature. A similar situation was described earlier for prfA, a transcription factor for the expression of virulence genes in *Listeria monocytogenes* (Johansson et al., 2002). In accordance with this prediction, mutations that weaken the secondary structure favor the temperature independence, whereas complementary mutations retain the dependence, suggesting that the structure, rather than the sequence are important for the regulation.

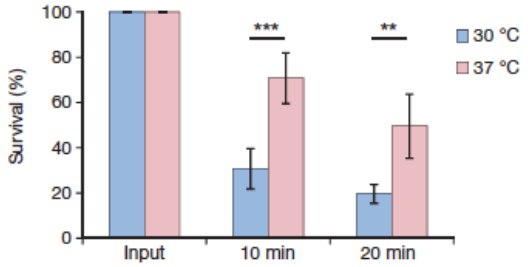




Similar to CssA (capsule biosynthesis), fHbp (Factor H binding protein) and Lst (lipopolysaccharide, LPS, sialylation) proteins show higher expression at 37°C than at 30°C, compared to control genes.



The question remains, why *N. meningitides* would circumvent the innate immune response, since a dead host is an end without issue and contra productive for the obligatory commensal bacterium. One hypothesis given by the authors is that the bacterium attempts to avoid the immune response initiated by the flu virus. Consistent with this, pretreatment at 37°C increases the survival of the bacterium in serum.



Reference: An RNA thermosensor controls expression of virulence genes in Listeria monocytogenes. Johansson J, Mandin P, Renzoni A, Chiaruttini C, Springer M, Cossart P., Cell. 110:551-61, 2002