Microbial escape of innate immunity

Dubrovnik 1.10.2010

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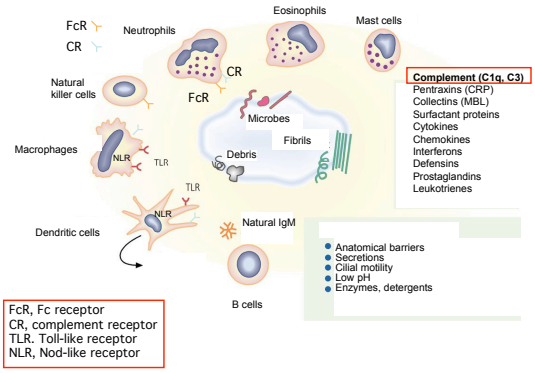
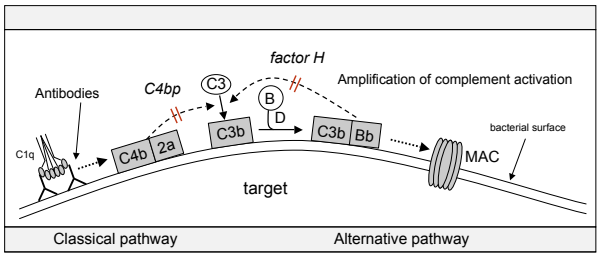
Innate immune defence mechanisms



Complement activation

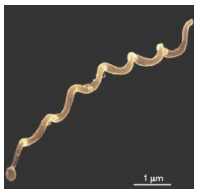


Complement inhibitors: *C4bp, factor H*
MAC, membrane attack complex

Borrelia

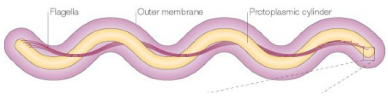
Spirochete

Internal flagella – motile



~10µm long

- Animal disease
- Lyme disease
- Relapsing fever



How can *Borrelia burgdorferi* escape immune attack?

Borreliae can survive in blood and tissues for months

Slow and inefficient phagocytosis

Can vary surface antigens

<u>Basis of serum resistance?</u>

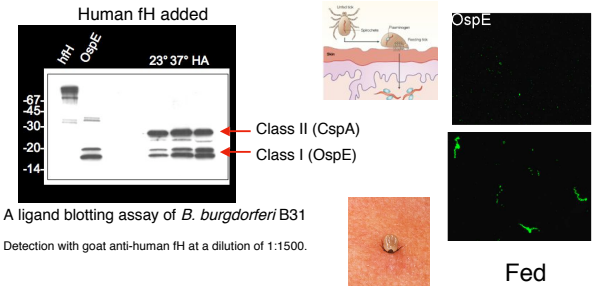
Which molecules are responsible?

Differences between strains?

Regulation of expression ?

Borrelia burgdorferi binds factor H via two proteins

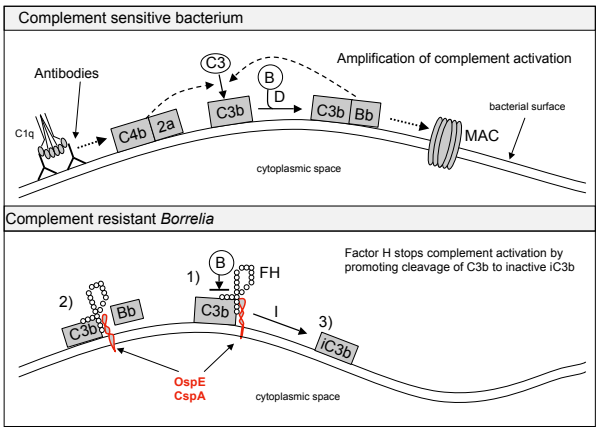
Body temperature (37°C) and host adaptation increase the expression of fH binding molecules



A ligand blotting assay of *B. burgdorferi* B31

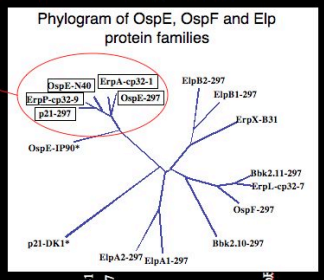
Detection with goat anti-human fH at a dilution of 1:1500.

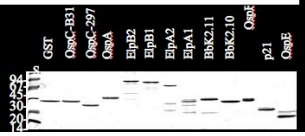
Alitalo et al, I&I 2001, JI 2002, JI 2004; Hellwage et al JBC 2001



Factor H binding by cp32-plasmid-encoded OspE surface proteins from *B. burgdorferi*

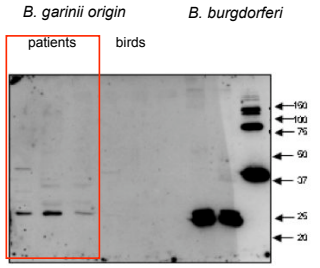
- The OspE/p21/ErpA family proteins (but not OspF or Elps) show factor H binding
- A single strain can have multiple paralogous OspE proteins encoded on separate cp32 plasmids
- The OspE proteins may constitute a family of virulence factors expressed in different hosts





Alitalo et al, J Immunol, 2002, 2004

B. garinii is serum sensitive *in vitro* yet it can cause neuroborreliosis - why ?



Borrelial factor H binding proteins are produced in patients but not under *in vitro* conditions

Meningococcal sepsis and meningitis

- caused by 9 main capsule types, most common: A, B, C, W135, Y
- incidence: ≈ 1/100 000/year
- mortality: 10-20% (WHO: 1.2 mill. deaths/year)
- infants (< 2y) the major risk group
- carriage up to 20% in young adults

Complement and meningococcus

- complement deficiencies (H, P, D, C6, C7, C8, C9) predispose to meningococcal disease (risk ≈1000x)
- GWAS: meningococcal meningitis linked to FH, FHR-3 (chr. 1)
- in complement deficiency meningococcal disease may recur, but is usually milder

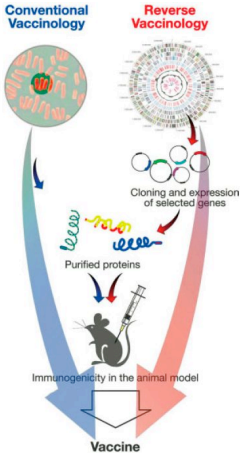
Complement evasion by meningococcus

- binding of C4bp by PorA (Jarva et al, JI, 2005)
- binding of factor H by GNA1870 (Madico et al, JI, 2006)

Meningococcal vaccines

- Existing vaccines
  - capsule vaccines (A, C, W135, Y)
- Problems with menB
  - poorly immunogenic (α2-8 polysialic acid capsule)
  - potentially cross-reactive with human neuronal tissue (Finne et al, 1983)
- potential
  - outer membrane vesicles (OMVs)
  - new antigens from "reverse vaccinology" (Giuliani et al, 2006)

New ways to make vaccines



Pizza & Rappuoli, 2010

New meningococcal vaccines

1. **rMenB** (Novartis)
   -NadA (Neisserial adhesin A)
   -FHBP (GNA1870; factor H binding protein)
   -GNA2091
   -GNA2132 (Neisserial heparin binding antigen)
   -GNA1030
   - now in phase 2b and 3 trials in infants, toddlers and adolescents

2. **rLP2086** (Wyeth)
   2 (out of 3) variants of FHBP
   - in phase 1 and 2 trials in infants

Challenges for a men B vaccine

1. Immunogenicity in infants

2. Variations in the vaccine antigens

3. Strong binding of factor H by FHBP
   - masking of important epitopes

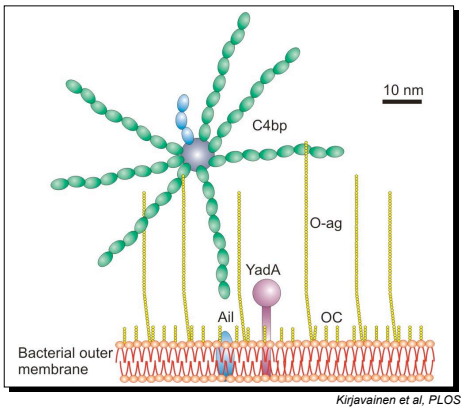
Microbial inhibitors of complement as vaccine candidates

Microbe	Interacting protein	Key structural feature	Mechanism of action	Variability	Potential as a vaccine
GAS	M-protein	α	H, C4bp	+++	++
GBS	**β (Bac)**	α	H	+	+++
S. pneumoniae	**PspC**	α	H	+++	++
S. aureus	Sbi	α	C3		
B. burgdorferi	**OspE** CspA	 α	H H	+++ +	+ ++
B. pertussis	FHA	β	C4bp	+	++
Y. enterocolitica	**YadA** **Ail**	α β	H, C4bp H, C4bp	++ ++	+ -
Y. pestis	**Pla**	β	E	+	±
S. typhimurium	**Rck** **PgtE**	β β	TCC/FH E	+ +	± ±
N. meningitidis	**GNA1870** **PorA**	β β	H C4bp	++ ++	++ +
N. gonorrhoeae	Por1A Por1B	β β	H, C4bp C4bp	+ +	+ +

α, alpha-helical/coiled-coil; β, beta-barrel; E, enzymatic activity

Meri et al, Vaccine, 2008

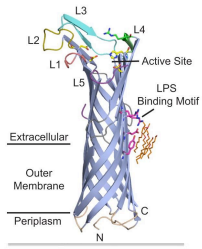
Y. enterocolitica surface



Kirjavainen et al, PLOS Pathog 2008

Pla of *Yersinia pestis*

- outer membrane β-barrel protein
- homologues in omptin family e.g.
  - PgtE of *Salmonella enterica*
  - OmpT *of Escherichia coli*



Eren et al. Structure 2010

Kukkonen et al. (2004) Mol. Microbiol. **51**: 215-225

Microbial tools for complement evasion

Acknowledgements

- **Helsinki, Finland**
  Hanna Jarva, Sakari Jokiranta, Derek Ho, Taru Meri, Antti Alitalo, Jaana Panelius, Timo Korhonen, Rauna Riva, Päivi Ramu, Nathalie Friberg, Kaarina Lähteenmäki, Vesa Kirjavainen, Marta Biedzka-Sarek, Mikael Skurnik, Markus Lehtinen, Arnab Bhattacharjee, Tommi Kajander, Adrian Goldman
- **Malmö, Sweden**
  Anna Blom, Barbara Albiger
- **Würzburg, Germany**
  Markus Jördens, Ulrich Vogel
- **Boston, US**
  Sanjay Ram, Peter Rice
- **Oklahoma City, US**
  Darrin Akins, Chad Brooks
- **Milan, Italy**
  Livija Deban, Barbara Bottazzi, Cecilia Garlanda, Alberto Mantovani
- **Novartis, Siena, Italy**
  Kate Seib, Mariagrazia Pizza, Rino Rappuoli