Molecular pathogenesis of infections caused by *Moraxella catarrhalis* in children

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Summary

Moraxella catarrhalis (*M. catarrhalis*) is a human-restricted commensal of the normal bacterial flora in the upper respiratory tract of children, and – during the previous two decades – has been recognised as a true human pathogen. *M. catarrhalis* is the third most common pathogen causing acute otitis media in children, which is the most common reason to visit a paediatrician during childhood. Acute otitis media thus causes a high clinical and economical burden. With the introduction of the conjugate pneumococcal vaccines the microbiomic pattern in the nasopharyngeal flora of children has changed, and the frequency of isolation of *M. catarrhalis* has increased. Compared to adults, children are more often colonised with *M. catarrhalis*.

Over the last three decades there has been a dramatic increase in the acquisition of β-lactam resistance in *M. catarrhalis*. Today 95–100% of clinically isolated *M. catarrhalis* produce β-lactamase. It is thus desirable to reduce the burden of *M. catarrhalis* disease by developing a vaccine. There are several potential vaccine antigen candidates in different stages of development, but none of them has entered clinical trials at the present time.

Key words: Moraxella catarrhalis; pathogenesis; child

Introduction

Moraxella catarrhalis (*M. catarrhalis*) is an important, exclusively human respiratory tract pathogen. The Gram-neg-

Abbreviations	
AOM	Acute otitis media
CEACAM	Carcinoembryotic antigen -related cell adhesion molecule
COPD	Chronic obstructive pulmonary disease
hag/MID	Human erythrocyte agglutinin/Moraxella immunoglobulin D-binding protein
LOS	Lipooligosaccharide
PCR	Polymerase chain reaction
PRR	Pathogen recognition receptors
RSV	Respiratory syncytial virus
UspA	Ubiquitous surface protein A

ative diplococcus was first described in 1896 and was named *Micrococcus catarrhalis* [1]. In 1963 the pathogen was renamed *Neisseria catarrhalis* [2]. Microscopically *M. catarrhalis* resembles *Neisseria meningitidis* and *Neisseria gonorrhoeae,* but there is only limited chromosomal DNA-homology with these species. Therefore, it was moved to the new genus *Branhamella* as *Branhamella catarrhalis* in 1970 [3]. Its classification as a member of the Genus *Moraxella* as *Moraxella catarrhalis* was established in 1984 and it remained so since that time [4].

Two major phylogenetic subpopulations (type 1 and type 2 strains) of the species have been identified [5, 6]. Wirth *et al.* suggested that the older type 2 subpopulation has existed since ~50 million years, whereas the younger type 1 lineage appeared ~4 millions ago together with *Homo sapiens* [6]. The phylogenetically younger type 1 subpopulation has adapted to the human host, and possesses various virulence factors, such as human complement resistance ("seroresistance") and adherence to human epithelial cells [6]. In a collection of 268 *M. catarrhalis* isolates from diverse geographic regions, 83% of the isolates were found to belong to the seroresistant subpopulation [6]. The seroresistant subpopulation has also been found to be naturally transformation competent [7], which in turn leads to frequent homologous recombination.

In children, *M. catarrhalis* causes mainly upper respiratory tract infections (otitis media), whereas in adults the pathogen causes lower respiratory tract infections in previously compromised airways (acute exacerbation of chronic obstructive pulmonary disease [COPD]). Invasive infections such as bacteraemia, meningitis, septic arthritis, ventriculitis and endocarditis, are very rare and during the past three decades less than 80 cases have been reported (summarised by [8]).

Microbiological diagnosis

Grown on blood agar, colonies of *M. catarrhalis* appear round, gray, opaque and convex and they can easily be pushed intact over the surface. This phenomenon is the so-called "hockey puck sign".

The gram negative diplococcus is difficult to distinguish from *Neisseria spp*. in a typical Gram staining. Various biochemical test methods exist to distinguish the species. *M. catarrhalis* is DNAse, catalase and oxidase positive, and furthermore the pathogen hydrolyses tributyrin and reduces N_2 to NH_3 and is unable to produce acid from glucose, lactose, maltose fructose and sucrose. None of these tests are 100% sensitive or specific. The inforamative value of more sensitive DNA methods such as polymerase chain reaction (PCR) has been demonstrated [9], but as of today commercially available PCR assays are not available.

Epidemiology, colonisation and immune response

M. catarrhalis colonises the nasopharynx in early childhood [10–12]. Many factors affect nasopharyngeal carriage of *M. catarrhalis*, such as the presence of siblings, respiratory illnesses and visiting nursery schools [11–14]. By the age of 6 months the cumulative colonisation rate varies between 22% and 55% [11, 15].

Furthermore, several nosocomial outbreaks of *M. catarrhalis* infections in adults and in children have been reported [16, 17]. Winter and spring season as well as multibed wards were found to be significant risk factors for nosocomial transmission [17].

In healthy children, a seasonal cyclic variation of colonisation, with a peak in autumn/winter, has been demonstrated [12]. Other studies reported seasonal peaks of *M. catarrhalis* infections in winter and spring [18, 19]. This seasonality is also observed in viral respiratory tract infection such as respiratory syncytial virus (RSV) [20]. It has been demonstrated that children with a high nasopharyngeal RSV load have an increased risk for the development of acute otitis media (AOM), which suggests that viral infection often paves the way for subsequent bacterial AOM [21]. Another potential factor is the physiologic cold shock response of *M. catarrhalis* [22]. Cold shock describes the physiologic rapid reduction of temperature in the upper respiratory tract to approximately 26 °C when humans breathe cold air for a prolonged period of time, a phenomenon which occurs mainly during the winter season in temperate and cold climates. This physiologic cold shock has been shown to up-regulate the expression of important virulence factors, such as adherence to epithelial cells, iron acquisition, complement resistance and immune evasion [23]. An increased expression of the UspA1 adhesin on the surface of *M. catarrhalis* at 26 °C leads to an increased adherence to upper respiratory tract epithelial cells *in vitro*. Furthermore, cold shock increases the release of interleukin-8, a pro-inflammatory cytokine in pharyngeal epithelial cells [24]. These mechanisms in turn may lead to an increased bacterial density during the cold season, which has been shown to increase the risk of the development of AOM [15]. The seasonality of viral respiratory tract infections and the physiologic cold shock response appear to be important contributors to the seasonal peak in *M. catarrhalis* infections.

In adults the pharyngeal carriage rate is noticeably lower and varies between 1% and 5% [13, 14]. It increases again in adults older than 60 years of age [13]. Specific mucosal

IgA antibody responses against outer membrane proteins have been detected in early childhood, but they do not prevent colonisation [25]. The presence of bactericidal serum anti-*M. catarrhalis* antibodies have been detected in both children and adults [26, 27]. The IgG3 antibody subclass response to *M. catarrhalis* is assumed to play an important role. The development of mature specific IgG antibodies is age-dependent. The subclass IgG1 develops during the first year of life and the subclass IgG3 after the second year of life, respectively. It has been demonstrated that children younger than 4 years of age have very low titers of IgG antibodies against *M. catarrhalis* [28]. This fact could explain the high colonisation rate of >80% and the high rate of AOM in children younger than 2 years of age.

After the introduction of the conjugate pneumococcal vaccines, the colonisation pattern in children has changed towards an increased prevalence of *M. catarrhalis*, *H. influenzae* and the non-vaccine serotypes of *S. pneumonia*. *M. catarrhalis* was found significantly more often in immunised children with AOM [29].

Paediatric infections

Acute otitis media

Acute otitis media is the most common bacterial infection treated with antibiotics in children. *M. catarrhalis* is the second or third most common pathogen to cause acute otitis media together with *Streptococcus pneumoniae* and nontypable *H. influenzae* [30]. It should be noted that tympanocentesis and culture of middle ear fluid is required for the correct microbiologic diagnosis of bacterial AOM. Tympanocentesis is not routinely performed and the rate of *M. catarrhalis* AOM may thus be underestimated. Compared to *S. pneumoniae* and *H. influenzae*, *M. catarrhalis* causes a relatively mild course of AOM. *S. pneumoniae*
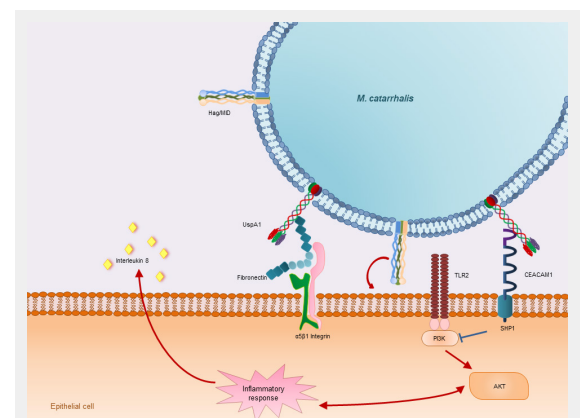

Figure 1

Adherence to host epithelial cells. UspA1 activates the carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM 1). Binding and activating of CEACAM 1 leads to recruitment of the SH2 containing protein tyrosin phosphatase 1 (SHP1). SHP1 inhibits the phosphoinositide 3-kinase (PI3K) phosphorylation which leads to a suppression of the AKT-mediated pro-inflammatory response. Furthermore UspA1 binds to the extracellular matrix glycoprotein fibronectin which in turn binds to α5β1 Integrin on the surface of the host epithelial cells. Hag/MID is known to be involved in the adherence of *M. catarrhalis* to host epithelial cells. The exact mechanism and the receptors involved are not yet known.

AOM are clinically more severe than those caused by *H. influenzae* and *M. catarrhalis* and are more often associated with high fever, tympanic membrane bulging and redness and severe otalgia [31]. In one study, a lower spontaneous tympanic membrane perforation rate and no case of mastoiditis in children younger than 5 years of age with *M. catarrhalis* AOM was observed [30].

Multiple factors influence the pathogenesis of acute otitis media in children. One of the most important factors is upper respiratory tract viral infection. During infection, pathogens migrate into the middle ear along the eustachian tube and cause inflammation, leading to congestion of the eustachian tube, which in turn causes a negative pressure in the middle ear [32]. Bacteria migrating or aspirated into the middle ear cavity can proliferate and cause AOM. *M. catarrhalis* possesses different virulence factors, which play an important role in this sequence of events.

Otitis prone children

Children with recurrent episodes of AOM are defined as otitis prone children if they have four or more episodes during one year [33]. Otitis prone children are at risk of developing delayed speech and language development due to conductive hearing loss caused by recurrent AOM with effusion [34]. Interestingly, *M. catarrhalis* DNA is more often detected in patients with middle ear effusion than in those with AOM [35]. This observation underlines the necessity of the development of a vaccine against *M. catarrhalis*, because as mentioned above, chronic or recurrent middle ear effusion can impair the child's cognitive development.

Acute bacterial sinusitis

Acute bacterial sinusitis is not very common in children and accounts for approximately 5–10% of the complications of upper respiratory tract infections [36]. Acute bacterial sinusitis is defined as nasal discharge and cough during day and night-time for more than 10 days and less than 30 days [36]. The development of the paranasal sinuses is age dependent. The maxillary and ethmoidal sinuses are present at birth, whereas the sphenoidal sinus develops around 5–6 years of age. The frontal sinus develops last and completes the pneumatisation of the skull in young adulthood. As in AOM, bacteria migrate from the nasopharynx into the adjacent sinuses and proliferate if the secretions persist in the sinus cavity. Fluid retention occurs if the mucociliar clearance mechanism is disturbed, the ostia are obstructed, or if the viscosity of the discharge is increased. *M. catarrhalis* accounts for approximately 10–20% of the bacterial pathogens isolated in acute bacterial sinusitis [37].

Treatment

Today 90–100% of the *M. catarrhalis* isolates are resistant to ampicillin by producing β-lactamase. In the 1970s only a small proportion of *M. catarrhalis* isolates were β-lactamase producing and since then the number of resistant isolates has increased dramatically. Three different enzymes, BRO-1, BRO-2 and BRO-3, have been identified [38, 39]. BRO-1 is found in >90% of the resistant strains

and is assumed to induce higher minimal inhibitory concentrations than BRO-2 producing strains [40]. Recent studies have reported an increase in resistance to trimethoprim/sulfamethoxazole (cotrimoxazole) of 18.5% in Taiwan to 82.5% in India [41, 42]. On the other hand, in two studies from Europe, a decrease in cotrimoxazole resistance was observed over the last decade [43, 44].

As tympanocentesis with subsequent bacterial culture of the middle ear effusion is not routinely performed, the treatment for AOM caused by *M. catarrhalis* is almost always empirical and is directed against the three most important bacterial pathogens (*S. pneumoniae, H. influenzae* and *M. catarrhalis*). To date the first line treatment of AOM remains standard high dose amoxicillin in Europe and in the USA [45]. In case of treatment failure, the addition of clavulanat is recommended. Macrolides as an alternative treatment option should be reserved for patients with amoxicillin allergy, because treatment failure occurs more often [46]. Furthermore, the indication for the use of extended spectrum cephalosporins, tetracyclines and fluoroquinolons should be made very restrictively.

Pathogenesis – host-bacterium interaction – virulence factors

Long considered as a non-pathogenic commensal, recent research has established its clinical relevance, identifying a number of strategies, with which *M. catarrhalis* maintains its niche in the nasopharynx, and causes clinical disease [47–49]. *M. catarrhalis* exhibits different virulence mechanism to interact with the human host.

Adherence

Adherence to human epithelial cells and in particular to respiratory mucosal cells is considered a pivotal initial step in bacterial colonisation, which allows the bacteria to remain firmly attached to host epithelial cells. *M. catarrhalis* expresses various adhesins, which include the ubiquitous surface protein A family (UspA), the human erythrocyte agglutinin/Moraxella immunoglobulin D-binding protein (hag/MID) [50], the outer membrane protein CD (OMP CD) [51], *M. catarrhalis* adherence protein (McaP) [52], and lipoligosaccharide (LOS) [53] (fig. 1).

UspA1, UspA2 and the closely related hybrid protein UspA2H show a lollipop like structure with an N-terminal head based on a β-sheet-structure, a coiled-coil stalk region and a C-terminal anchor region with 4 β-strands forming a β-barrel in the membrane, which shows homology to the YadA protein of *Yersinia spp.* [54, 55]. These proteins are typical bacterial auto-transporter proteins [56]. The N-terminus of the UspA2H protein is similar to the UspA1 domain, and its C-terminus resembles that of UspA2 [57]. Homologies between UspA1 and UspA2 were found in the stalk region, whereas the anchor region and the N-terminal head domain diverge widely [57]. UspA1 belongs to the major adhesins of *M. catarrhalis* [58]. Interestingly, the UspA1 gene is present in both phylogenetic lineages, but only the the seroresistant type 1 expresses the corresponding protein on its surface [59]. UspA1 and UspA2 bind to host cells through multi-functional binding sites.

UspA1 binds carcino-embryotic antigen -related cell adhesion molecules (CEACAMs) through a binding site on the stalk region. CEACAMs are expressed on the surface of human respiratory tract epithelial cells [60]. UspA1 and UspA2 were also found to bind to components of the extracellular matrix proteins such as fibronectin and laminin [61, 62]. UspA1 expression varies in accordance to phase variation, which in turns mediates the binding to host cells [63]. Furthermore, cold shock up-regulates the expression of UspA1, at least in part by prolonging *uspA1* mRNA half-life [22].

Hag/MID is another important multifunctional outer membrane protein of *M. catarrhalis*. The adherence to different respiratory tract cell lines (e.g. human middle ear cells, Chang conjunctival cells, A549 lung cells) is mediated by hag/MID [50, 64]. Similar to UspA1, the expression of Hag/MID is regulated by phase variation [50, 65].

Lipooligosaccharide (LOS) is another essential major component of the *M. catarrhalis* outer membrane, and is involved in the adherence to human respiratory cells [66]. Three serotypes have been identified (LOS A, B and C) [13]. Interestingly, serotype B has only been found in the seroresistant type 1 lineage and is more prevalent in adults than in children [67]. Thus, *M. catarrhalis* is able to exhibit various binding properties, which could be beneficial for its survival in different conditions and on different sites of the human respiratory tract.
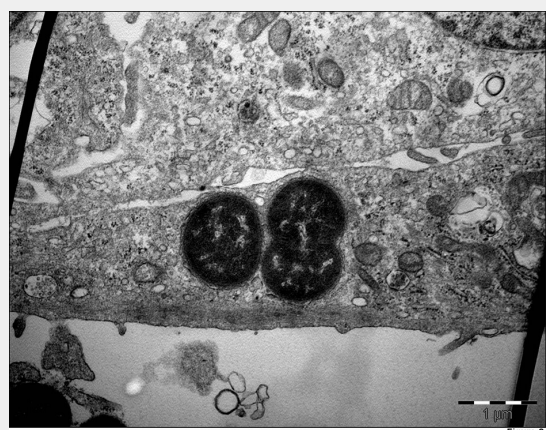

Figure 2

Transmission electron micrographs, demonstrating *M. catarrhalis* (strain 287) invasion in Detroit 526 pharyngeal cells.

Invasion

Invasion of human respiratory epithelial cells has been observed mainly *in vitro* [68, 69]. Invasion is regulated by the expression of LOS, UspA1 [68] and probably other outer membrane components. Slevogt et al. first described the capacity of *M. catarrhalis* to invade respiratory tract epithelial cells *in vitro* [69], and Heiniger et al. demonstrated its capacity to invade sub-epithelial pharyngeal lymphoid tissue *in vivo* [70]. It seems that invasion allows *M. catarrhalis* to escape killing by the host immune-system and extracellular antibiotics. The relevance and mechanisms of *M. catarrhalis* invasion are incompletely understood, and further studies are warranted (fig. 2).

Biofilm formation

Microbial communities, enclosed by a self-produced extracellular polymeric matrix substance adhering to surfaces are defined as biofilms [71]. Biofilm formation is a well-known virulence factor in many respiratory tract pathogens [71, 72]. *M. catarrhalis* has been found to be able to form biofilms *in vitro* and *in vivo* [71, 73]. The UspA family and Hag/MID are involved in the regulation of biofilm formation [73]. Verhaegh et al. demonstrated age-dependence in the capacity to from biofilms, with clinical isolates from children being able to form more extensive biofilms than those isolated from adults [67]. Further, biofilms of *M. catarrhalis* have been detected in middle ear effusion of children with otitis media [71]. These two observations may be clinically relevant and could contribute to the understanding of the pathogenesis of recurrent/chronic AOM with effusion.

Immune evasion strategies – complement resistance

To escape immune mediated killing is another important challenge for *M. catarrhalis*. The innate immune system consists of several components, such as the complement system and pathogen recognition receptors (PRR). PRR recognise pathogen-associated molecular patterns and include toll-like receptors. Complement resistance is likely to be an important virulence factor of *M. catarrhalis*. This statement is emphasised by the observation that clinical isolates able to survive in normal human serum are more prevalent in strains recovered from infected patients, than in those isolated from colonised but asymptomatic patients [74]. *M. catarrhalis* exhibits different mechanisms to inhibit complement mediated killing. It is able to activate all three pathways of the human complement system and both major outer membrane proteins (UspAs, OMP E, OMP CD, CopB) and surface exposed structures (LOS) are involved in complement defence (summarised by [47, 48]). *M.* catarrhalis is able to bind to the regulator protein C4b binding protein through UspA1 and UspA2 [75]. In addition, UspA2 is able to bind C3 and vitronectin and thereby inhibits the activation of the alternative complement pathway [75–77]. Another interesting observation is that outer membrane vesicles of *M. catarrhalis* carrying UspA1 and UspA2 are able to contribute to an improved survival of

serum sensitive *H. influenzae* through inactivation of C3 [78].

Vaccines

Both, AOM and exacerbation of COPD cause a significant human and economical burden. The development of a *M. catarrhalis* vaccine is desirable to reduce this burden. One challenge in the development of a vaccine to prevent *M. catarrhalis* infection is the lack of a suitable animal model. Several antigens are currently under investigation as potential vaccine antigens (summarised by [49, 79, 80]). A requirement for such an antigen is its conserved expression on the bacterial surface during infection. The gene expression of several potential antigen candidate proteins (e.g. UspA1 and hag/MID) of *M. catarrhalis* undergoes phase variation [63, 65], which in turn represents another obstacle in the development of a successful vaccine.

Concluding remarks

M. catarrhalis has been recognised as an important, exclusively human pathogen and commensal, causing upper respiratory tract infections in children and lower respiratory tract infections in adults. In children, *M. catarrhalis* is responsible for up 20% of all AOM episodes. With the widespread introduction of the conjugate vaccines against *S. pneumoniae* a change in the colonisation and infection pattern may appear with a consequent increase in the number of *M. catarrhalis* infections. Further research is needed to understand the pathogenetic mechanisms, especially with a focus on the direction of a vaccine development against *M. catarrhalis*.

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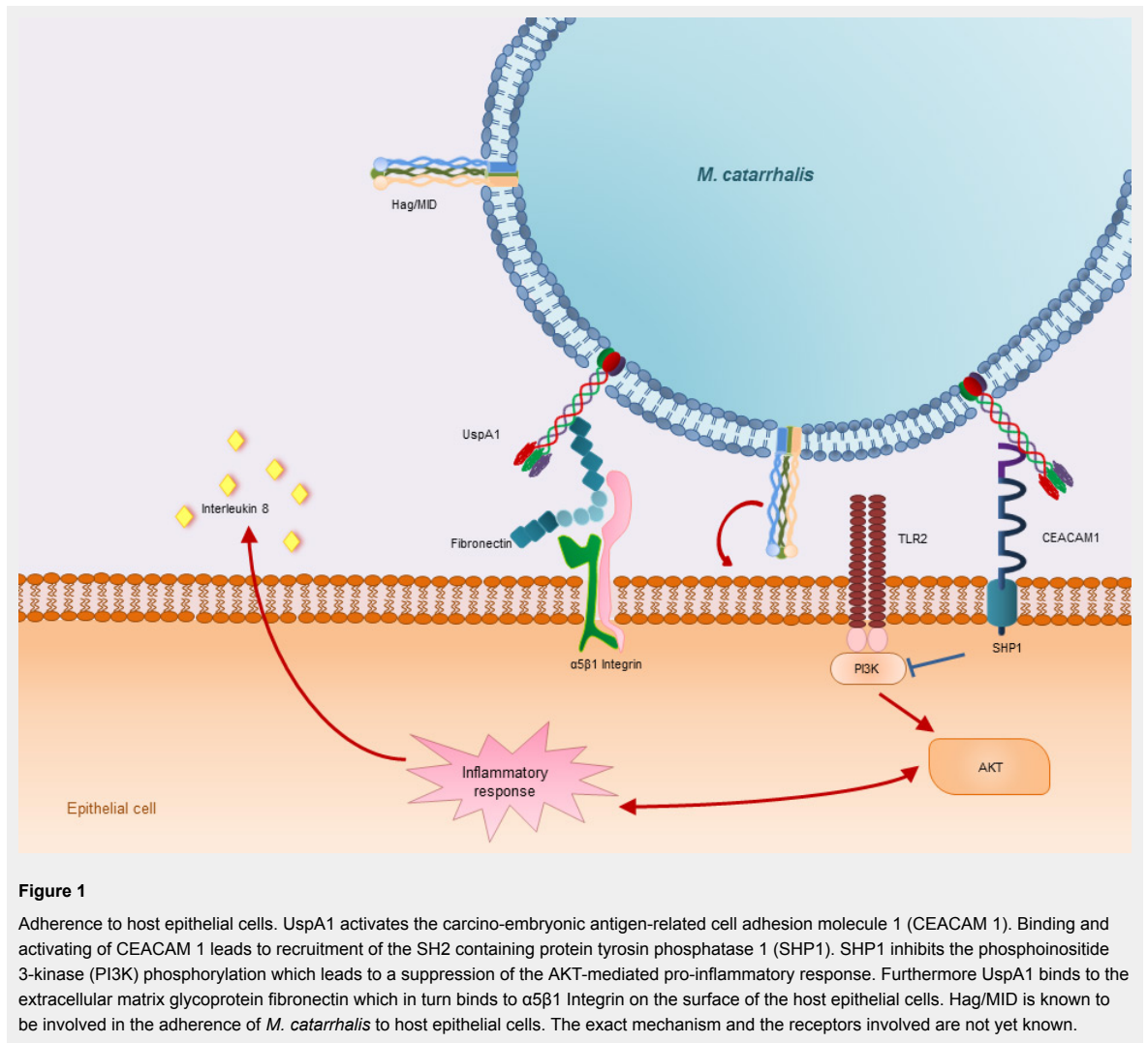
Figures (large format)

Figure 1

Adherence to host epithelial cells. UspA1 activates the carcino-embryonic antigen-related cell adhesion molecule 1 (CEACAM 1). Binding and activating of CEACAM 1 leads to recruitment of the SH2 containing protein tyrosin phosphatase 1 (SHP1). SHP1 inhibits the phosphoinositide 3-kinase (PI3K) phosphorylation which leads to a suppression of the AKT-mediated pro-inflammatory response. Furthermore UspA1 binds to the extracellular matrix glycoprotein fibronectin which in turn binds to α5β1 Integrin on the surface of the host epithelial cells. Hag/MID is known to be involved in the adherence of *M. catarrhalis* to host epithelial cells. The exact mechanism and the receptors involved are not yet known.

Figure 2

Transmission electron micrographs, demonstrating *M. catarrhalis* (strain 287) invasion in Detroit 526 pharyngeal cells.