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Temporal upregulation of host surface receptors provides a window of opportunity for bacterial adhesion and disease

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Review

Temporal upregulation of host surface receptors provides a window of opportunity for bacterial adhesion and disease

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Short Title: Upregulation of receptors for bacterial adhesion

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List of Abbreviations

AIEC: adherent-invasive *E. coli*
BBB: blood brain barrier
BM: basement membrane
CEACAM: carcinoembryonic antigen related cell adhesion molecule
CFTR: cystic fibrosis transmembrane conductance regulator
ChoP: phosphorylcholine
COPD: chronic obstructive pulmonary disease
CUP: chaperone-usher pili
DAEC: diffusely adhering *E. coli*
DAF: decay-accelerating factor
ECM: extracellular matrix
EHEC: enterohemorrhagic *E. coli*
EMMPRIN: extracellular matrix metalloproteinase inducer
EPEC: enteropathogenic *E. coli*
ER: endoplasmic reticulum
ETEC: enterotoxigenic *E. coli*
Fn: fibronectin
HCP: hemorrhagic coli pilus
HIF-1: hypoxia inducible factor 1
HPIV: human parainfluenza virus
HSPG: heparan sulfate proteoglycan
ICAM-1: intercellular cell adhesion molecule 1
IFNγ: interferon-gamma
IgCAM: immunoglobulin superfamily cell adhesion molecule
IL-1: interleukin-1
IRF-1: interferon regulatory factor 1 which binds
ISRE: interferon-stimulated response element
LFA-1: lymphocyte function-associated antigen 1
Ln: laminin
Mac-1: macrophage adhesion ligand 1
MAPK: mitogen activated protein kinase
NFκB: nuclear factor kappa B
NTHi: non-typeable *Haemophilus influenzae*
OMP: outer membrane protein
P pilus: pyelonephritis-associated pilus
PAF: platelet activating factor
PAFR: platelet activating factor receptor
PavA: pneumococcal adherence and virulence factor A

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PECAM-1: platelet endothelial cell adhesion molecule 1
PepO: pneumococcal endopeptidase O
PfbA: plasmin-fibronectin binding protein A
pIgR: poly Immunoglobulin receptor
Sp1: specificity protein 1
TfP: type IV pili
TGF-β: transforming growth factor
TNFα: tumour necrosis factor alpha
UC: ulcerative colitis
UPEC: uropathogenic *E. coli*
UspA1: ubiquitous surface protein A1
UTI: urinary tract infection

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Abstract

Host surface receptors provide bacteria with a foothold from which to attach, colonize and in some cases, invade tissue and elicit human disease. In this review, we discuss several key host receptors and cognate adhesins that function in bacterial pathogenesis. In particular, we examine the elevated expression of host surface receptors such as CEACAM-1, CEACAM-6, ICAM-1 and PAFR in response to specific stimuli. We explore how upregulated receptors, in turn, expose the host to a range of bacterial infections in the respiratory tract. It is apparent that exploitation of receptor induction for bacterial adherence is not unique to one body system, but is also observed in the central nervous, gastrointestinal, and urogenital systems. Prokaryotic pathogens which utilize this mechanism for their infectivity include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Escherichia coli*. A number of approaches have been used, in both *in vitro* and *in vivo* experimental models, to inhibit bacterial attachment to temporally-expressed host receptors. Some of these novel strategies may advance future targeted interventions for the prevention and treatment of bacterial disease.

Introduction

Mucosal surfaces of the respiratory, intestinal, and genitourinary tracts are important routes of entry into the host for bacterial pathogens (1). Multiple studies have shown that efficient binding between bacterial adhesins and host epithelial/endothelial surfaces is a prerequisite for establishing successful colonization (2). Therefore, the optimal presentation of host receptors for adhesion is critical for bacterial infection and subsequent disease. To date, much of the emphasis in the field of bacterial pathogenesis has been placed on the kinetics of expression of bacterial adhesins. This has often occurred in the context of assumed constitutive availability of cognate host surface receptors. However, it is becoming apparent that for bacterial diseases of a number of body systems including the respiratory, central nervous, gastrointestinal, and genitourinary systems, host receptors are appreciably induced in the presence of specific environmental or other stimuli.

In this review, we discuss the different types of host cell receptors, their interaction with their respective bacterial adhesins, and the regulation of their expression in different body sites. Finally, we provide an insight into potential clinically relevant strategies that are being

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explored to inhibit the specific interactions between bacterial adhesins and temporally upregulated host cell receptors.

Host surface receptors for bacterial colonization

Bacteria utilize a wide variety of molecules on host surfaces as docking sites for tissue adhesion and host colonization. Of particular interest, are the extracellular matrix (ECM) proteins, cell adhesion molecules (*e.g.* integrins, cadherins), and platelet-activating factor receptor (PAFR), which upon stimulation by certain environmental and/or immunogenic insults, undergo transient upregulation. This enhances bacterial adherence and subsequent tissue invasion (3-5).

ECM, the acellular proteinaceous part of animal connective tissue, constitutes the anchoring platform for epithelia, designated the basement membrane (BM), and also surrounds blood capillaries and neurons (6). It consists of collagen, elastin, fibrillin, laminin (Ln), fibronectin (Fn), vitronectin, thrombospondin, proteoglycans and hyaluronic acid. Besides its ubiquitous distribution, ECM biosynthesis is significantly enhanced following viral infections (*e.g.* influenza A virus) and traumatic injury (*e.g.* ligament rupture) as a natural response to tissue repair, and is therefore, an attractive target for adherence and invasion by several bacterial pathogens, such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, and non-typeable *Haemophilus influenzae* (3, 7-11).

In addition to ECM components, cell adhesion molecules, including integrins, cadherins, selectins, and members of the immunoglobulin superfamily of cell adhesion molecules (IgCAMs), are also involved in bacterial adhesion (4, 12). Integrins are heterodimeric (composed of two subunits, α and β) transmembrane glycoproteins that attach cells to extracellular matrix proteins of the basement membrane or to ligands on other cells (13, 14). Several bacteria bind to integrins directly whereas others engage them via ECM proteins, such as fibronectin and collagen. Bacterial-integrin binding can trigger host intracellular signalling leading to actin cytoskeleton remodelling and subsequent bacterial invasion (4).

IgCAMs including, carcinoembryonic antigen-related cell adhesion molecule (CEACAM) and intercellular cell adhesion molecule 1 (ICAM-1), constitute the other major class of host cell receptors utilized by bacterial adhesion systems (4). The CEACAM family is a group of highly glycosylated intercellular adhesion molecules involved in signalling events that mediate key

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cellular processes that include cell adhesion, proliferation, differentiation and tumour suppression (15). They comprise an N-terminal Ig variable (IgV)-like domain followed by up to six Ig(C) domains. Twelve different CEACAM proteins have been identified in humans to date with CEACAM-1, CEACAM-5 and CEACAM-6 found in epithelial cells, and CEACAM-3 present exclusively in granulocytes (16).

ICAM-1 (CD54) is a cell surface glycoprotein that serves as a counter-receptor for leucocyte β2 integrins, lymphocyte function associated antigen (LFA-1) (CD11a/CD18) and macrophage adhesion ligand 1 (Mac-1) (CD11b/CD18) (17). It is constitutively expressed in low levels on endothelium, fibroblasts and various epithelia (*e.g.* bronchial, intestinal, and urinary tract), however, its expression is markedly upregulated at sites of inflammation (18-22). Interactions between ICAM-1 and β2 integrins are known to have a central role in mediating leukocyte recruitment in the inflammatory response. This may lead to partial protection from invading pathogens but may also result in neutrophil-induced chronic epithelial injury (23, 24). A sustained inflammatory process may further upregulate adhesion receptors.

Finally, the other class of host cell receptor, platelet-activating factor receptor (PAFR) is a G-protein-coupled 7-transmembrane domain receptor, physiologically recognized by a phospholipid, platelet activating factor (PAF) (25). PAFR plays a role in a wide range of biological processes such as vasodilation, cell proliferation, angiogenesis, and regulation of the inflammatory response (25). Also, over the last decade, there has been increasing evidence emerging that PAFR is a major epithelial receptor used by specific respiratory and intestinal bacteria for adhesion to and also invasion of host epithelium (5, 26). Moreover, PAFR expression is inducible and is directly linked to increased susceptibility to infection by both Gram-positive and Gram-negative bacteria (26, 27).

Temporal host surface receptor upregulation in different body systems

(i) Respiratory System

Worldwide, respiratory diseases affect several hundred million people and cause approximately four million deaths annually (28). Two of the major contributors to respiratory-related deaths globally are chronic obstructive pulmonary disease (COPD) and acute respiratory infections. Major respiratory bacteria, such as nontypeable *Haemophilus*

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influenzae (NTHi)*, Streptococcus pneumoniae*, and *Moraxella catarrhalis,* are common asymptomatic colonizers of the upper respiratory tract, but under certain circumstances may disseminate and cause infections, such as otitis media, sinusitis, and lower respiratory tract ailments including bronchitis, pneumonia, and acute exacerbations of COPD (29-32). These species interact with and adhere to a variety of host cell receptors including ECM components and CEACAM-1, ICAM-1, and PAFR (5, 33, 34) (Figure 1).

Pneumococci are equipped with three different types of fibronectin-binding proteins: pneumococcal adherence and virulence factor A (PavA); plasmin-fibronectin binding protein A (PfbA); and pneumococcal endopeptidase O (PepO), which mediate adhesion to airway epithelia (10, 35, 36). Adherence of NTHi to fibronectin, laminin and type IV collagen is mediated by an autotransporter, *Haemophilus* adhesion and penetration protein (Hap) (37). Recently, NTHi lipoprotein P4 has demonstrated effective binding to nasopharyngeal, type II alveolar, and bronchial epithelial cells via fibronectin (7). Some respiratory viruses, such as Influenza A virus, Influenza B virus and Human Parainfluenza virus (HPIV) enhance the susceptibility to pneumococci and NTHi via upregulation of fibronectin and integrin expression. These viruses release neuraminidase which cleaves the sialic acid from latent transforming growth factor beta (TGF-β), thereby activating it. This stimulates the Smad signalling pathway resulting in the upregulation of both fibronectin and integrin expression (9).

P1, an outer membrane protein in NTHi is reported to be implicated in CEACAM-1 and CEACAM-5 binding, thus, facilitating adhesion and invasion of the nasopharynx and lower respiratory epithelium (38). Similarly, CEACAM-1-engaging adhesins have also been identified in *M. catarrhalis*. Ubiquitous surface protein A1 (UspA1), an outer membrane protein in *M. catarrhalis*, targets and interacts with CEACAM-1 facilitating adhesion and invasion of respiratory epithelium (39). NTHi and *M. catarrhalis* induce the expression of their own receptor, CEACAM-1, on host cells, thereby increasing the host susceptibility to bacterial infection (40).

S. pneumoniae and NTHi, along with some strains of *Pseudomonas aeruginosa*, a major bacterial pathogen in cystic fibrosis, share another common adhesin, known as phosphorylcholine (ChoP), in their cell wall (12, 41, 42). ChoP mimics PAF which is the natural arachidonic acid derived ligand for PAFR expressed on bronchial and alveolar epithelial cells. PAFR has been shown to be upregulated in human airway epithelial cells exposed to cigarette

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smoke extract, as well as urban particulate matter (43-45). Furthermore, elevated PAFR expression resulted in higher levels of adhesion to bronchial epithelial cells by NTHi and *S. pneumoniae*, the major causes of acute exacerbations of COPD (46).

Although the regulation of PAFR expression in response to cigarette smoke still requires elucidation, the pathway for ICAM-1 enhancement has recently been delineated (47). Cigarette smoke results in higher levels of tumour necrosis factor-alpha (TNFα) in the airway which increase expression of ICAM-1 via nuclear factor kappa B (NFκB). Upregulated ICAM-1 is exploited as a receptor for upper respiratory tract infection by the major group rhinoviruses (approximately 60% of serotypes) (48-51). Notably, ICAM-1 expression is further stimulated by rhinovirus infection, again via the NFκB pathway, which increases the susceptibility of airway epithelial cells to secondary bacterial infection (49). In addition to Rhinoviruses, NTHi has also been reported to utilize ICAM-1 for adherence to airway epithelium (52). Moreover, NTHi also upregulates the expression of the ICAM-1 receptor which successively increases the susceptibility to rhinoviral infection (53). ICAM-1 expression on respiratory epithelium is also elevated under different respiratory conditions, including COPD and bronchiectasis (22, 51, 54, 55).

Besides rhinovirus, other respiratory viruses are also implicated in predisposition to secondary bacterial infections (56). A variety of cytokines released, following viral infection, such as TNFα, interferon-gamma (IFNγ) and interleukin 1-beta (IL-1β) can target the respiratory epithelium and induce the expression of adhesive molecules, including CEACAM-1 and PAFR (57). IFNγ, in particular, is the most potent inflammatory cytokine that increases the expression of CEACAM-1, ICAM-1, and PAFR via the NFκB pathway (58). Notably, IFNγ has also been reported to directly induce CEACAM-1 expression via activation of interferon regulatory factor 1 (IRF-1), which binds interferon-stimulated response element (ISRE) in the CEACAM-1 promoter (59).

(ii) Central Nervous System

Temporal receptor upregulation is not unique to the respiratory system, and similar observations have been recorded in other body systems, including the endothelium in the central nervous system. The major central nervous system disease, meningitis, is manifested by a specific and limited number of bacterial pathogens, including *S. pneumoniae*, and *N. meningitidis*. The global incidence of pneumococcal meningitis was 0.1 million in children

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younger than 5 years in 2000, whereas, the worldwide annual prevalence of meningococcal meningitis is 1.2 million with 135,000 deaths yearly (60, 61). Pneumococci utilize a similar set of host surface receptors, including PAFR, for both adherence to the respiratory epithelium and for penetrating the endothelial lining of the blood-brain barrier (BBB) (34). In addition, poly immunoglobulin receptor (pIgR), which transports immunoglobulins across mucosal epithelium, and platelet endothelial cell adhesion molecule-1 (PECAM-1), that is involved in leukocyte migration and angiogenesis in the endothelium, have also been found to be utilised by pneumococci for endothelium adhesion and invasion (62, 63). It has been proposed that pneumococcal infection in itself may upregulate pIgR and PECAM-1 expression via a PAFR mediated signalling mechanism (64). Pneumococcal cellular components, such as choline binding proteins and pneumolysin, or PAF synthesized by host innate immune response, are believed to mediate binding to PAFR. This interaction in turn stimulates multiple signal transduction pathways including phospholipase C, D, A2, mitogen-activated protein kinases (MAPKs) and the phosphatidylinositol-calcium second messenger system thereby, increasing the expression of pneumococcal adhesion receptors pIgR or PECAM-1 (64-66). In addition, pneumococcal pilus-1 adhesin RrgA and pilus-2 adhesin PitB have been implicated in pneumococci mediated adhesion and invasion of brain endothelial cells and respiratory epithelial cells (67-69).

Meningococci express a different set of adhesins to attach to and invade the cerebrovascular endothelial lining. Colony opacity-associated (Opa) protein and opacity class 5 protein, Opc, are outer membrane proteins, which mediate meningococcal adhesion specifically to CEACAM-1, heparan sulfate proteoglycan (HSPG) and integrins via the extracellular matrix proteins fibronectin and vitronectin (70, 71). Meningococci have been shown to trigger the expression of the CEACAM-1 receptor on primary endothelial cells via NFκB activation, which increases Opa/CEACAM-1-specific bacterial binding and internalization (72). In contrast, Opc primarily binds to ECM proteins, such as fibronectin and vitronectin, and is particularly implicated in host cell invasion of endothelial cells (73). Expression of fibronectin and its major receptor, α5β1 integrin, is enhanced during cerebral hypoxia, and therefore, may predispose the host to meningococcal meningitis (74) (Figure 2).

Recently, a novel receptor, CD147, a member of the immunoglobulin superfamily, also called extracellular matrix metalloproteinase inducer (EMMPRIN) or Basigin, has been described as a major receptor that is recognized by the meningococcal type IV pilus (Tfp). *N. meningitidis*

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utilizes CD147 for adhesion during infection (75). Interestingly, CD147 expression has been shown to be upregulated by hypoxia through a combined effect of transcription factors hypoxia inducible factor 1 (HIF-1) and specificity protein 1 (Sp1) on the activation of the CD147 gene promoter (76).

(iii) Digestive System

Diarrhoea, the major gastrointestinal disorder, is the second leading cause of mortality worldwide among children under the age of five (77). In the gastrointestinal tract, various bacteria including different pathotypes of *E. coli i.e.* enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), adherent-invasive *E. coli* (AIEC), diffusely adhering *E. coli* (DAEC), and *Salmonella* spp. mediate their pathogenesis via adhesion to and/or invasion of intestinal epithelial cells (2). The chaperone-usher pathway (CUP) type I pilus adhesin, FimH, mediates adhesion to D-mannosyl residues of CEACAMs, including CEACAM-1, CEACAM-5, and CEACAM-6, and has been associated with EPEC and DAEC infections (78). In addition to type I pili, DAEC also expresses the CUP adhesins Afa/Dr which have been shown to recognize and bind the CEACAM-1, CEACAM-5 and CEACAM-6 receptors in the intestinal epithelial cells (79). Similar to the respiratory tract, CEACAMs in intestinal epithelial cells are normally expressed at low levels, which prevents their use by opportunistic pathogenic bacteria for attachment (80). However, in inflammatory conditions such as Crohn's disease, released cytokines TNFα and IFNγ induce CEACAM-6 expression which promotes the adhesion to ileal epithelial cells by AIEC (81). Furthermore, overexpression of the endoplasmic reticulum (ER)-localised stress response chaperone protein Gp96 has been detected in Crohn's disease , and crucially is utilized as a receptor for the adhesin OmpA expressed by AIEC, thereby facilitating the bacterium's invasion (82).

Type IV pili such as PilS in *Salmonella enterica*, and haemorrhagic coli pilus (HCP) in enterohaemorrhagic *E. coli* (EHEC) mediate adherence to and invasion of intestinal epithelial cells leading to typhoid fever and haemorrhagic colitis, respectively (83, 84). *S. enterica* has been identified to utilize the adhesin PilS, interacting with the epithelial receptor, cystic fibrosis transmembrane conductance regulator (CFTR), allowing entry to the intestinal epithelial cells (85). Interestingly, CFTR gene expression has been shown to be induced in ulcerative colitis (UC), which might predispose an individual with this condition to subsequent *Salmonella* infection (86). On the other hand, EHEC has been demonstrated to bind to various

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ECM proteins, including laminin, type IV collagen, and fibronectin via CUP and type IV pili (87, 88). Expression of the ECM component, fibronectin, has been found to be upregulated in intestinal epithelial cells during colitis, in both the acute phase as well as the recovery phase of the disease (89). In addition, PAFR is upregulated during intestinal inflammation via the hypoxia-inducible factor-1 alpha (26). The Gram-positive intestinal bacterial species, *Enterococcus faecalis*, exploits this upregulation of PAFR to translocate across the intestinal epithelial barrier (26) (Figure 3).

(iv) Urogenital System

The annual global burden of urinary tract infection (UTI) is estimated to be 150 million cases, resulting in an economic burden of more than 6 billion dollars per year (90). Uropathogenic *E. coli* (UPEC) is the most common bacterial pathogen associated with UTI, both uncomplicated and complicated. Uncomplicated UTIs typically affect individuals who are otherwise healthy and have no structural or neurological abnormalities and are differentiated into lower UTIs (cystitis) and upper UTIs (pyelonephritis). Complicated UTIs are associated with factors that compromise the urinary tract or host defense, including renal failure, urinary retention, pregnancy and the presence of urethral catheters (91, 92). UPEC has the ability to bind directly to kidney cells and bladder epithelium. The CUP pyelonephritis-associated (P) pilus adhesin, PapG, mediates binding to the α-galactopyranosyl-(1-4)-β-D-galactopyranoside moiety of glycolipids on the kidney cells (93).

Besides P pili, some UPEC strains express type I pili, which via the FimH adhesin confer binding to α-D-mannosylated proteins, such as uroplakins on bladder epithelia, allowing colonization of the urinary tract (94). There is a paucity of data in relation to factors affecting uroplakin expression, although it has been shown to be associated with malignant transformation in the uroepithelium (95) (Figure 4).

In addition to pili, Afa/Dr-positive UPEC utilizes Dr adhesins to interact with type IV collagen in the kidney (96). The Dr adhesin has also been shown to bind to CEACAM-1, CEACAM-5 and CEACAM-6 receptor and decay accelerating factor (DAF) in bladder epithelial cells (79, 97). Interestingly, DAF expression is upregulated during pregnancy which predisposes pregnant women to UTI by Afa/Dr-positive UPEC (98). Furthermore, cell culture studies have confirmed that the extent of Afa/Dr-positive *E. coli* attachment to host epithelial cell is proportional to the level of DAF expression (99).

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Inhibiting specific bacterial adhesin-host receptor interactions

Bacterial infections, one of the major causes of morbidity and mortality worldwide, are becoming increasingly problematic to treat due to the growing acquisition of antibiotic resistance by major pathogens, as well as challenges to the generation of new clinically-approval antimicrobials (100). The potential for developing a novel alternative approach to prevent and/or treat life-threatening bacterial infections through interfering with bacterial/host tissue interfaces is timely. This could be achieved using a number of different strategies.

The first strategy is the inhibition/disruption of bacterial adhesin assembly by using small molecule inhibitors. Curlicides FN075 and BibC6 have been found to block the biogenesis of amyloid fibres curli, thereby inhibiting *in vitro* the UPEC biofilm formation (101). Moreover, UTI infection was significantly reduced *in vivo* by the pretreatment of UPEC with FN075 thereby suggesting the anti-virulence property of curlicides (101). Pilicide ec240, small molecule inhibitor of CUP pili has recently been reported to inhibit the assembly of type 1 and P pili in an *in vitro* culture of cystitis isolate of UPEC (102).

A second strategy involves inhibiting the upregulation of host cell receptors. Two important pathways for receptor upregulation, the NFκB and TGF-β-Smad signalling pathways, could be potential therapeutic targets. The NFκB inhibitor, diferuloylmethane (curcumin) has been shown to significantly reduce the infectivity of the bacteria *N. gonorrhoeae, Helicobacter pylori* and *N. meningitidis in vitro* by blocking the expression of their cognate adhesion receptors (58, 103, 104). Similarly, in an *in vitro* study with human alveolar epithelial cells, the TGFβ inhibitor SB431542 has been reported to reduce infection associated with *S. pneumoniae*, *S. aureus* and NTHi following exposure to viral infections (9). *In vivo* studies are now needed to evaluate the therapeutic utility of NFκB and TGF-β inhibitors.

Finally, the third and perhaps most utilized strategy is the disruption of the bacterial-host cell adhesive interaction with specific competitive inhibitors or receptor antagonists. Mannose derivative 4-methylumbelliferyl alpha-mannoside has been found to inhibit type 1 fimbriae-mediated binding of *E. coli* to guinea pig ileal epithelial cells (105). Also, methyl alpha-mannoside was reported to inhibit *E.coli* and *Salmonella* binding to glycoprotein CEACAM *in vitro* (78). Also, selective FimH binding mannosides have been indicated in preventing urinary tract infection in a preclinical murine model (106). *In vitro* studies have found that anti-CEACAM antibodies block the adhesion of *M. catarrhalis*, *N. meningitidis*, and NTHi to airway

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epithelial cells (39, 71, 107). Also, NTHi adherence to A549 alveolar epithelial cells *in vitro*, was shown to be inhibited in a dose-dependent manner with increasing concentrations of anti-ICAM-1 monoclonal antibodies (52). An *in vivo* study conducted in chinchillas reported that anti-CEACAM-1 antibody YTH71.3 effectively blocked NTHi attachment to the nasopharynx (108).

In terms of specific receptor antagonists, a number of PAFR antagonists, such as Ginkgolide-B (BN52021), CV-3988, PCA-4248, CAS-99103-16-9, and WEB-2086, have been reported to block the attachment of bacterial pathogens to respiratory epithelium (12, 42, 109, 110). Of these, WEB-2086 has recently been demonstrated to significantly inhibit both NTHi and *S. pneumoniae* adherence to bronchial epithelial cells *in vitro* (46). WEB-2086 also caused a significant reduction in exotoxin ExoU-expressing *P. aeruginosa* bacterial load in both *in vitro* and *in vivo* infections of A549 human alveolar epithelial cells and mouse lungs, respectively (111). Besides WEB-2086, CAS-99103-16-9 has been shown to inhibit *Pseudomonas aeruginosa* infection in both *in vitro* and *in vivo* experimental model (42). In a mouse model of occupational exposure to welding fumes, PAF analogue CV-3988 significantly inhibited *S. pneumoniae* infection (112). In a mouse model of sickle cell disease, impact of PAFR antagonist BN-52021 was evaluated by challenge of PAFR knock out mice (113). Sickle cell disease was found associated with elevated levels of PAFR expression and BN-52021 was found to reduce the extent of pneumococcal disease (113).

There is good evidence that PAFR antagonists are well tolerated in humans based on earlier asthma clinical trials. SR27417 inhibited PAF-induced symptoms in patients with only minor side effects (114). Similarly, CV-3988 was not associated with any major adverse events at doses of 750-2000 μg/kg (115). In terms of returning to pre-treatment levels, no clinically evident adverse effects were reported for PAFR antagonist BN52021 nearly one year after a clinical trial in asthmatic children (116).

In vitro studies are robust, replicable, and economical for detemining the mechanisms involved in adhesin-receptor interactions and also for measuring the inhibitory activity of new candidate drugs. However, the absence of cell-cell interactions, and the use of artificial culture conditons are among the main limitations (117). Outcomes from *in vitro* studies are not always applicable at the whole organism level. Hence, a priority is more *in vivo* work to establish the efficacy of the host receptor inhibitors in preventing bacterial infections and disease.

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Summary and Conclusions

All bacterial pathogens, including respiratory, intestinal and urinary tract pathogens, have evolved strategies to survive and colonize within their respective niches. They are equipped with adhesins that facilitate the binding, and in some cases, invasion of protective epithelial barriers. Host tissue can resist infection through reducing the presentation of surface receptors for bacterial adhesion. However, in the respiratory tract, certain stimuli such as viral infection, cigarette smoke exposure, and inflammation related to chronic illnesses including COPD, have been found to temporally heighten the expression of receptors. Among these are CAECAM-1, ICAM-1, and PAFR, that promote adherence by pathogens such as *H. influenzae* and *S. pneumoniae*. Upregulation of CAECAM-1 on endothelial cells enables breaching of the blood-brain barrier by *N. meningitidis* which is acutely linked to meningitis. In the intestine, Crohn's disease is associated with elevated expression of CAECAM-6 which promotes colonization by adherent-invasive *E. coli*. A number of inhibitors have been identified to date which block the adhesion of bacterial pathogens to upregulated host surface receptors indicating that such interactions could be amenable to therapeutic intervention. This may offer new avenues for the development of treatments for respiratory and other types of infections. However, validation of this approach, through further animal studies and subsequent investment in appropriate clinical trials, is needed.

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Conflicts of interest

None declared.

Ethical approval

Not applicable.

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Figure 1. Temporal upregulation of host surface receptors in the respiratory system.

Host surface receptors in the respiratory tract are upregulated in response to viral infection, exposure to cigarette and biomass fuel smoke, as well as inflammatory cytokines. Bacterial pathogens including non-typeable *Haemophilus influenzae*, *Streptococcus pneumoniae, Pseudomonas aeruginosa* and *Moraxella catarrhalis* exploit the upregulated receptors for attachment via their cognate adhesins. Strategies which have been found to inhibit such interactions are illustrated. PavA, pneumococcal adhesion and virulence A; PfbA, plasmin-fibronectin binding protein A; PepO, pneumococcal endopeptidase O; TGFβR, transforming growth factor-beta receptor; COPD, chronic obstructive pulmonary disease; PAFR, platelet activating factor receptor; Hap, haemophilus adhesion and penetration; OMP, outer membrane protein; Anti-CEACAM Ab, anti-carcinoembryonic antigen cell adhesion molecule; UspA1, ubiquitous surface protein A1; IL-1, interleukin 1; TNFα, tumour necrosis factor-alpha; IFNγ, interferon-gamma. Yellow, blue and orange coloured text boxes represent bacteria, inhibitors and factors affecting expression of host cell receptors, respectively. Green and red coloured texts represent bacterial adhesins and their cognate host cell receptors, respectively.

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Figure 2. Temporal upregulation of host surface receptors associated with bacterial disease of the central nervous system.

Host receptors on endothelial surfaces are upregulated in response to viral infection, hypoxia, and inflammatory cytokines. Bacterial pathogens including *Streptococcus pneumoniae* and *Neisseria meningitidis* adhere to the upregulated receptors via their cognate adhesins which can facilitate invasion of the blood-brain barrier. Approaches which have been found to inhibit such interactions are illustrated. Opa, opacity-associated; Opc, opacity class 5; Tfp, type IV pili. Yellow, blue and orange coloured text boxes represent bacteria, inhibitors, and factors affecting expression of host cell receptors, respectively. Green and red coloured texts represent bacterial adhesins and their cognate host cell receptors, respectively.

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Figure 3. Temporal upregulation of host surface receptors in the digestive system.

Host surface receptors in the digestive tract are upregulated in response to Crohn's disease, colitis, and signals that include hypoxia. Bacterial pathogens including EPEC, ETEC, AIEC, DAEC, *Salmonella enterica* and *Enterococcus faecalis* bind to the upregulated receptors via their cognate adhesins. Strategies which have been found to inhibit such interactions are illustrated. CFTR, conductance fibrosis transmembrane receptor; EPEC, enteropathogenic *E. coli*; DAEC, diffusely adhering *E. coli*; EHEC, enterohemorrhagic *E. coli*; AIEC, adherently invasive *E. coli*; DAF, decay accelerating factor; HCP, hemorrhagic coli pilus. ChoP, phosphorylcholine. Yellow, blue and orange coloured text boxes represent bacteria, inhibitors, and factors affecting expression of host cell receptors, respectively. Green and red coloured texts represent bacterial adhesins and their cognate host cell receptors, respectively.

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Figure 4. Temporal upregulation of host surface receptors in the urogenital system.

Host surface receptors in the urogenital tract are upregulated in response to transitional cell carcinoma and pregnancy. UPEC binds to the upregulated receptors via its P pili, type I pili, and Afa/Dr adhesins. Strategies which have been found to inhibit the adhesive interactions are illustrated. P pili, pyelonephritis pili; UPEC, uropathogenic *E. coli*; NO, nitric oxide. Yellow, blue and orange coloured text boxes represent bacteria, inhibitors, and factors affecting expression of host cell receptors, respectively. Green and red coloured texts represent bacterial adhesins and their cognate host cell receptors, respectively.

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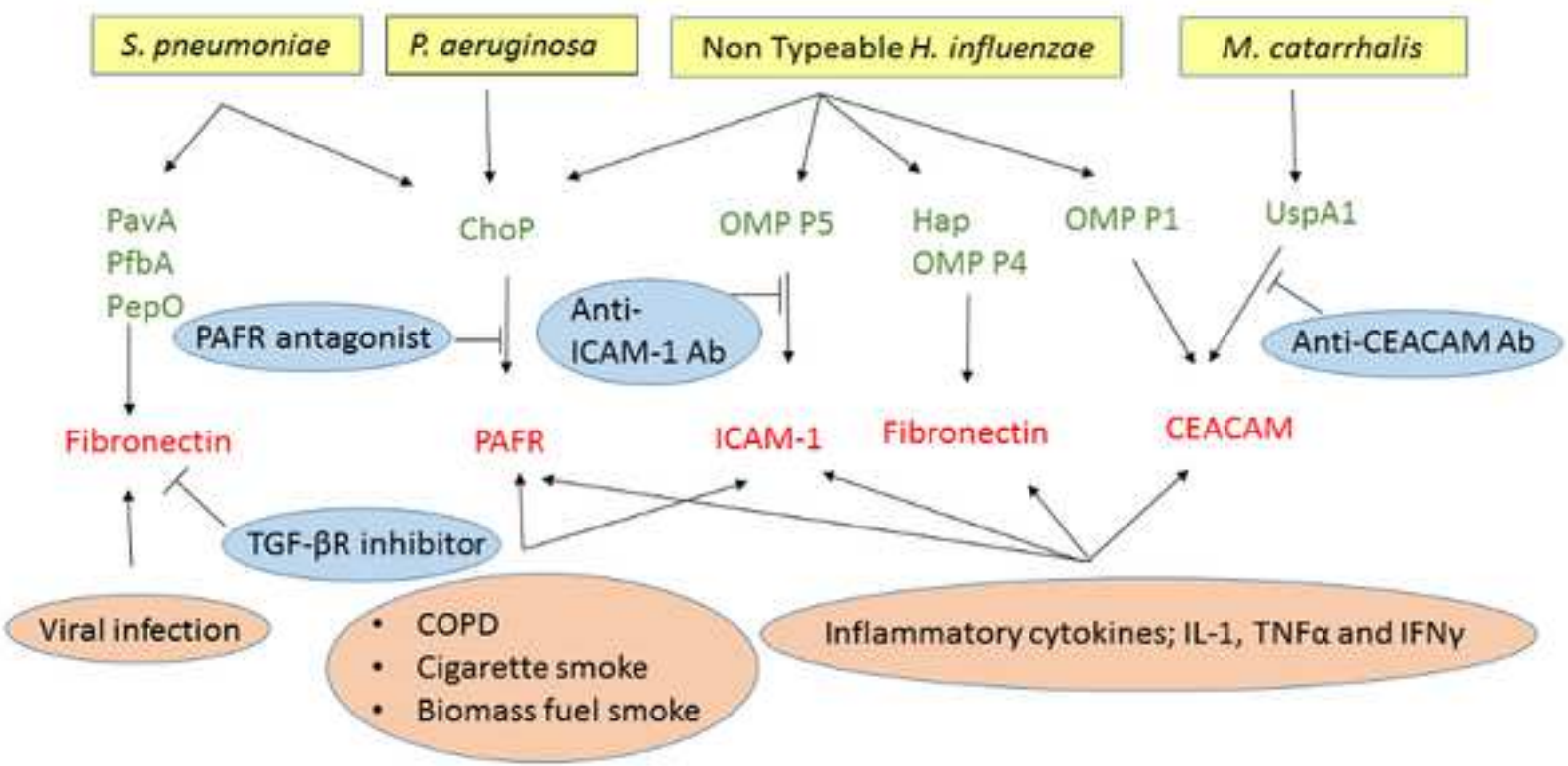

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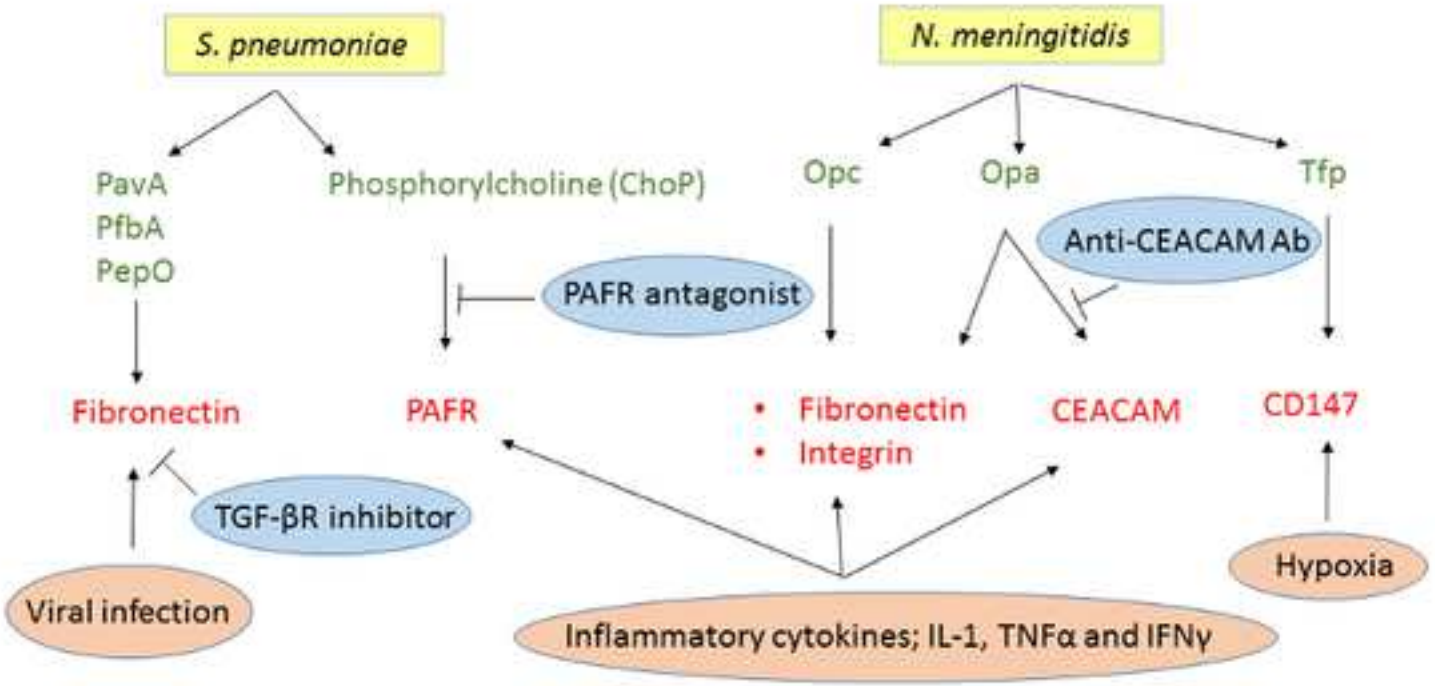

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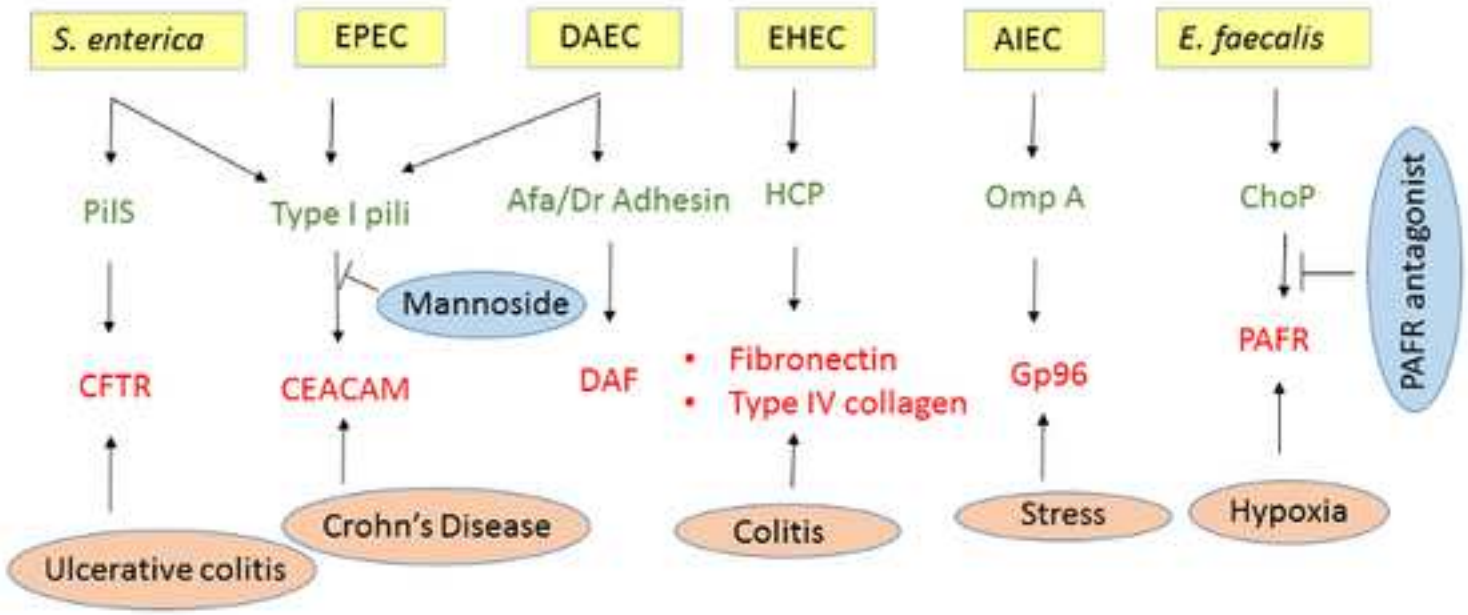

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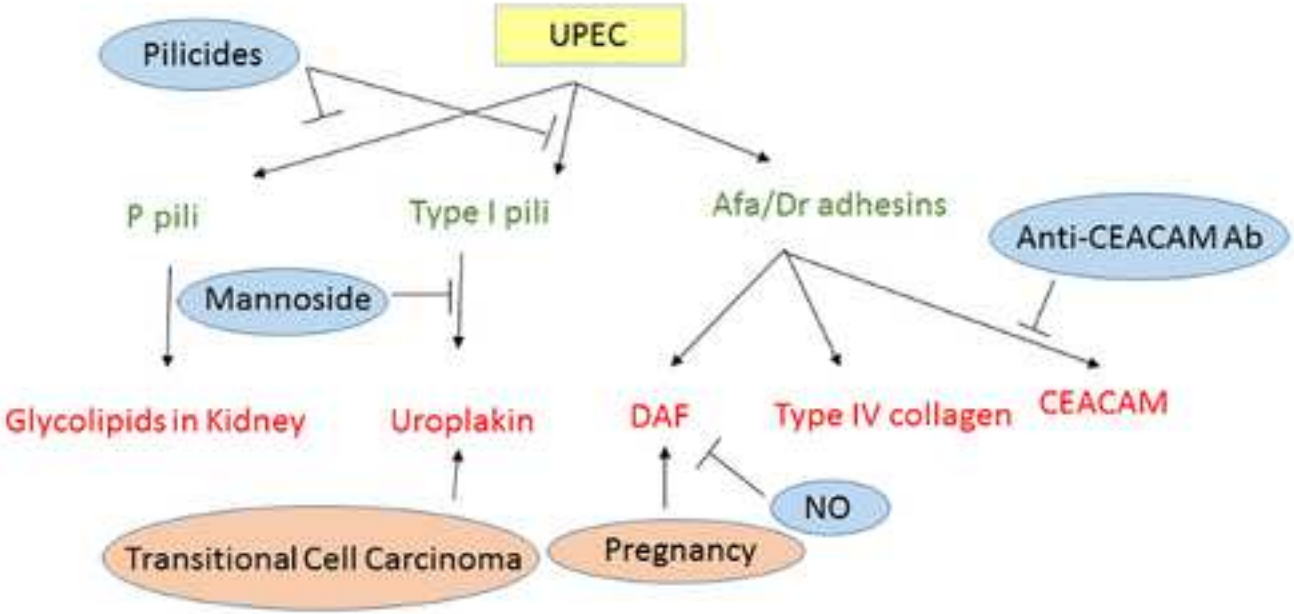

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