

Cell adhesion molecules in the pathogenesis of and host defence against microbial infection

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Abstract

Eukaryotic cell adhesion molecules (CAMs) are used by various cells and extracellular molecules in host defence against infection. They are involved in many processes including recognition by circulating phagocytes of a site of inflammation, transmigration through the endothelial barrier, diapodesis through basement membrane and extracellular matrix, and release of effector mechanisms at the infected site. CAMs involved in leucocyte–endothelial cell interaction include the selectins, integrins, and members of the immunoglobulin superfamily. However, CAMs are also used by various microorganisms (protozoa, fungi, bacteria, and viruses) during their pathogenesis. For example, bacteria that utilise CAMs include *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *Yersinia* spp, enteropathogenic *Escherichia coli*, *Shigella* spp, *Neisseria* spp, *Bordetella* spp, and *Borrelia burgdorferi*. In addition, CAMs are involved in the pathogenetic effects of the RTX toxins of *Pasteurella haemolytica*, *Actinobacillus actinomycetemcomitans*, and the superantigen exotoxins of *Staphylococcus aureus* and *Streptococcus pyogenes*. A recurrent and topical theme of potential importance within the bacterial group is the intimate relation between CAMs, bacterial protein receptors, and type III secretion systems. For example, the IpaBCD protein complex is secreted by the type III system of *Shigella flexneri* and interacts with $\alpha_5\beta_1$ integrin on the eukaryotic cell surface, followed by Rho mediated internalisation; this illustrates the relevance of cellular microbiology. CAMs might prove to be novel therapeutic targets. Comparative genomics has provided the knowledge of shared virulence determinants among diverse bacterial genera, and will continue to deepen our understanding of microbial pathogenesis, particularly in the context of the interaction of prokaryotic and eukaryotic molecules.

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The environment of any cell is a complex mixture of soluble molecules in the extracellular matrix (ECM), other cells, and insoluble molecules that form tissue matrices. Cell adhesion molecules (CAMs) are the means by which a

cell communicates with other cells and the ECM. Thus, the cell samples its environment by means of complex arrays of CAMs present on the cell surface and integrated into the cell membrane. Although named “cell adhesion molecules” because they mediate cellular attachment to other cells and the ECM, this “stickiness” is not always the prime function of a particular molecule. For example, cellular attachment is the means by which a cell maintains itself in a certain relative location, to allow the cell to sample its environment and respond to molecules that are part of neighbouring cells and insoluble matrices.¹

All CAMs are transmembrane glycoproteins and have extracellular, transmembrane, and intracellular domains; thus, they connect the interior and exterior of a cell. All molecules bind their specific receptor or ligand, and this binding leads to a conformational change in the extracellular domain. All CAMs are attached to an intracellular molecule, which affects the function of the cell through the “second messenger pathway”, producing changes in the cytoskeleton or the chemical composition of the cell. There are six families of CAMs; the immunoglobulin-like superfamily, the cadherins, the integrins, the receptor protein tyrosine phosphatases, the selectins, and the hyaluronate receptors. For information on each of their features, ligands and functions see the review by Freemont.¹ CAMs can modulate disease processes, whether they are expressed normally or not.² The role of CAMs or their ligands in abnormal processes occurs either as part of a physiological response to a pathological event—for example, inflammation or infection—or as part of the pathological process itself.¹

Microorganisms have developed various strategies to subvert host defences and permit their particular lifestyle, among which several general themes have emerged. To enable succinct and meaningful documentation of particular microbial–CAM interactions under the headings below, I will first outline some general concepts and their relation to microbial pathogenesis.

Current and relevant topics in microbial pathogenesis

GRAM NEGATIVE BACTERIAL SECRETION SYSTEMS
Four types of secretion in Gram negative bacteria have been documented: types I, II, III, and IV.³ Type I is sec independent and is exemplified by the secretion of α -haemolysin by *Escherichia coli*; it secretes effector proteins across the inner membrane, periplasm, and outer membrane in a one step process. Type II secretion is sec dependent and secretes effector

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proteins across the inner membrane into the periplasm using the general secretory pathway (GSP)⁴; in the periplasm, the C-terminal sequence is removed and the protein is then secreted across the outer membrane by a complex of 12 or more proteins; known as the terminal branch of the GSP. The best studied example of type II secretion is the pullulanase (pulA) enzyme of *Klebsiella oxytoca*.⁴ Type III secretion occurs on host cell contact, and facilitates the translocation of effector molecules directly into the host cell cytoplasm. Type III systems are thought to be direct descendants of the flagellar assembly and consist of 20 or more proteins, which span the cell envelope. Type III systems are crucial for virulence in various organisms including *Salmonella* spp, *Shigella* spp, enteropathogenic *E coli* (EPEC), and *Bordetella* spp.³ Effector proteins are targeted for type III secretion by the N-terminal sequence of their encoding mRNA molecule.⁵ Type IV secretion occurs in various species and is responsible for secretion of—for example, *Bordetella pertussis* P.69 pertactin and the serum resistance protein, brkA. Transport across the inner membrane, periplasm, and outer membrane probably occurs in three separate stages with N-terminal and C-terminal processing of the transported protein.⁶

CELLULAR MICROBIOLOGY

Microorganisms depend on their ability to subvert and subjugate eukaryotic host cells for their pathogenesis, and knowledge of eukaryotic cell physiology is becoming increasingly relevant to understanding microbial pathogenesis.⁷ Examples include viral adhesion/invasion and bacterial type III secretion systems, which facilitate bacterial internalisation and persistence. Pedestal formation in EPEC infection and phagocytosis are both mediated by cellular GTPases (Rho, Rac, and Cdc42), which are molecular switches for control of signal transduction pathways, linking membrane receptors to mitogen activated protein kinase and the actin cytoskeleton in various cell types.

RTX (repeats in toxin) toxins—for example, *E coli* α -haemolysin (hlyA), bind to lymphocyte function associated antigen 1 (LFA-1), a β_2 integrin (CD11a/CD18),⁸ causing pore formation and cytolysis. Several studies suggest that RTX toxins kill target cells by apoptosis.

Host defences are frequently responsible for disease manifestations, either directly in the case of the early response of plants to plant pathogens, or indirectly in the case of the utilisation of a particular pathway of phagocytosis that lacks a respiratory burst and enables intracellular survival in humans. Phagocytosis is an important host defence and in macrophages it is mediated by at least two receptors: complement receptor 3 (CR3), a β_2 integrin, and the immunoglobulin receptor (Fc γ R). CR3 consists of a 165 kDa α subunit (CD11b) and an 85 kDa β subunit (CD18). Rho, Rac, and Cdc42 are GTPases that act as molecular switches in the reorganisation of the actin cytoskeleton, and the profile of their involvement depends on the particular phagocytic mechanism.⁹ Immunoglobulin dependent uptake (type I phagocytosis) requires Cdc42 and Rac and involves pseudopod extension, membrane ruffling, a respiratory burst, and an inflammatory response. CR3 dependent uptake (type II phagocytosis) is mediated by CR3, requires only Rho, and occurs without a respiratory burst.^{10 11} Differential GTPase involvement between the two types of phagocytosis probably determines the physiological differences between Fc γ R and CR3 mediated phagocytosis.^{12 13}

The purpose of this review is to document the interaction of eukaryotic CAMs and microorganisms in the context of: (1) the microbe in its strategy to gain access to and cause disease in the host, and (2) the host in its strategy to defend itself against infection. These aspects will be dealt with in this order.

Microbial pathogenesis facilitated by CAMs

In general, the interaction of microbes with eukaryotic CAMs can be divided arbitrarily into those interactions mediated by microbial molecules that remain associated with the prokaryotic or eukaryotic cell envelope, and those mediated by secreted microbial products and toxins.

PROTOZOA

Table 1 summarises the interactions of eukaryotic CAMs with protozoa. Erythrocytes infected with the malaria parasite, *Plasmodium falciparum*, sequester in deep tissues by binding to endothelial cells. This favours parasite

Table 1 Protozoa and fungi that interact with eukaryotic cell adhesion molecules (CAMs) during their pathogenesis

Protozoan/fungus	Microbial molecules	Eukaryotic CAM	Role in pathogenesis	Refs
<i>Plasmodium falciparum</i>	PfEMP-1, erythrocyte band 3 related adhesin, sequestrin, and break point open reading frame	Endothelial CD36, ICAM-1, ELAM-1, VCAM-1	Sequestration of infected RBCs in deep tissues by endothelial cell binding; probably responsible for cerebral malaria	15–18
<i>Leishmania major</i>		CR3 (a β_2 integrin)	Mediates CR3 phagocytosis with reduced or absent respiratory burst	19
<i>Entamoeba histolytica</i>	170 kDa Gal/GalNAc lectin	?	Lectin similar to β_2 integrin and probably regulates integrin expression	20
<i>Candida albicans</i>	INT1 (α_M/α_X integrin-like)	—	Int1 has homology to human integrins and is crucial for adhesion, hyphal growth, and pathogenicity	21, 22
<i>Candida tropicalis</i>	β_1 Integrin-like protein	—	Adhesion	23
Yeasts		CR3 (a β_2 integrin)	CR3 phagocytosis	24
<i>Histoplasma capsulatum</i>	?	CR3 (a β_2 integrin)	CR3 phagocytosis	25, 26
<i>Pneumocystis carinii</i>	Gp120 (integrin-like protein)	? α Integrin subunit	Interaction of gp120 with A549 cells upregulates host cell α_5 integrin expression	27

CR3, complement receptor 3; ELAM-1, endothelial leucocyte adhesion molecule 1; ICAM-1, intercellular adhesion molecule 1; PfEMP-1, *Plasmodium falciparum* erythrocyte membrane protein 1; VCAM-1, vascular cell adhesion molecule 1.

growth, evasion of host defences, and occlusion of the microcirculation leading to hypoxia and lactic acidosis, which together are probably responsible for cerebral malaria.¹⁴ Several CAMs on endothelial and other cells mediate the interaction with infected erythrocytes, including CD36,^{15 16} intercellular cell adhesion molecule 1 (ICAM-1),¹⁷ endothelial leucocyte adhesion molecule 1 (ELAM-1), and vascular cell adhesion molecule 1 (VCAM-1).¹⁸

Leishmania major, the cause of leishmaniasis, is dependent for its pathogenesis on an intracellular lifestyle in the macrophage. The promastigote binds to CR3 and is phagocytosed by a type II pathway.¹⁹

Entamoeba histolytica kills host cells by adhering via a 170 kDa Gal/GalNAc lectin on its surface. This molecule contains a cytoplasmic domain with similarity to the β_2 integrin motif, a crucial regulator of integrin activities in other systems mediated by inside out signalling.²⁰

FUNGI

Table 1 summarises interactions of eukaryotic CAMs with fungi. Fibronectin receptors consisting of integrin-like proteins have been identified in *Candida albicans* and *Candida tropicalis* using various approaches, including monoclonal and polyclonal antibodies to $\alpha_5\beta_1$ integrins.^{23 28 29} The *C. albicans* INT1 gene encodes a surface protein that has 18% amino acid identity with the ligand binding (I) domain of the human α_M integrin, and is necessary for adhesion, filamentous growth, and virulence.^{21 22} However, proteins other than integrins may be involved because RGD motif (Arg-Gly-Asp) deletion in recombinant fibronectin does not decrease adherence.²⁷ Yeasts also bind CR3 and are thus phagocytosed by macrophages by a type II pathway.²⁴

Histoplasma capsulatum is a dimorphic, facultative intracellular fungus causing a broad spectrum of disease, including disseminated disease in the immunocompromised host.²⁵ *Histoplasma capsulatum* yeasts and microconidia bind to macrophage CR3, mediating phagocytosis by a type II pathway, with a reduced or absent respiratory burst,²⁵ and also bind to LFA-1 (CD11a) and p150,95 (CD11c).^{26 30} However, the fungal ligand(s) are unknown at present. The organism multiplies within the macrophage phagosome by controlling the intraphagosomal environment and is then disseminated throughout the host.²⁵

Pneumocystis carinii recognises ECM proteins such as fibronectin, vitronectin, and laminin on alveolar epithelial cells. *Pneumocystis carinii* encodes gp120, a membrane glycoprotein, which binds fibronectin in the presence of divalent cations, and this binding is inhibited by RGDS (Arg-Gly-Asp-Ser) from the fibronectin binding domain. Binding of gp120 to A549 pulmonary epithelial cells upregulates eukaryotic α_5 integrins.²⁷ These data suggest that an α integrin on the host cell interacts with a β integrin on the microbial surface to produce an integrin heterodimer.

BACTERIA

Table 2 summarises interactions of eukaryotic CAMs with bacteria. *Staphylococcus aureus* and *Streptococcus pyogenes* produce various proteins of the superantigen family that bind specifically to the V β chains of the T cell receptor with high affinity, activating larger numbers of T cells than processed antigens and resulting in massive cytokine release.³¹ Several clinical syndromes have been linked with superantigens such as food poisoning, toxic shock syndrome, and Kawasaki syndrome.³¹ Bacterial superantigens implicated in human disease include toxic shock syndrome toxin 1 (TSST-1), staphylococcal enterotoxin A (SEA), staphylococcal enterotoxin B (SEB), staphylococcal enterotoxin C (SEC), and streptococcal pyrogenic exotoxin A (SpeA). Released cytokines upregulate vascular and neutrophil adhesion molecules, leading to neutrophil influx. Leucocyte recruitment occurs through sequential involvement of different CAM families: selectins (E, P, and L), integrins (α_4 , β_1 , β_2), and members of the immunoglobulin superfamily (ICAM-1, ICAM-2, and VCAM).³²⁻³⁵ *Streptococcus pyogenes* pyrogenic exotoxin B (SpeB) is a crucial virulence factor for invasive disease. A variant of SpeB, SpeB2, produced by all isolates of the virulent M1 serotype, contains an RGD sequence that mediates binding to $\alpha_v\beta_3$ or $\alpha_{2b}\beta_3$ integrins on endothelial cells and platelets, respectively.³⁶

Mycobacterium tuberculosis is a facultative intracellular pathogen that enters alveolar macrophages, resists macrophage killing mechanisms, establishes a chronic infection, and disseminates via the blood and lymph, frequently in the absence of symptoms. The organism may bind to a number of receptors including the integrins, CR3, and CR4. CR3 binding leads to CR3 phagocytosis with an absent respiratory burst. Binding of macrophage CR3 also reduces interleukin 12 production, with a consequent suppression of macrophage responses and T helper type 1 (Th1) dependent cell mediated immunity.^{37 38} On the other hand, CR4 binding results in phagocytosis with a respiratory burst. In addition, *M. tuberculosis* chaperonin 60 (heat shock protein 65) upregulates E selectin and ICAM-1 on vascular endothelium,³⁹ and is thus proinflammatory and immunomodulatory, with the potential to induce tissue pathology.

Listeria monocytogenes is a Gram positive bacillus capable of intracellular replication in enterocytes, fibroblasts, dendritic cells, and macrophages. The normal route of infection is via the intestinal epithelial M cells of the Peyer's patches, followed by basolateral invasion of enterocytes, and dissemination by blood and lymphatics to other tissues. Bacterial internalin A (InlA), a cell wall associated protein, binds E-cadherin on epithelial cells and is essential for internalisation.⁴⁰ Internalin B (InlB) is required for entry into hepatocytes but its receptor is unknown.⁴¹ InlA and InlB contain leucine rich repeats and are members of a superfamily of leucine rich repeat containing proteins that are found only in pathogenic bacteria—for example, *Shigella flexneri* ipaH,

Table 2 Bacteria that interact with eukaryotic cell adhesion molecules (CAMs) during their pathogenesis

Bacterium	Bacterial molecule	Eukaryotic CAM	Role in pathogenesis	Refs
<i>Staphylococcus aureus</i>	TSST-1, SEA, SEB, SEC	P, E, L selectins, $\alpha_4\beta_1\beta_2$ integrins, ICAM-1, VCAM	Mitogenic with massive cytokine release	32–35
<i>Streptococcus pyogenes</i>	SpeA	P, E, L selectins, $\alpha_4\beta_1\beta_2$ integrins, ICAM-1, VCAM	Mitogenic with massive cytokine release	31
	SpeB	$\alpha_4\beta_3 + \alpha_{2b}\beta_3$ Integrins	RGD mediated adhesion to endothelium and platelets	36
<i>Mycobacterium tuberculosis</i>		CR3 (β_2 integrin CD11b/CD18)	CR3 phagocytosis without O ₂ burst	38
	Chaperonin 60 (hsp65)	CR4 (β_2 integrin CD11c/CD18) Upregulation of E selectin and ICAM-1 on vascular endothelium	CR4 phagocytosis with O ₂ burst Proinflammatory and immunomodulatory	38 39
<i>Listeria monocytogenes</i>	Internalin A	E-cadherin	Invasion of epithelial (including M) cells	40
	Internalin B	?	Invasion of epithelial (including M) cells and hepatocytes	41
<i>Escherichia coli</i>	Antigen 43	Integrins	RGD motif; secreted by type IV pathway	42
	α -Haemolysin	β_2 Integrin (LFA-1) CD11a/CD18	Adherence, pore formation, and cytolysis	8
Enteropathogenic <i>E. coli</i> (EPEC)	Intimin	Tir + β integrins	Adherence and pathogenesis of A/E lesion	43–45
<i>Shigella flexneri</i>	IpaBCD complex	$\alpha_5\beta_1$ Integrin	Uptake into CHO cells	46, 47
<i>Yersinia pseudotuberculosis</i>	Invasin	β_1 Integrins	Bacterial translocation via M cells	48–50
<i>Serratia marcescens</i>	Ssp	Integrins	RGD motif; secreted by type IV pathway	51
<i>Legionella pneumophila</i>		CR3 integrin	Adhesion and phagocytosis	52
<i>Neisseria</i> spp.	Opa	HSPG	Invasion of Chang epithelial cells	53, 54
	Opa	HSPG + $\alpha_5\beta_1$ integrin	Invasion of HeLa/CHO cells	55, 56
	Opa	HSPG + $\alpha_5\beta_1$ integrin	Invasion of HEP-2 cells	57
	Opa	CD66	Invasion of neutrophils	58
<i>Bordetella pertussis</i>	fimD	Integrin VLA-5	Adhesion	59
	PT	CR3 integrin, Mac-1 integrin receptor (CD11b/CD18)	CR3 upregulation as a result of selectin mimicry. Monocyte cell adhesion	60, 61
	FHA	Integrins	Adhesion and invasion via CR3 phagocytosis	62
	P.69 pertactin	Integrins	Adherence may be mediated by RGD motif; secreted by type IV pathway	61, 63
	BrkA	Integrins	RGD motif; secreted by type IV pathway; mediates serum resistance	64
	TcfA	Integrins	RGD motif; secreted by type IV pathway; contributes to tracheal colonisation	65
				RGD motif; secreted by type IV pathway
<i>Bordetella parapertussis</i>	P.70	Integrins	RGD motif; secreted by type IV pathway	67
<i>Bordetella bronchiseptica</i>	P.68	Integrins	RGD motif; secreted by type IV pathway	68
<i>Bartonella bacilliformis</i>	?	$\alpha_5\beta_1$ Integrin	Bacterial translocation into Hep2 cells	69
<i>Pasteurella haemolytica</i>	Leucotoxin	β_2 Integrin (LFA-1) (CD11a/CD18)	RTX toxin binding, pore formation, and apoptosis	70
<i>Borrelia burgdorferi</i>		CR3 integrin, $\alpha_{11}\beta_3$ integrin	CR3 phagocytosis. Adhesion to platelets	71 72
<i>Prohpyromonas gingivalis</i>	LPS	Upregulation of E and P selectins	?Ability to colonise and cause chronic disease	73
<i>Actinobacillus actinomycetemcomitans</i>	?	Integrins	Invasion	74
	Leucotoxin	β_2 Integrin (LFA-1) CD11a/CD18	RTX toxin binding, pore formation, and cytolysis	8
<i>Mycoplasma penetrans</i>	Membrane lipoprotein	CD18 (β subunit of β_2 integrins)	Mitogenicity	75, 76

A/E attaching and effacing; CHO, chinese hamster ovary; CR3, complement receptor 3; FHA, filamentous haemagglutinin; fimD, minor fimbrial subunit D; hsp65, heat shock protein 65; HSPG, heparan sulphate proteoglycan; ICAM-1, intercellular adhesion molecule 1; LFA, lymphocyte function associated antigen 1; LPS, lipopolysaccharide; PT, pertussis toxin; SEA, staphylococcal enterotoxin A; SpeA, streptococcal pyrogenic exotoxin A; tcfA, tracheal colonisation factor A; 1; Tir, translocated intimin receptor; TSST-1, toxic shock syndrome toxin 1; VCAM-1, vascular cell adhesion molecule.

Yersinia pestis yopM, *B. pertussis* filamentous haemagglutinin (FHA), and *Treponema pallidum* TpLRR.^{77–80} The leucine rich repeat region of InlA mediates binding to caco-2 cells.⁸¹

Escherichia coli hlyA is an RTX toxin that kills human immune cells. It is secreted by a type I pathway and is localised to the surface of lymphocytes by binding to LFA-1, a β_2 integrin (CD11a/CD18).⁸ EPEC is the prototype of a family of pathogens that causes “attaching and effacing” lesions, characterised by intimate adherence between bacteria and epithelial cells and effacement of intestinal microvilli.⁴³ Several proteins, designated Esps, translocated by a type III system, are essential for this activity. Adherence was shown to occur as a result of the binding of a bacterial intimin protein to a “eukaryotic” receptor. However, it has been discovered recently that the host receptor is in fact a bacterial product whose transfer into host cells is dependent on the type III system and two other proteins (espA and espB), and it has been renamed Tir (translocated intimin receptor) or espE. In addition, β_1 integrin may act as an alternative receptor.^{43–45}

Shigella flexneri, the cause of bacillary dysentery, enters epithelial cells by reorganising the actin cytoskeleton, a process requiring the Ipa

proteins secreted by the type III system.⁴⁶ The shigella IpaBCD complex has been shown to bind $\alpha_5\beta_1$ integrin, an interaction that appears to play an active role during entry.⁴⁷ Because β_1 integrins can associate with the actin cytoskeleton via the C-terminus, this may mediate invasion. The fact that Rho, a small GTPase involved in focal adhesion formation, is required for this is consistent with this hypothesis.⁴⁶

Yersinia pseudotuberculosis and *Yersinia enterocolitica* cause food poisoning and, after ingestion, translocate across the intestinal epithelial barrier via the M cells of Peyer’s patches. M cells are a major site of invasion of bacteria at least during the early stages of infection. In the mouse, M cells are invaded by both *Y. pseudotuberculosis*⁴⁸ and *Y. enterocolitica*.⁸¹ *Yersinia pseudotuberculosis* invasin protein attaches to β_1 integrins on M cells, leading to invasion.^{48–50} Murine Peyer’s patch M cells express β_1 integrins but enterocytes do not.⁴⁸ Internalisation requires high affinity binding and focal adhesion kinase activity.⁸² Invasin also promotes binding to and activation of B lymphocytes via β_1 integrin.⁸³

Legionella pneumophila is an aerobic Gram negative bacillus, which causes Legionnaire’s

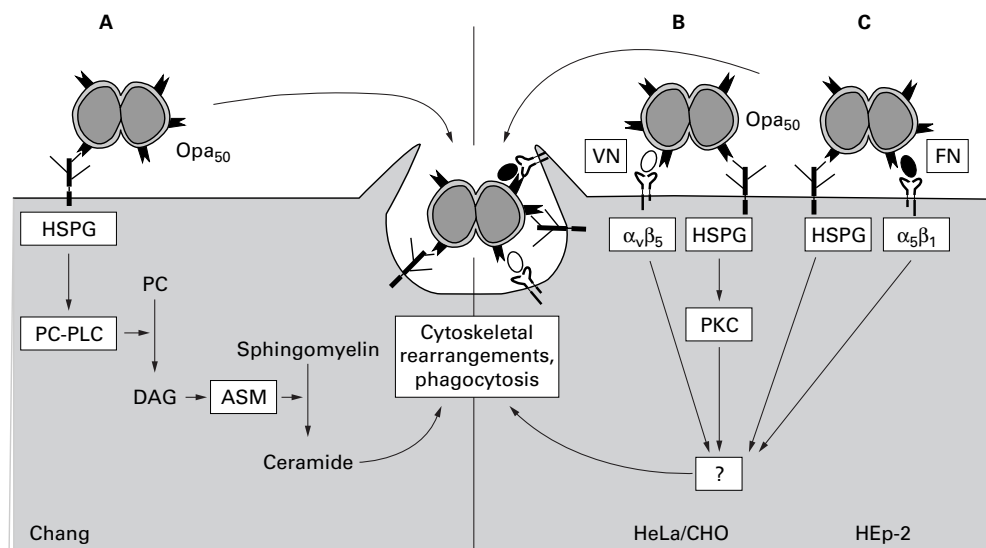


Figure 1 Mechanisms of Opa₅₀ mediated internalisation into different epithelial cell lines. (a) In Chang conjunctiva epithelial cells, heparan sulphate proteoglycan (HSPG) dependent internalisation involves the activation of phosphatidylcholine dependent phospholipase C (PC-PLC), which results in the generation of the second messenger diacylglycerol (DAG) from phosphatidylcholine (PC). DAG activates the acidic sphingomyelinase (ASM), which then generates ceramide from sphingomyelin. By an unknown process, ceramide is implicated in mediating cytoskeletal reorganisation and bacterial uptake by a mechanism that resembles conventional phagocytosis. (b) Efficient bacterial uptake into HeLa cervical carcinoma cells and Chinese hamster ovary (CHO) cells also relies on the ability of Opa₅₀ to mediate binding to the extracellular matrix protein, vitronectin (VN) and thereby to co-ligate HSPGs and α₅β₅ integrin vitronectin (VN) receptors, including α₅β₅. This internalisation process appears to be dependent on the activity of protein kinase C (PKC). (c) In HEp-2 larynx carcinoma cells, efficient bacterial uptake of Opa₅₀ expressing gonococci requires binding of the extracellular matrix protein, fibronectin (FN), which results in a co-ligation of HSPGs and the FN receptor α₅β₁ integrin; however, the mechanism of entry is still poorly understood. Reproduced from Dehio et al,⁵⁸ with the permission of Elsevier Science, Oxford, UK.

disease in predisposed individuals. The organism has an intracellular lifestyle and replicates in alveolar macrophages after opsonin dependent, CR3 mediated phagocytosis mediated by actin polymerisation at the site of entry, which is dependent on tyrosine phosphorylation of various host proteins.⁵²

Neisseria gonorrhoeae and *Neisseria meningitidis* colonise the human host, and this can either be asymptomatic or lead to the severe local or systemic inflammatory responses that characterise gonorrhoea and meningococcal meningitis, respectively. Primary attachment is mediated by bacterial pili, with a more intimate attachment mediated by the bacterial opacity associated (Opa) proteins, originally identified because their expression results in a change of colony opacity and colour as a result of bacterial aggregation.⁵⁸ Opa proteins utilise heparan sulphate proteoglycan (HSPG) in Chang conjunctiva cells for intimate adhesion and invasion.⁵³⁻⁵⁴ An alternate pathway of HSPG dependent invasion exists in HeLa and HEp-2 cells, which is triggered in the presence of serum. The serum factor is vitronectin, which binds specifically to Opa expressing gonococci, stimulating bacterial uptake in a α₅β₅ integrin dependent manner (fig 1).⁵⁵⁻⁵⁷ Opa proteins also bind CD66 on neutrophils, an interaction that mediates uptake.⁵⁸

Bordetella pertussis is a small Gram negative bacillus, which after aerosol transmission by respiratory droplets causes whooping cough in children and adults. The organism produces several adhesins and toxins that are coordinately regulated by the products of the BvgAS locus. Several of these virulence factors are dependent on host cell integrins for their

pathogenesis. The minor fimbrial subunit, fimD, has been shown to bind to integrin VLA-5 (very large antigen 5) and heparin, an interaction that is important for colonisation of the mouse respiratory tract.⁵⁹ Bacterial uptake into alveolar macrophages relies on selectin and integrin mimicry by PT and FHA, respectively.⁸⁴ Pertussis toxin S2 and S3 treatment of human macrophages upregulates CR3 as a result of selectin mimicry⁶⁰⁻⁶¹ (selectins have been shown to upregulate integrins).⁶³ Secreted FHA, which has binding sites for both integrins and the bacterial surface itself, coats the bacteria and mediates CR3 binding and phagocytosis, permitting avoidance of the respiratory burst and intracellular multiplication.⁶¹ Pertussis toxin has also been shown to bind the Mac-1 integrin receptor (CD11b/CD18,) leading to tyrosine phosphorylation and monocytic cell adhesion in serum.⁶²

Several proteins secreted by a type IV pathway (autotransporters) contain RGD motifs, which are associated with attachment to mammalian cells via binding of β integrins on the plasma membrane.⁸⁵ These include *B. pertussis* brkA,⁶⁵ P.69 pertactin,⁶⁴ and tcfA,⁶⁶ *Bordetella parapertussis* P.70,⁶⁷ *Bordetella bronchiseptica* P.68,⁶⁸ *E. coli* antigen 43,⁴² and *Serratia marcescens* ssp.⁵¹ Most RGD containing autotransporters contain two RGD sites, one within the passenger domain and one within the β domain.⁶ The importance of these RGD motifs has yet to be determined, but they probably play a role in the adhesion of *B. pertussis* P.69 pertactin.⁸⁶

Bartonella bacilliformis is a fastidious Gram negative bacillus, transmitted by the sandfly, which causes bartonellosis.⁸⁷ It is a facultative

Table 3 Viruses that interact with eukaryotic cell adhesion molecules (CAMs) during their pathogenesis

Virus	Eukaryotic CAM	Role in pathogenesis	Refs
Poliovirus 1-3	PVR (Ig-like)	Adhesion and invasion	89
Coxsackie virus A13, A18, A21	ICAM-1	Adhesion and invasion	92
Coxsackie virus A9	$\alpha_5\beta_1$ Integrins	Adhesion and invasion	88
Coxsackie virus B1-6	CAR (Ig-like)	Adhesion and invasion	99
Coxsackie virus B1, B3, B5	DAF; $\alpha_v\beta_6$ integrins	Adhesion and invasion	95, 96
Adenovirus	CAR (Ig-like)	Adhesion and invasion	97
Echovirus 1	$\alpha_5\beta_1$ Integrin	Adhesion and invasion	98
Echovirus 3, 6, 7, 11-13, 20, 21, 24, 29, 33	DAF	Adhesion and invasion	98-100
Echovirus 22	$\alpha_5\beta_1$ Integrin	Adhesion and invasion	101, 102
Hepatitis A (enterovirus 72; HAV)	HAVcr-1 (Ig-like)	Adhesion and invasion	103
Rhinovirus major gp (91 serotypes)	ICAM-1	Adhesion and invasion	93,94
Foot and mouth disease virus	$\alpha_5\beta_1$ Integrin	Adhesion and invasion	91
Encephalomyocarditis virus	VCAM-1	Adhesion and invasion	104
HIV-1	CD4	Adhesion and invasion of T lymphocytes	105
	PMN CD11a, CD11b, L selectin	HIV related PMN dysfunction	106
Human herpesvirus-7	CD4	Adhesion and invasion of T lymphocytes; downregulation of CD4	107, 108
Cytomegalovirus	$\alpha_5\beta_1$ Integrin	Immune evasion by downregulation of $\alpha_5\beta_1$ integrin on fibroblasts	109
Adeno associated virus (AAV)	$\alpha_5\beta_1$ Integrin	Adhesion and invasion	110
Hantaviruses	$\alpha_5\beta_1$ Integrins	Adhesion and invasion of platelets and endothelial cells	90
Bovine leukaemia virus	CD11c integrin	Pathogenesis of lymphocytosis involves upregulation of CD11c on B and T lymphocytes	111

CAR, coxsackie adenovirus receptor; DAF, decay accelerating factor; HIV, human immunodeficiency virus; ICAM-1, intercellular adhesion molecule 1; PMN, polymorphonuclear leucocyte; PVR, poliovirus receptor; VCAM-1, vascular cell adhesion molecule 1.

intracellular pathogen that binds to $\alpha_5\beta_1$ integrin on human epithelial cells, with the induction of tyrosine phosphorylation of several host proteins and subsequent uptake.⁶⁹

Pasteurella haemolytica is a Gram negative bacillus that produces a leucotoxin that kills bovine immune cells and causes bovine pasteurellosis. The leucotoxin is a member of the RTX family of pore forming toxins, which are thought to effect cellular killing by induction of apoptosis. An early step for induction of apoptosis is the binding of leucotoxin to β_2 integrin on bovine leucocytes.⁷⁰

The Lyme disease spirochaete, *Borrelia burgdorferi*, is transmitted by the bite of an infected tick, causing localised infection, which disseminates, leading to chronicity. It is a facultative intracellular pathogen, and binds CR3 leading to CR3 phagocytosis.⁷¹ The organism also binds platelets via $\alpha_5\beta_3$ integrin, which may be important in dissemination.⁷²

Porphyromonas gingivalis is an anaerobic Gram negative bacillus crucial for the development of adult periodontitis. *Porphyromonas gingivalis* lipopolysaccharide (LPS) has been shown to upregulate E selectins and P selectins, among other activities,⁷³ and this might be important in colonisation and pathogenicity. *Actinobacillus actinomycetemcomitans*, another coloniser of the gingival sulcus and a periodontal pathogen, enters host cells through ruffled apertures by an actin dependent mechanism, which may depend on host cell integrins for internalisation.⁷⁴ *Actinobacillus actinomycetemcomitans* also produces a leucotoxin that is a member of the RTX family of toxins. The leucotoxin binds LFA-1, a β_2 integrin, on leucocytes, resulting in pore formation and cytolysis.⁸

Mycoplasmas are minute prokaryotes without a cell wall, which enter an appropriate host and multiply and survive for extended periods of time. Mycoplasmas stimulate lymphocytes in a non-specific polyclonal manner. For example, *Mycoplasma penetrans* possesses several B and T cell mitogens, including a membrane lipoprotein whose activity is inhibited in a dose dependent manner by a

monoclonal antibody against CD18, the β subunit of β_2 integrins.⁷⁵ In addition, *Mycoplasma arthritidis* produces a superantigen.⁷⁶

VIRUSES

Table 3 summarises interactions of eukaryotic CAMs with viruses. Replication of a virus begins with attachment to its receptor (a eukaryotic cell surface molecule), followed by entry of the virus into the cell, and there are many examples of the use of CAMs in viral pathogenesis. Picornaviruses utilise at least nine distinct receptors for cell entry.⁸⁸ All three serotypes of poliovirus bind to the poliovirus receptor (PVR), which is a three immunoglobulin-like domain type I membrane glycoprotein, whose cellular function is unknown.⁸⁹ At present, no other picornavirus is known to use this receptor.⁸⁸ Coxsackie virus A9 (CVA9) uses the vitronectin receptor ($\alpha_v\beta_3$ integrin), also used by hantaviruses⁹⁰ and foot and mouth disease virus.⁹¹ CVA9 has an RGD integrin binding motif at the carboxyl end of VP1 (viral protein 1), and virus binding is blocked by RGD containing peptides; however, because trypsin mediated inactivation of this motif does not block infection of African green monkey cells, there may be an alternative receptor.⁸⁸ ICAM-1 is used by coxsackie viruses A13, A18, and A21⁹² and the major group of rhinoviruses (91 serotypes).^{93, 94} The coxsackie viruses, especially CVB3, may use decay accelerating factor (DAF) in association with $\alpha_v\beta_6$ integrin,^{95, 96} or the immunoglobulin-like coxsackievirus adenovirus receptor (CAR), also used by the adenoviruses.⁹⁷ Echoviruses use $\alpha_2\beta_1$ integrin,⁹⁸ DAF,⁹⁸⁻¹⁰⁰ or $\alpha_v\beta_3$ integrin.^{101, 102} Hepatitis A (enterovirus 72; HAV) uses the HAV cellular receptor 1 (HAVcr-1), whose cellular function is unknown, although is known to be immunoglobulin and mucin-like.¹⁰³ Encephalomyocarditis virus uses VCAM-1 for adhesion and invasion.¹⁰⁴

Human immunodeficiency virus 1 (HIV-1) gp120 binds CD4, a member of the immunoglobulin superfamily, on mature circulating T helper/inducer lymphocytes as a first step in

Table 4 Human cell adhesion molecules (CAMs) mediating leucocyte–endothelial cell interaction during host defence against infection¹⁵

Leucocyte receptor	Leucocyte distribution	Endothelial ligand	Expression	Function
Selectins				
L selectin (CD62L)	All leucocytes	GlyCAM-1 and others	Constitutive	Rolling
Integrins				
$\alpha_M\beta_2$ (Mac-1, Mo-1, CD11b/CD18)	Monocytes, PMN	ICAM-1, ?ICAM-2	Induced by IFN- γ and others	Firm adhesion
$\alpha_L\beta_2$ (LFA-1, CD11a/CD18)	All leucocytes	ICAM-1 ICAM-2	Induced by IFN- γ Constitutive	Firm adhesion
$\alpha_4\beta_1$ (CD49d/CD29)	All leucocytes	VCAM-1	Induced by TNF- α and others	Firm adhesion or rolling
$\alpha_4\beta_7$ Lymphocytes	MAdCAM	?	Rolling	
$\alpha_5\beta_1$	Lymphocytes, PMN	PECAM (CD31)	Constitutive	Transmigration
Immunoglobulin superfamily				
IAP (CD47)	All leucocytes	?	Constitutive	Transmigration
PECAM (CD31)	PMN	PECAM ? $\alpha_5\beta_1$	Constitutive	Transmigration
Others				
PSGL-1	PMN	P selectin (CD62P)	Constitutive	Rolling
ESL	PMN	E selectin (CD62E)	Induced by IFN- γ	Rolling
CD44	All leucocytes	Hyaluronate	Constitutive	?

ESL, E selectin ligand; GlyCAM-1, glycosylation dependent cell adhesion molecule 1; IAP, integrin associated protein; ICAM-1, intercellular adhesion molecule 1; IFN- γ , interferon γ ; LFA-1, lymphocyte function associated antigen 1; MAdCAM, mucosal addressin cell adhesion molecule; PECAM, platelet endothelial adhesion molecule; PSGL, P selectin glycoprotein ligand; PMN, polymorphonuclear leucocyte; TNF- α , tumour necrosis factor α ; VCAM, vascular cell adhesion molecule 1.

infection.¹⁰⁵ In addition, CD4–gp120 interaction is necessary for cell–cell spread of HIV. This led to early investigation of recombinant soluble CD4 (rsCD4) as an anti-HIV treatment. High dose intravenous rsCD4 abrogates viraemia in a dose dependent manner; however, the duration of the effect is limited by the pharmacokinetics of rsCD4. Although pharmacokinetics have been improved by combining rsCD4 with immunoglobulin molecules (rsCD4–IgG), therapeutic benefit in the treatment of established HIV infection has been limited. However, there may be some benefit in prophylaxis of perinatal and needle stick infections.¹¹² In addition, dysregulated neutrophil function in HIV infection is mediated by integrins and selectins.¹⁰⁶

Human herpesvirus 7 (HHV7) grows well in CD4 positive lymphocytes and also uses the CD4 molecule as its receptor.¹⁰⁷ HHV7 also downregulates expression of CD4 and, therefore, the use of its envelope has been suggested in anti-HIV treatment.¹⁰⁸

Cytomegalovirus (CMV), another herpesvirus, achieves permanent coexistence with its hosts by establishing latent infection in specific “privileged” tissues to evade immune surveillance.¹¹³ Mechanisms to this end include the CMV mediated downregulation of $\alpha_1\beta_1$ integrin in human fibroblasts,¹⁰⁹ and the possible production of a putative superantigen that is present on infected monocytes, leading to selective expansion of V β T cell receptor bearing lymphocytes.¹¹⁴ Alternatively, this superantigen may be a human gene product transcriptionally activated by CMV expression, which may induce active infection from the latent state.¹¹³

Adeno associated virus 2 (AAV-2), a ubiquitous human parvovirus, which is used as a vector in various experimental gene therapies, uses HSPG as a primary receptor, but is also dependent on $\alpha_v\beta_3$ integrin to increase susceptibility of cells to infection.¹¹⁰ $\alpha_v\beta_3$ Integrin is involved in facilitating virus internalisation, a finding that has relevance for human gene therapy.

Bovine leukaemia virus (BLV), human T lymphotropic virus 1 (HTLV-1), and HTLV-II belong to the same family of oncogenic retroviruses that causes spontaneous lym-

phocyte proliferation. Infection with these viruses is associated with increased expression of lymphocyte integrins, CD11c and CD18. Lymphocyte dysregulation in spontaneous lymphocyte proliferation probably involves signalling through these lymphocyte surface molecules.¹¹¹

CAMs in the host defence against infection

The cellular immune system is a potent force which, if controlled and directed correctly, is effective against an enemy and forms an appropriate host defence; however, if uncontrolled, it is ineffective against the enemy and can actually be harmful to the host itself. Therefore, leucocyte action must be held in check in the circulation, and discharged at the site of infection. This is achieved through the leucocyte adhesion molecules, which recognise areas of tissue damage and direct their own transendothelial migration into the tissues. Important in this process are integrins, selectins, and immunoglobulin-like superfamily members.¹¹⁵

LEUCOCYTE ADHESION MOLECULES

Leucocyte migration to sites of infection requires several separate adhesion events, namely: tissue damage recognition, endothelial interaction, transendothelial migration, and migration through the extracellular matrix to the site of infection. CAM families that mediate leucocyte and endothelial cell interaction and which are primarily responsible for these events include the integrins, selectins, and immunoglobulin superfamily. They recognise each other as a result of their affinities and their location on the plasma membrane. Table 4 summarises their expression and interactions. Because of the constitutive expression of certain leucocyte CAMs and the expression of certain other CAMs by the endothelial cells only at sites of inflammation, the leucocyte is always ready to recognise the endothelium at sites of infection.

Integrins exist in the membrane as heterodimers and function in cell–cell and cell–matrix interactions in almost all cells.¹¹⁶ Each heterodimer consists of an α and β chain encoded by their respective genes. There are 14 known α genes and eight known β genes, which

can combine to express 22 different integrins. The integrins modulate ligand binding kinetics in response to environmental signals and facilitate the need of leucocytes for migration, flexibility of function, and rapid response. Several leucocyte integrins are crucial to leucocyte adhesion, rolling, and transmigration, such as $\alpha_M\beta_2$, $\alpha_L\beta_2$, $\alpha_X\beta_2$, and $\alpha_4\beta_7$ (table 4).

Selectins are calcium dependent, and expressed on leucocytes and endothelial cells.¹¹⁷ L selectins are expressed constitutively on virtually all leucocytes and E selectins and P selectins are expressed on endothelial cells. E selectin is not expressed on resting endothelium but is expressed after stimulation by a number of cytokines released in response to inflammation, tissue damage, and immune responses.¹¹⁸ P selectin is expressed constitutively in many endothelial cells; not at the plasma membrane, but in regulated secretory Wiebel-Palade bodies.^{119 120} This stored P selectin is rapidly mobilised to the plasma membrane in response to inflammatory stimuli, such as thrombin or histamine, and is then recognised by circulating leucocytes. All known specific ligands for the selectins are mucins.

Immunoglobulin superfamily members mediate cell adhesion for a variety of different cell types. For example, on endothelial cells, ICAM-1 and ICAM-2 are recognised by leucocyte integrins; VCAM-1 is a ligand for $\alpha_4\beta_1$ integrin on monocytes and lymphocytes, and mucosal addressin CAM (MAdCAM) is recognised by $\alpha_4\beta_7$ and L-selectin on Peyer's patch lymphocytes,^{121 122} and has both integrin binding immunoglobulin domains and a selectin binding mucin domain. Two immunoglobulin superfamily members involved in leucocyte transendothelial migration are platelet endothelial adhesion molecule (PECAM) and integrin associated protein (IAP). PECAM is expressed at endothelial cell-cell junctions and on all leucocytes. IAP is present on fibroblasts, platelets, erythrocytes, neurones, epithelium, endothelium, and leucocytes.^{123 124} Both PECAM and IAP are expressed on leucocytes and endothelium and are probably involved in leucocyte transendothelial migration.^{125 126}

LEUCOCYTE TRANSENDOTHELIAL MIGRATION

The current leucocyte-endothelial adhesion model involves three steps.³⁴ In the first step, leucocytes are slowed in the circulation, most often by low affinity selectin-mucin interaction. This leads to leucocyte rolling along the vessel wall, with increased exposure of the leucocyte to the vessel environment, and thus increased sampling of signals from cytokines, chemoattractants, lipopolysaccharide, or abnormal homeostasis. Prevention of the rolling process severely impedes migration. Rolling leads to leucocyte activation as a result of stimulation of receptors, which include the serpentine family.¹²⁷ Leucocyte adhesion deficiency (LAD) type II comprises a syndrome of mental retardation, short stature, and defective polymorphonuclear cell function caused by an absence of sialyl-Lewis-X, an essential part of

selectin ligands, which results in greatly decreased leucocyte rolling.¹²⁸⁻¹³⁰

The second step is endothelial adhesion mediated by high avidity integrin activation, which for its efficient recruitment requires prior leucocyte rolling. This adhesion is inhibited by anti- β_2 integrin antibodies and is defective in LAD type I, a syndrome of delayed umbilical cord separation, and recurrent bacterial infections caused by a defect in polymorphonuclear cell migration and activation.¹³¹ LAD type I is caused by a defect in the β_2 (CD18) gene resulting in a failure to express β_2 integrins.¹³²

The third step is leucocyte transmigration through the intercellular junctions of the endothelium, requiring polymorphonuclear cell chemotaxis and endothelial cell signalling. Immunoglobulin superfamily members required for this step are PECAM-a (CD31) and IAP (CD47), which both interact with integrin $\alpha_v\beta_3$.^{133 134} It has been suggested that PECAM on tightly adherent leucocytes binds endothelial $\alpha_v\beta_3$, with a consequent loosening of cell-cell junctions, allowing the leucocytes to migrate through.¹³⁵ Once they have left the vascular compartment, leucocytes migrate to sites of infection on extracellular matrix proteins.

LEUCOCYTE ACTIVATION AT SITES OF INFECTION

Leucocytes at sites of infection and inflammation have a very different phenotype from those present in the circulation: they are metabolically active, highly adherent, and destructive. Many mediators can signal this phenotypic change, but among the most potent are the proteins of the ECM. This mechanism depends on β_3 integrin as the leucocyte receptor; called the leucocyte response integrin.¹³⁶⁻¹³⁸ IAP probably forms a complex with the leucocyte response integrin on the plasma membrane, a complex that acts as the signalling unit through which the ECM proteins mediate polymorphonuclear cell activation. Integrins also cooperate with other host defence receptors, such as Fc γ R and Mac-1.¹¹⁵

Conclusion and future prospects

In conclusion, eukaryotic CAMs are essential for the host defence against infection, and from present knowledge they are an integral facilitating factor in the pathogenesis of many protozoal, fungal, bacterial, and viral infections. Currently, the number of antibiotic options for treatment of infectious disease are limited because of the development of resistance. This has led to measures to preserve the usefulness of antibiotics, develop new classes of antibiotic, and develop alternative strategies for the treatment of infectious disease—for example, human recombinant antibodies, bacteriophage treatment, and the identification of novel bacterial targets for antibiotic treatment and for passive and active immunisation. The CAMs may represent such a target. For example, the RGD motif occurs in many microbial proteins and mediates binding to human integrins. RGD peptides and mimetics not only provide insights into microbial pathogenesis, but are potential therapeutics for various infec-

tious diseases, in addition to thrombosis and cancer.⁸⁵

The complete genome sequence is known for 10 bacterial pathogens and ~30 more are anticipated by the year 2000 (<http://www.tigr.org>). Comparative genomics, increasingly important, has provided the knowledge that shared virulence determinants exist in several different bacterial genera, and that the pathogens among these have modified these determinants to perform particular functions and therefore facilitate their particular lifestyles. Currently, using nucleotide sequence data, we can compare entire microbial genomes and identify putative virulence factors with homologous function. In addition, the human genome mapping project will provide insights into the pathogenesis of microbial infection, particularly in the context of the interaction of prokaryotic and eukaryotic molecules. With improvements in animal modelling and probes for global microbial gene expression under different conditions such as microarrays, our understanding of the pathogenesis of infectious disease and its treatment and prevention will continue to improve.¹³⁹

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