Silencing the alarm: insights into the interaction between host and pathogen

Conference on Microbial Pathogenesis: Mechanisms of Infectious Disease

Laurel L. Lenz¹⁺ & Helene L. Andrews-Polymenis²⁺⁺

¹National Jewish Medical and Research Center, Denver, Colorado, USA and ²Texas A&M University System Health Science Center, College of Medicine, College Station, Texas, USA

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¹Integrated Department of Immunology, National Jewish Medical and Research Center, Goodman Building, K510, 1400 Jackson Street, Denver, Colorado 80206, USA

²Department of Microbial and Molecular Pathogenesis, Texas A&M University System Health Science Center, College of Medicine, 407 Reynolds Medical Building, College Station, Texas 77843-1114, USA

*Corresponding author. Tel: +1 303 398 1767; Fax: +1 303 398 1396; E-mail: lenzl@njc.org

**Corresponding author. Tel: +1 979 845 9438; Fax: +1 979 845 3479; E-mail: handrews@medicine.tamhsc.edu

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Introduction

The biannual conference on Microbial Pathogenesis: Mechanisms of Infectious Disease, held between 21 and 26 July 2007, in Aspen, Colorado, USA, was a terrific venue for scientific interaction on topics covering diverse microbial species and the complex interactions with their hosts (Fig 1). It was clear from this meeting that the explosion of data and new techniques available in the genomic era is revolutionizing the study of host–pathogen interactions. Small interfering RNA (siRNA), the development of libraries of targeted deletions, and tools for using large amounts of gene expression data to assign function to hypothetical genes were featured in numerous talks. The use of such methodologies has added a new element to discoveries about the immune responses to pathogens, immune subversion and evasion, diverse pathogenic strategies, and new therapeutics and vaccines. Owing to space constraints, we are unable to discuss all of the findings presented; instead, we highlight several interwoven themes that tied together these diverse topics.

Microbe detection and innate resistance

To establish an infection in mammalian hosts, microbes must first overcome innate immunity. Trypanosome lytic factors (TLFs) are a novel innate barrier in primates against infection by African trypanosomes. J. Raper (New York, NY, USA) reported that TLF1 is a complex of several high-density lipoproteins, two of which are unique to humans: apolipoprotein L 1 (APOL1) and haptoglobin-related protein (HPR). Mice transiently expressing normal levels of human APOL1 are protected from *Trypanosoma brucei brucei* challenge, which identifies APOL1 as the protective component of TLF1. Expression of APOL1 also reduces infection in mice challenged with the vacuolar pathogens *Leishmania* and *Salmonella enterica* serotype Typhimurium, but does not protect them from challenge with the cytosolic pathogen *T. cruzi*. The elimination of vacuolar intracellular pathogens seems to require the rupture of parasite vacuoles and lysosomes by the TLF complex at low pH (approximately 5.5; Molina-Portela *et al*, 2005).

Phagocytes are also an early barrier to infection. Macrophages, dendritic cells and neutrophils use diverse receptors to detect microbial products and to activate other immune cells. Dectin-1—a C-type

Fig 1 | The diverse outcomes of host–microbe interactions. Bacteria, viruses, fungi and eukaryotic parasites occupy various niches within the host. The figure shows some of the interactions discussed in the text that contribute to colonization, disease and the resolution of infections. During colonization of mucosal tissues by commensal organisms (left), immune quiescence is actively maintained by both host and microbial factors. Conversely, the host immune system is activated during invasive infections (centre), although pathogenic microbes attempt to suppress immune activation. Some non-lethal invasive infections are resolved by the elimination of the infectious agent through (often adaptive) immune responses (centre right). Alternatively, some microbes can deflect the immune response through immune suppression or activation, enabling them to establish chronic infections (right). B, B cell; CXC, CXC chemokines; DC, dendritic cell; γHSV68, γ-herpes simplex virus 68; IFNγ, interferon-γ; IL, interleukin; Mo, macrophage; PMN, polymorphonuclear cell or neutrophil; T, T cell; TGFβ, transforming growth factor-β.

lectin receptor present on all phagocytes—binds to β-glucans present in yeast cell walls (also known as zymozan). Dectin-1 is necessary and sufficient for phagocytosis of zymozan in Dectin-1 transfected human embryonic kidney (HEK) 239 cells. Zymozan binding to Dectin-1 synergizes with Toll-like receptor 2 (TLR2) to induce nuclear factor κB (NFκB) translocation, the production of reactive oxygen species and the transcription of early growth response (EGR) transcription factors, as reported by D. Underhill (Los Angeles, CA, USA; Gantner *et al*, 2003). Mice deficient in Dectin-1 are highly susceptible to fungal infections because Dectin-1 can no longer bind to exposed β-glucans in commensal and pathogenic yeast.

TLRs and Nod-like receptors (NLRs; Nod for nucleotide-binding oligomerization domain) are two main families of innate receptors that activate NFκB and cytokine expression in response to microbial products. TLRs are transmembrane proteins that initiate responses to extracellular or vacuolar stimuli through the cytosolic adaptor protein MyD88. NLR proteins Nod1 and Nod2 require the cytosolic serine-threonine kinase Rip2 for NFκB activation. Mice deficient

for either MyD88 or Rip2 differ in their production of inflammatory cytokines and interferon-γ (IFNγ). C. Roy (New Haven, CT, USA) showed that, although mice deficient in MyD88 survive lung infection following intranasal inoculation with a low dose of the vacuolar pathogen *Legionella pneumophila*, mice deficient for both MyD88 and Rip2 succumb to *Legionella*. This observation suggests that either TLRs or NLRs are sufficient to protect against this pathogen. Both TLR- and NLR-dependent protection is observed in the absence of IFNγ.

Overzealous TLR signalling might be expected to have deleterious effects on the host by disrupting immunological homeostasis and inducing inappropriate inflammation. Indeed, J. Weis (Salt Lake City, UT, USA) reported that TLR2 deficiency increases the susceptibility of C57BL/6 (B6) mice to severe Lyme disease-like arthritis after infection with *Borrelia burgdorferi* (Wooten & Weis, 2001). Gene expression analysis using microarray experiments has shown strong pro-inflammatory IFN-driven responses in both C57BL/6.TLR2^{−/−} and arthritis-prone C3H mice following *B. burgdorferi* challenge.

Cytotoxic T-cell responses to intracellular pathogens

Appropriate activation of CD8⁺ cytotoxic T lymphocytes (CTLs) is particularly important to mediate immunity against many intracellular viral, bacterial and protozoan pathogens. Some viruses can avoid the immunological consequences of primed CTL responses by a selection of mutant antigenic alleles. P. Doherty (Melbourne, Australia) summarized his Nobel Prize-winning work on the role of class I molecules of the major histocompatibility complex (MHC I) in 'restricting' CTL responses (for a review, see Zinkernagel & Doherty, 1997), and presented new data showing that 'escape mutant' viruses direct the CTL response to otherwise silent peptide epitopes with lower affinities but broader specificities. J. Harty (Iowa City, IA, USA) reported a new vaccination strategy using initial immunization with peptide-coated dendritic cells, which accelerates memory CD8⁺ T-cell development and shortens the interval required for these cells to make a vigorous secondary response to booster immunization.

CTLs protect the host by producing immune regulatory cytokines and killing infected cells. Killing of uninfected target cells by antigen-specific CTLs requires the recognition of a small number of MHC I-peptide complexes. However, the killing of virus-infected cells is more difficult as these cells might be recognized by CTLs without being killed. A. Hill (Portland, OR, USA) showed that the murine cytomegalovirus (MCMV) proteins M4, M6 and M152—which reduce MHC I surface expression on infected cells—are particularly important in protecting cells infected with MCMV from lysis. Murine γ -herpesvirus 68 (γ -HSV68) also establishes latent infections in immune-competent mice. Control of latent infection requires IFN γ production and polyconal activation/expansion of V β 4⁺ CD8⁺ T cells, as they seem to mediate a portion of the IFN γ response. A. Evans (Atlanta, GA, USA) showed that the viral M1 protein is responsible for expansion of V β 4⁺ CD8⁺ T cells by a direct mechanism that is similar to, but distinct from, conventional superantigens.

CD4⁺ helper T cells and antibody

The Th1 and Th2 subsets of CD4⁺ 'helper' T cells promote strong CTL memory, as well as antibody class switching and somatic hypermutation. A third CD4⁺ helper T-cell subset—interleukin (IL)-17 producing (Th17) CD4⁺ T cells—promotes granulocyte responses and immune resistance to bacterial infection. M. Raffatellu (Davis, CA, USA) studied Th17 cells in the intestinal epithelium and observed that they are crucial for the paracrine induction of CXC chemokines and neutrophil recruitment. Simian immunodeficiency virus (SIV)-positive and SIV-negative macaques were infected with the intestinal pathogen *S. enterica* serotype Typhimurium. The SIV-infected animals had reduced memory CD4⁺ T cells in the intestinal mucosa, markedly reduced production of IL-17 and CXC chemokines, and increased numbers of *Salmonella* in the draining mesenteric lymph nodes. The observation that Th17 cells were specifically depleted from the intestinal mucosa of the SIV-infected macaques might explain the clinical observation that human immunodeficiency virus type 1 (HIV1)-positive humans suffer more frequently from systemic salmonellosis.

The activation of CD4⁺ T cells relies on the appropriate recognition of peptide antigens presented by MHC class II molecules (MHC II). Antigens presented by MHC II are processed in a vacuolar compartment of specialized antigen-presenting cells (APCs). Several *Mycobacterium tuberculosis* lipoproteins, including LpqH, inhibit MHC II presentation and CD4⁺ T-cell activation in a TLR2-dependent manner. C. Harding (Cleveland, OH, USA) presented gene expression studies revealing that *M. tuberculosis* suppresses IFN γ -induced

expression of class II transactivator (CIITA), MHC II and other antigen presentation genes. These effects are associated with the induction of β and δ isoforms of the CCAAT/enhancer binding protein (C/EBP) transcription factor, which might impair expression of the crucial transcriptional activator of MHC II expression, CIITA. Suppression of MHC II antigen presentation might promote the establishment of chronic *M. tuberculosis* infections or protect the host from excessive CD4⁺ T-cell responses.

Selective deficiency of IgA antibody production is the most common primary immune deficiency in humans, with an incidence as high as approximately 1 in 400 (Hammarström *et al*, 2000). Secretory IgA (slgA) is secreted onto mucosal surfaces by transcytosis across mucosal epithelia, a process mediated by the polymeric immunoglobulin receptor (plgR). R. Strugnell (Melbourne, Australia) showed that plgR-knockout mice produce serum IgA, but fail to secrete it across mucosal surfaces into faeces, saliva or bile. Specific slgA antibodies are required to protect against intoxication with cholera toxin, and naive slgA protect against intestinal challenge with *Salmonella* (Wijburg *et al*, 2006). When orally infected 'spreader' mice were mixed with uninfected wild-type mice and plgR-knockout mice, the plgR-knockout mice were selectively infected with *Salmonella* and developed fatal disease. plgR-knockout mice that were fed chicken ovalbumin (OVA) showed increased production of IgG specific for gut flora and increased intestinal proliferation of OVA-specific CD4⁺ transgenic T cells. Thus, immune responses to environmental antigens are dampened by antigen-binding to slgA and transcytosis to the intestinal lumen.

Immune subversion

Organisms that primarily cause acute infections are particularly useful models to study the strategies for manipulating or subverting innate immunity. Acute infections in murine models by most highly virulent strains of influenza virus result in neuraminidase-dependent activation of transforming growth factor- β (TGF β), as shown by S. Schultz-Cherry (Madison, WI, USA). The addition of TGF β to mice infected with influenza strains that fail to activate TGF β results in reduced viral titres and morbidity, whereas depletion of TGF β or the apoptosis-inducing protein p53 increases morbidity. *Yersinia pestis* also causes acute lung infections with a high degree of mortality. P. Dube (San Antonio, TX, USA) showed that *Y. pestis* inhibits production of CXC-ELR chemokines (CXC chemokines having an ELR motif) and IL-6 within the first 24 h of infection, reducing neutrophil recruitment and promoting increased bacterial growth. Aberrant activation of the immune system also contributes to persistent systemic *Salmonella* infection. During chronic infection of SV129 mice with *S. enterica* serotype Typhimurium, C. Detweiler (Boulder, CO, USA) showed that bacteria are found preferentially within haemophagocytic macrophages in systemic organs such as the liver. Haemophagocytosis is a common feature of typhoid fever and other persistent infections in humans.

Antigenic variation, a common strategy used by pathogens to avoid adaptive immunity, occurs in TprK, one member of a family of *Treponema pallidum* proteins (for a review, see LaFond & Lukehart, 2006). S. Lukehart (Seattle, WA, USA) reported that TprK sequences from different *T. pallidum* isolates vary extensively within seven hypervariable regions. Sequence variation—owing to segmental gene conversion—can be observed during the weeks following infection in the rabbit model of syphilis, suggesting that new variants of TprK are selected by their ability to evade the adaptive immune responses (LaFond *et al*, 2006). Similarly, *Plasmodium falciparum*

isolates harbour approximately 60 distinct versions of the *var* gene, each of which encodes an antigenically distinct erythrocyte membrane protein 1 (EMP1) virulence protein. Only a single *var* gene is expressed by a given parasite at any one time. K. Deitsch (New York, NY, USA) studied the mechanisms controlling *var* expression (Frank *et al*, 2007), and found that allelic exclusion is mediated by interactions between an upstream promoter and a second promoter located near the 3' end of each *var* gene. Manipulation of *var* gene exclusion also provided evidence that switching to expression of different EMP1 proteins is driven by the immune response to the surface-exposed EMP1 protein in *P. falciparum*.

Inflammasome activation

NLR-dependent detection of microbial products can lead to assembly and activation of the inflammasome. This multi-protein complex activates caspase-1 to cleave IL-1 β and IL-18, and can lead to death of the host cell. ASC (apoptosis associated speck-like protein containing a caspase recruitment domain) is an adaptor protein of the NLR family shown by D. Monack (Stanford, CA, USA) to have a crucial role in triggering *Francisella novicida*-mediated caspase 1 activation. *F. novicida*—a cytosolic bacterial pathogen—also strongly induces type I IFN production, which enhances both caspase-1 activation and the death of infected macrophages. It is not clear how cytosolic *F. novicida* is detected by the host as IPAF1 (IPAF for ice-protease activating protein), NALP3 (NALP for Nacht, LRR, PYD containing protein), NALP12, NAIP5 (NAIP for neuronal apoptosis inhibitory protein) and NOD2 are not required. Infection-induced cell death was also increased following infection of host cells with *F. novicida* that were mutated in the *FTT0584* or *FTT0748* genes.

The term 'pyroptosis' was recently coined to describe the pro-inflammatory form of caspase-1-dependent cell death (for a review, see Fink & Cookson, 2005). Some non-cytosolic pathogens also induce pyroptosis, including *Y. pseudotuberculosis*, as reported by T. Bergsbaken (Seattle, WA, USA); in this case, an unidentified secreted bacterial factor is responsible for inflammasome activation. Interestingly, secretion of this factor requires a functional type III secretion system (T3SS) but none of the known T3SS effector protein substrates seem to be required.

Microbial regulation of host-cell fate

Microorganisms use several other means to regulate host cell death and proliferation. Host cell death can result from intoxication by adenylate cyclase toxin (ACT), such as that of *Bordetella pertussis*. E. Hewlett (Charlottesville, VA, USA) showed that this toxin kills J774 macrophages by both apoptotic and non-apoptotic mechanisms. The traditional mechanism of killing by ACT is thought to involve the generation of excessive cAMP, but ACT also kills J774 cells by the depletion of ATP and by cytotoxicity resulting from pore formation. Low concentrations of ACT or oedema toxin from *Bacillus anthracis* also block progression through the cell cycle by reducing levels of cyclin D1. Another new toxin from enteropathogenic *Escherichia coli* (EPEC)—a food and water borne gastrointestinal pathogen—paralyses and kills the model host *Caenorhabditis elegans*. The exact nature of the secreted toxin is still being investigated, but D. Kalman (Atlanta, GA, USA) reported that live EPEC, exogenous tryptophan and regulation of the locus of enterocyte effacement (LEE) are required (Anyanful *et al*, 2005). Host susceptibility to EPEC involves DAF-2, an IGF1 (insulin-like growth factor receptor) homologue that prevents DAF-16 from

translocating to the nucleus to upregulate antimicrobial and survival genes and downregulate anti-ageing genes.

Kaposi-sarcoma-associated herpesvirus (KSHV) induces proliferation and differentiation of the host cells it infects. Spindle cells, of endothelial origin, are the predominant cell type in KS tumours. M. Lukanoff (Seattle, WA, USA) discussed studies on KSHV infection of blood endothelial cells in culture. *In vitro* KSHV-infected blood endothelial cells develop the morphology of spindle cells and KSHV infection remains latent. After KSHV infection, vascular endothelial growth factor receptor 1 (VEGFR1) expression is increased through the induction of hypoxia-induced transcriptional factors, and markers of lymphatic endothelial cells—such as VEGFR3—are also upregulated through the transcription factor PROX1 (Prospero homeobox 1).

Phase differentiation

Pathogenic fungi must be in the correct developmental state to be virulent. Much of the research effort in this area is now focused on determining how pathogenic fungi regulate the transitions between developmental states and on the functions of phase-specific factors (for a review, see Rappleye & Goldman, 2006). B. Klein (Madison, WI, USA) described forward genetic screens in the pathogenic fungus *Blastomyces dermatitidis* that identified candidate genes involved in the regulation of the transitions between the yeast (pathogenic) and mould phases. The histidine kinase *drk1* (drk for dimorphism-regulating histidine kinase) was identified as a crucial regulator of the transition to the yeast form and coordinately, of the expression of virulence genes such as *bad1* (blastomyces adhesin 1); however, the environmental signal that activates *drk1* is unknown. Regulators of the opposite transition, from yeast to mould, in *Blastomyces* include a repressor of siderophore biosynthesis—a GATA family transcription factor—which is similar to Cir1 (Cryptococcus iron-regulator 1). *Cir1* is a central regulator of the iron regulon and of virulence in another pathogenic fungus, *Cryptococcus neoformans*.

W. Goldman (St Louis, MO, USA) reported the identification and characterization of two yeast phase-specific factors in *Histoplasma capsulatum*, calcium-binding protein (CBP) and α -(1,3)-glucan. Nuclear magnetic resonance revealed that CBP is a homodimer with structural homology to the saposin family lipid- and membrane-binding proteins. In *H. capsulatum*-infected macrophages, CBP is secreted into the vacuole containing the yeast and might interact with host lipids. The minimum infectious dose of CBP mutants required to recover organisms from infected mice is 1,000-fold higher than for wild-type *H. capsulatum*. A second factor specific for the yeast phase, α -(1,3) glucan, obscures the recognition of underlying β -glucan by Dectin-1.

C. Kumamoto (Boston, MA, USA) discussed the formation of hyphal filaments by *Candida albicans*. Hyphal filaments—which are the pathogenic form of this fungus—are formed in response to high temperature, serum and surface contact. Mutations in Dif1 (Duolp-interacting protein), an integral plasma membrane protein, cause a failure to form filaments in response to surface contact. Kumamoto also showed that the *EFH1* gene is expressed in the intestine and regulates commensal colonization by *Candida* in this niche as Efh1-null mutants hypercolonize the intestinal tract in murine models. The *RBT1* and *RBT4* (RBT for Repressed by Tup 1) genes are also expressed during commensalism, but are not required for its establishment. Mutants in RBT1 and RBT4 have reduced virulence, suggesting that *Candida* produces

‘virulence factors’ during commensalism to exploit conditions that are favourable to the pathogenic form as they occur.

Microbial colonization and virulence strategies

Many microbes colonize various niches within the host; these organisms might be pathogens in one niche, but co-exist as commensals in another. Another twist on this theme occurs when a bacterium acts as a non-pathogenic commensal in one host species and a pathogen in another.

Campylobacter jejuni is a highly prevalent commensal in poultry and is the leading cause of bacterial food-borne illness in humans. *C. jejuni* survives and grows primarily in the mucous layer of the chick caecum. V. DiRita (Ann Arbor, MI, USA) reported that, in experimental *Campylobacter* infections of one-day-old chicks, the levels of proinflammatory cytokines—IL-1 β , IL-8 and TGF β —are elevated at day 1 after infection but rapidly return to pre-infection levels. Heterophils—the avian equivalent of neutrophils—are recruited to the caecum and remain elevated until day 7 after infection. The genes necessary for this commensal colonization were defined by using signature tagged mutagenesis (Hendrixson & DiRita, 2004). Flagellar genes, chemotaxis genes and protein glycosylation locus (*pgl*) genes involved in N-linked glycosylation are all necessary for colonization of chicks by *C. jejuni*. Developing an understanding of the commensal state will provide a basis for the development of new methods to reduce transmission of *C. jejuni* to humans.

Enterohaemorrhagic *E. coli* (EHEC, O157:H7) is a commensal of livestock species, but causes serious disease in humans. V. Sperandio (Dallas, TX, USA) has previously shown that EHEC communicates with both host microflora and the host itself by sensing the bacterial autoinducer molecule AI-3 and the host hormone adrenaline/noradrenaline, respectively (Sperandio *et al.*, 2002, 2003). Sperandio and colleagues reported that the sensing of these molecules by the EHEC histidine kinase QseC results in the activation of a complex regulatory cascade that activates bacterial factors necessary for pathogenicity, including the flagellar regulon, the LEE and Shiga toxin. The components of this remarkable ‘inter-kingdom’ signalling cascade exist in other enterobacteriaceae (*Shigella*, *Salmonella* and *Yersinia* spp.), and also in bacteria such as *Coxiella burnetii*, *Pasteurella* and *Haemophilus* species for which the primary pathogenic niche in humans is outside the intestinal tract.

Several important Gram-negative bacterial pathogens use T3SS to promote colonization and virulence through the secretion of substrate proteins—which might also be toxins—into eukaryotic cells. The respiratory opportunist *Pseudomonas aeruginosa* has a T3SS and injects up to four enzymes—ExoS, ExoT, ExoY and ExoU—into infected eukaryotic cells; the most toxic protein is the phospholipase ExoU (Sato & Frank, 2004). D. Frank (Madison, WI, USA) reported that cell death presumably occurs owing to plasma membrane degradation, although a non-catalytic ExoU is found in the cytoplasm of infected cells. Superoxide dismutase (SOD1)—a cofactor for ExoU—is also localized cytoplasmically, suggesting internal eukaryotic membranes might be the primary cellular targets of ExoU (Sato *et al.*, 2006). C. Collins (Seattle, WA, USA) discussed a recently identified locus, *yit/yip* that encodes effectors of T3SS in *Y. pestis*, the causative agent of plague. The *yit/yip* locus is orthologous to a locus encoding insecticidal toxins in *Photobacterium luminescens* (Gendlina *et al.*, 2007). *Yit/yip* genes are expressed in the midgut of the flea and are hypothesized to promote transmission from the flea to the human host.

Intracellular transport

Numerous pathogens can manipulate the host cell to establish an intracellular compartment favourable for survival and growth of the pathogen. Extensive fluorescence, confocal and electron microscopy studies have provided a new window on the establishment and diversity of these compartments. *Brucella abortus*—the causative agent of undulant fever in humans—survives and replicates inside a specialized phagosome called the *Brucella*-containing vacuole (BCV; for a review, see Celli, 2006). J. Celli (Hamilton, MT, USA) explained that this compartment is initially positive for the late endosomal/lysosomal marker lysosome-associated membrane protein 1 (LAMP1), is acidified and is permissive for the expression of the *VirB* type 4 secretion system (*virB*). Blocking acidification of the BCV early in infection prevents *Brucella* survival and growth. In HeLa cells—which are less bactericidal than macrophages but support similar trafficking—intermediate BCV (I-BCV) acquires the late endosomal markers Rab7, LAMP1 and CD63, is accessible to fluid-phase markers and fuses with the lysosomal compartment, showing trafficking along the endocytic pathway. Such events are required for further trafficking towards the endoplasmic reticulum and biogenesis of the replication-permissive compartment.

The protozoan parasite *Toxoplasma gondii* inhabits a unique intracellular vacuole—the parasitophorous vacuole—which is different from that described for *Brucella*. The unusual biochemical properties of the parasitophorous vacuole membrane create a non-fusogenic vacuole that secures the parasite from lysosomal degradation. *Toxoplasma* relies on nutrients, such as cholesterol, diverted from the host cell lysosomes for its survival and growth in mammalian cells (Sehgal *et al.*, 2005). I. Coppens (Baltimore, MD, USA) showed that *Toxoplasma* recruits endoplasmic reticulum around the parasitophorous vacuole 2 min after infection. The parasitophorous vacuole then rapidly moves adjacent to, and becomes anchored to, the host cell nucleus. *Toxoplasma* also remodels the microtubular network of the host, attracting host acidic organelles; the surface of the parasitophorous vacuole is lined with microtubules located in deep invaginations of the parasitophorous vacuole membrane that facilitate the delivery of host endolysosomes. *Toxoplasma* modulates the properties of the parasitophorous vacuole independently of host nuclear functions such as gene transcription, mRNA processing and signalling cascades dependent on the host nucleus.

Conclusions

The studies of commensal host-microbe interactions discussed at this meeting shed light on new virulence strategies, as did the work on the mechanisms of host invasion and microbial virulence factors contributing to disease. Studies on the host immune response and mechanisms of immune subversion brought into focus the importance of stimulating appropriate immune responses for protection against infectious agents. Furthermore, the proceedings and discussions highlighted several promising approaches to improve therapeutics and vaccines. Progress in our understanding of the complex and important health issues in infectious disease and host response is clearly benefiting from new technologies of the genomic era, but will nonetheless require continued basic and applied research on many diverse fronts.

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