The Molecular Koch’s Postulates and Surgical Infection: a View Forward.

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Introduction:

The only way I know how to make sense out of the last fifty years of molecular biology is to abandon the mechanistic and atomistic ideas of the pre-DNA era and embrace a more organic, cognitive and computational view of cells and genomes. There are no units, only interactive systems. Bacteria continually pick up and process information about the environment, internal conditions and other cells to decide on appropriate biochemical and biomechanical actions…..The take-home lesson of more than half a century of molecular microbiology is to recognize that bacterial information processing is far more powerful than human technology from Bacteria are small but not stupid: cognition, natural genetic engineering and socio-bacteriology1- James A. Shapiro PhD.

Everything touches everything- Jorge Luis Borges

Over a century ago Robert Koch set forth the postulates of causality for microbial disease that guide the investigation and management of infection. Koch’s postulates state that in order to implicate an organism in the pathogenesis of a disease the organism should: 1) be found in abundance in individuals with the disease, 2) be isolated and cultured from affected individuals, and 3) reproduce the disease when inoculated into a healthy host. Shortly after their initial publication, Koch revised the postulates to accommodate a carrier state in which individuals may harbor the organism without developing disease. Although technical advances have expanded our understanding of the scope of infectious diseases to include a wide array of micro-organisms, viruses and even prions, these postulates continue to guide investigations of disease pathogenesis and influence clinical practice.

However, as mechanistic details of the pathogenesis of infection are uncovered via advances in genomics, proteomics, and molecular detection techniques, it is becoming increasingly clear that the original Koch’s postulates are inadequate to explain the occurrence, course, and outcome of many serious infections. For this reason a drafting of “molecular” Koch’s
postulates has emerged to characterize the patterns of expression of various host and microbe genes (Figure 1).\textsuperscript{2} It is the dynamic expression of these genes that ultimately dictates whether the host-pathogen interaction results in microbial containment or clinical infection. The recognition that microbes are constantly turning on and off virulence genes in a context dependent manner, that they promiscuously swap genes with one another to acquire unique phenotypes, and that the host response to a particular microbial phenotype is not only dependent on its genotype but also is confined by the temporal and spatial dynamics present at the precise site of the host-pathogen interaction, speaks to the need to more precisely define causative agents of clinical infection beyond current definitions. For the surgeon, this distinction is critical as decisions to operate for infection are often not only driven by the recovery of a microbe or microbial colony at a presumed site of tissue damage, but also on the clinical impression that a given infection cannot be treated by antibiotics alone. While surgeons have long recognized that variations in outcome from serious infection are the product of a complex interaction between pathogens and the immune response, recent discoveries on the dynamic interplay at the molecular level have transformed current thinking on how microbes cause disease. This review will present specific examples of how the pathogenesis of a surgical infection can be viewed as a bi-directional chemical dialogue between a pathogen and its host where ongoing information processing between both organisms leads to either symbiosis (i.e. molecular détente) or conflict (inflammation, organ failure). We will provide examples of how the molecular Koch’s postulates can be used as a framework to more completely understand the variability in outcome from complex surgical infections especially those that arise in the most vulnerable patients such as premature babies and the critically ill. Finally we will present the view that in order to capitalize on the evolving knowledge base of the host-pathogen interaction for the purpose of developing novel therapies, dynamic computer based representation of the
pathophysiology of surgical infection with tools such as agent based modeling can accelerate the discovery process.

**Bacterial Information Processing: sensors, cognition, and decision making about virulence**

Advances in molecular microbiology have demonstrated that virtually all microorganisms can be considered “opportunistic” given that they have evolved sophisticated mechanisms to sense changes in their environment and respond accordingly. Microbes are constantly making decisions about the cost versus benefits of expressing virulence versus controlling population growth. Under conditions where nutrients are abundant and predation is limited, microbial communities exist in a stable low-growth state while sharing nutrients. Alternatively, when their survival is threatened by fierce competition for resources (as might be encountered during extreme physiological stress within an injured host), microbial communities can become destabilized and express virulence tactics such as host nutrient scavenging (i.e via tissue invasion), up-regulation of multiple defense mechanisms such as biofilm formation, and even a toxic offensive (type III secretion). As such, bacteria have evolved multiple mechanisms to sense and respond in a context dependent manner using a variety of membrane based and multi-layered information processing systems (Figure 2A). Multi-component membrane biosensors have been demonstrated to recognize both physiochemical “cues” (pH, nutrients\(^3\), osmolality, etc) as well as soluble and structural components of their hosts such as epithelial membranes, immune elements (interferon gamma\(^4\), dynorphin\(^5\)), and end products of tissue damage (adenosine\(^6\)). Bacteria recognize these cues and process them to safely navigate various environments and compartments within the host. Local environmental cues are gathered by bacteria at the membrane level and transmitted to deeper circuits within their cytoplasm
Quorum sensing is a hierarchical system by which bacteria sense their population density and use cell-cell signaling molecules to synchronize complex assemblage behavior. Importantly, recent evidence has demonstrated that bacteria use the quorum sensing system to sense more than just a quorum. The quorum sensing system is not only activated in response to bacterial population density dynamics but also in response to various host elements released during surgical injury and ischemia such as immune elements and end products of tissue hypoxia such as adenosine. There is a wide range of inter-kingdom molecular crosstalk between the microbial quorum sensing system and various host tissues. For example, host defense molecules can either activate or silence microbial quorum sensing; conversely quorum sensing molecules can either activate host signals or silence them. This type of inter-species and inter-kingdom host-microbe and microbe-microbe crosstalk demonstrates the multi-directional communication network that forms the syntax and lexicon of the chemical language of infection. The ability of all of the microbiota to intercommunicate and process information about resource availability and the health status of the host has led to the concept of bacteria behaving as social groups or microbial consortia\(^1\) (Figure 2B). This emerging field known as sociomicrobiology, describes the chemical processes by which social networks develop among microbes to form structural and social communities via information “nodes” and “hubs.” Under rigorous laboratory conditions, community behavior can then be observed to vary from displaying stable growth and sharing of resources to spite, fratricide, or renegade behavior\(^7\). Application of sociomicrobiology to understand how our microbial partners sense and respond to the physiologic stress imposed by organ transplantation, tissue hypoxia, pharmacologic immunosuppression, etc, has the potential to shed enormous light on the critical role the surgeon can play in managing infection control through the course of complex surgery.
The challenge to controlling infection in conditions of extreme physiologic stress requires an understanding and characterization of the real-time dynamic interaction between various microbial communities as they are exposed to antibiotics and host signals indicating a degree of physiologic stress incompatible with survival. From the standpoint of a potentially pathogenic microbe unaccustomed to surviving in such an environment, certain host signals could trigger a program of virulence expression that mounts a lethal offensive against its host. Some microbiologists consider such pathogen behavior under these circumstances to be "short-sighted," i.e. the expenditure of excessive resources to harm the very host on whom their survival depends. This situation is particularly plausible during the delivery of "heroic" medical care, where a pathological state is created when accidental pathogens (i.e. those that have not co-evolved with their hosts-- MRSA, Pseudomonas, etc), are triggered to express a degree of virulence in response to environmental cues with no evolutionary precedent for host survival (i.e. low pH, shock states, severe inflammation). Evidence is accumulating that the virulence tactics used by many of these accidental pathogens are so subversive and spatially confined that they elude clinical and molecular detection. Therefore, while there is a natural bias to assume that infection develops as a chance encounter of a pathogen at a damaged tissue site with impaired immune competency, the present review suggests that this explanation can be seen as overly simplistic and insufficient to explain the variation known to exist in the clinical setting (see hyperoxygenation below).

**Framing Surgical Site Infections within the molecular Koch's postulates.**

Among the most devastating complications for a surgeon following a technically successful operation is a surgical site infection. Surgical site infections include anastomotic breakdown, wound infection, and abscess formation; all of which can result in severe sepsis, disability and
Epidemiologic studies to identify risk factors that predispose to surgical site infection invariably identify the same risk factors across surgical disciplines: age, degree of underlying illness, medical co-morbidities, blood loss, and length of operation\textsuperscript{9}. Surgical practice to reduce wound infections reflects the current bias that the pathophysiology of surgical site infections is a simple matter of the degree of bacterial contamination balanced against the degree of tissue damage and immune clearance at the site of infection. Trials using antibiotic wound irrigation protocols\textsuperscript{10}, prosthetic wound barriers\textsuperscript{11}, varying antibiotic regimens\textsuperscript{12, 13}, immune enhancers\textsuperscript{14, 15}, hyperoxygenation\textsuperscript{16}, and purgative bowel preparation solutions\textsuperscript{17-19}, have, in the aggregate, failed to show a consistent reduction in infection rate, and as a result are not consistently adopted by surgeons. We have certainly witnessed a reduction in wound infections as a result of antibiotic prophylaxis and overall improvements in care, as physiologic monitoring, precise temperature control, minimally invasive procedures, and new anesthetics have become routine.

In particular, studies verify that minimally invasive approaches to major organ surgery (i.e. colectomy\textsuperscript{20}, gastric bypass\textsuperscript{21}) result in lower blood loss, less immune activation, less perturbation in overall physiologic changes during surgery, and are associated with decreased surgical site infections\textsuperscript{22} (obviously with the wound being the major site). Smaller and less traumatized laparoscopic wounds are less vulnerable to microbial colonization, perhaps due to a lower degree of local environmental cues sensed by microbial colonies whose habitat is breached during laparoscopy compared to open, more invasive procedures. Examination of the transcriptomes of the microbes that colonize patients during open and laparoscopic surgery would test this hypothesis: virulence gene activation could be assessed and the degree of surgical injury correlated to activation of known pathways of infection such as adhesin (adherence proteins) and toxin formation. However, as such studies do not at this time exist, more currently readily available genomic, proteomic, and metabolomic whole-community analyses could be applied to surgical patients. Conventional reasoning is that surgical site...
infections result from inadequate antibiotic coverage either due to lack of spectrum or drug penetration. While this rationale certainly may have some merit, it falls short in high risk patients where the potential pathogens may be more intrinsically virulent and activating cues more abundant, thus explaining the failure of antibiotics regimens alone to control infection. A shift in thinking about the pathophysiology of infection has resulted in the emerging field of “virulence-based therapy”\textsuperscript{23}. In this approach, drugs are developed that suppress microbial virulence activation without actually killing the microbe, offering a more eco-neutral approach to infection control by potentially preserving the probiotic normal flora and obviating the development of antibiotic resistance. Pharmacological agents could also be developed that provide local microenvironmental control, preventing exposure of infecting microbes to key activating cues that enhance their invasiveness and toxin production. Thus the future of infection control for the surgical patient lies in a more precise elucidation of the mechanisms that cause infection at a surgical site that incorporates dynamic virulence expression of microbes in response to host injury within the framework of the molecular Koch’s postulates.

**Hyperoxygenation to prevent infection: microbes as biosensors for host health status.**

To demonstrate how the molecular Koch’s postulates can provide unique insight into the pathophysiology and treatment of surgical infection, consider two major surgical trials to decrease the incidence and complication of postoperative infection using intraoperative hyperoxygenation. The first prospective clinical trial demonstrated that intraoperative hyperoxygenation during gastrointestinal surgery reduces postoperative surgical site infection\textsuperscript{24, 25}, while follow-up randomized controlled trials\textsuperscript{16, 26, 27} failed to show clinical benefit and even an inferior outcome with hyperoxygenation\textsuperscript{27}. The rationale for hyperoxygenation is that operative trauma at the surgical site results in tissue hypoxia which is a known risk factor for
infection by mechanisms that remain unknown. Hyperoxygenation (80% FiO₂ versus 40%) during GI surgery theoretically would maintain normoxia at the operated site and hence prevent infection. Framed simplistically, local immune clearance is worsened by hypoxia and improved with normoxia during exposure to a microbial burden (define by number and type of microbes present) as occurs during GI surgery. Recent information linking the hypoxia induced transcriptional factor HIF1α to the immune transcriptional activator NFκB provides further rationale for preventing tissue hypoxia to preserve immune function. Further rationale is provided by work from our own laboratory demonstrating that hypoxia induces the release of host tissue factors (i.e adenosine, dynorphin) that directly activate the quorum sensing system of *P. aeruginosa* to express enhanced virulence. Thus “simple” logic would justify hyperoxygenation to prevent wound infection given that hypoxia adversely affects both microbe and local immune function. However, the narrow immunocentric view that hypoxia related infections are a result of perturbations in the inflammasome (collective host inflammatory response) fails to consider the consequences of too little oxygen or too much oxygen on the virulome (virulence related genes) of potential pathogens. There are no studies that have interrogated the genes or gene products of microbes that cause surgical site infections to determine which virulence factors are *in vivo* expressed during hypoxia or hyperoxia. This missing set of observations is critical given that for pathogens like *E. coli*, reactive oxygen species (ROS) such as those generated during hyperoxia, are sensed by highly conserved redox active membrane sensors, activating virulence circuits to express a more invasive phenotype. Therefore failure to consider that pathogens might respond to a hyperoxic wound environment by expressing enhanced virulence might have led to a different study design based on more basic empirical data.
Considering all of the complex molecular crosstalk between the sense and respond circuits of the various intestinal microbes capable of contaminating a surgical site with all of the host tissues factors that may be released during complex gastrointestinal surgery with its attendant blood loss, blood pressure fluctuations, tissue pH changes, etc, testing the hypothesis that manipulating oxygen will prevent wound infections seems untenable. However, ambiguity (in terms of the clinical trials) and complexity (as seen by the scope of interactions) need not be a permanent roadblock to investigation; rather they may be points of opportunity where essential and critical divergences of pathophysiological fates are determined. Exploiting the potential therapeutic possibilities at these control points will require computational based modeling to dynamically account for and represent the complex interaction that occurs between intestinal pathogens and a surgical site (vide infra).

Intestinal Microbes Driving Systemic Inflammation to the Point of Organ Failure:
Redefining Gut Derived Sepsis Using the Molecular Koch’s Postulates.

The term gut derived sepsis refers to a process whereby a given intestinal microbe, or community of microbes, are postulated to activate systemic inflammation to a degree that results in progressive organ dysfunction leading to severe sepsis syndrome and even death. In cases where there is no other identifiable source of infection other than the intestine, such as occurs with C. albicans and Enterococcal septicemia, the isolated organism is invoked based on association only. In other cases, such as with fulminant colitis due to C. difficile, there is confidence that the pathogen is the causative agent of the disease based on the fullfillment of Koch’s original hypotheses. In some cases, such as neonatal necrotizing enterocolitis (NEC), a microbe or microbial community is presumed to drive the epithelial inflammation and necrosis, but the microbiology of NEC remains ill defined as a significant number of intestinal bacteria
mucosal necrosis if provoked by the appropriate set of environmental cues. Again, conventional reasoning dictates that colonization with pathogenic microbes in the face of a weakened epithelial barrier and impaired immune system is sufficient to explain the occurrence, course, and outcome of infection. However, epidemiologically, most premature infants, critically ill and immunocompromised patients, who invariably become colonized by highly virulent pathogens, do not develop life-threatening lethal gut derived sepsis. Others have framed the question in an evolutionary context by questioning why our ubiquitous contact with micro-organisms does not cause disease more often \textsuperscript{32}. Neither microbial genotyping, characterization of the intestinal barrier, or immune profiling of patients have proved sufficient to predict the occurrence, course, and outcome of life-threatening gut derived sepsis across various clinical disorders such as NEC, ischemia reperfusion injury, and neutropenia. In clinical terms, neither the presence of \textit{C. difficile} toxins in the stool, serum biomarkers of inflammation, physical exam, or CT imaging appropriately guide the indications for, or timing of, colectomy for fulminant \textit{C. difficile} colitis. This notion is best exemplified by several recent published series of colectomy for fulminant \textit{C. difficile} colitis that continue to report a mortality rate of 50\% or greater \textsuperscript{33-36}.

In order to understand and control life-threatening gut derived sepsis, we must be able to dynamically represent the microbiome (microbe related virulence genes and gene products), the inflammasome (host derived inflammatory and immune-related genes and gene products), and the interactome (environmental cues and interkingdom cross- signals) that develops within a particular microscopic niche along the 200 \textit{M}^2 of intestinal epithelial surface through the course of disease. This is no easy feat as microbial genes and immune responses are highly spatially confined and serum based or stool based comprehensive genomic and proteomic analyses may not be representative of the microbial gene products that are interacting with the immune gene products at the precise site that is driving the disease. Harnessing this information to provide a
clinically useful readout is further complicated by the knowledge that microbes are constantly shifting and subverting the immune response, and in turn the immune response is shifting the rapidly evolving virulence trajectory of the microbial response. Furthermore, systemic or serum-based manifestation of these dynamic shifts is likely to lag significantly behind temporal control points for optimal intervention. Since microbes are able to rapidly adapt to a new virulence equilibrium in response to multiple cues, it is difficult to imagine that a serum-based comprehensive readout can be developed that will dynamically represent the course of disease for all of the possible microbes and horizontally exchanged microbial genes that can cause gut derived sepsis across multiple clinical disorders. Again, mechanistic computational representation of the complex interplay involved in the rapid adaptation of our microbial partners will be necessary to capture essential pathophysiologic dynamics as the consequences of the stress we impose on our environment and patients remains unpredictable.

Environmental control as a strategy to prevent infection

Thus far this review has presented the argument that the complexity and constant evolving nature of the host pathogen interaction presents a formidable challenge to clinicians to control microbial pathogenicity during extreme physiologic stress such as occurs during complex surgical injury. This argument is based on the assertion that pathogens that colonize our sickest patients can achieve a degree of evolutionary fitness and flexibility far greater than human technology at present can measure or control. We advance this argument further by noting that environmental cues released at sites of surgical injury are the activating signals that shift microbes from indolent colonizer to life-threatening pathogens. While it may be possible to control the release of such signals in the first place, it is likely that these cues provide essential molecular signals for normal containment and healing. Therefore, a more promising approach
might be to interdict in the interactome itself. By way of a specific example, we will present data from our laboratory that demonstrate that maintenance of phosphate sufficiency within the mucus layer of the intestine can prevent lethal gut-derived sepsis due to *P. aeruginosa* and potentially other phosphate sensitive opportunistic pathogens.

We have demonstrated that local environmental cues present in the mouse intestine during surgical injury shift the virulence of *P. aeruginosa* to express a lethal phenotype. In response to surgical injury, intestinal *P. aeruginosa* expresses a quorum sensing dependent virulence protein, the PA-I lectin/adhesin, that promotes the attachment to and disruption of the intestinal epithelial barrier causing permeation of its lethal cytotoxin, exotoxin A, into the systemic circulation resulting in lethal gut-derived sepsis. We have recently identified phosphate deficiency in the mucus layer of the distal intestine (ileum, cecum) to be a major cue for virulence expression of *P. aeruginosa* [37]. Surgical injury is known to cause the release of phosphatonin which increases urinary phosphate excretion resulting in phosphate depletion [38]. Intestinal *P. aeruginosa* “senses” phosphate depletion via a multi-component phosphosensor/regulator system PstS-PhoB that is highly conserved across a variety of pathogens that cause life threatening gut derived sepsis such as *Klebsiella*, *Serratia*, and *Enterococcus* [39]. We modeled these events using the *Caenorhabditis elegans* model and demonstrated that phosphate depletion is sufficient to cause lethality due to intestinal *P. aeruginosa* by mechanisms that involve connections between the PstS-PhoB system and quorum sensing [40]. Maintaining phosphate sufficiency with oral phosphate solutions prevented lethal sepsis due to intestinal *P. aeruginosa* across multiple animal models and strains including multi-drug resistant strains of *P. aeruginosa* [37]. These findings are intriguing given that phosphate sufficiency might be considered by microbes to be a universal cue indicating both adequate environmental resources as well as a state of host wellbeing. In the aggregate, our results demonstrate that environmental cues activate intestinal pathogens to express a lethal
phenotype within a spatially defined compartment during surgical injury, and that therapies can manipulate these cues to prevent molecular activation at the outset. Thus, working within the interactome and focusing on the local microenvironment allowed us to make an important observation on how to control infection using virulence based therapies. This emerging field offers the promise of a more eco-neutral approach that has the potential to prevent antibiotic resistance. One can imagine applying these findings to other compartments such as the wound and peritoneum where once local environmental cues are identified and the circuits that they activate in causative pathogens understood, specific non-microbicidal lavage solutions might be developed that control infection via virulence based mechanisms. Already such an approach to wound infection has been experimentally proposed. In summary, in keeping with the notion that all levels of biological organization have some bearing on the occurrence, course, and outcome of infection, as proposed by Colwell, surgeons can play an important role in advancing the understanding of basic microbiology as we consider our responsibility to control the operative environment.

Agent based modeling can infuse new insight into research to reduce surgical infections

In this review we have touched on a few principles that provide an update on the pathogenesis of surgical infection from the standpoint of the microbe. Efforts are now underway to define the human microbiome using metagenomics, metatranscriptomics, proteomics, and metabolomics approaches to personalize the response to disease and treatment. Although we may someday be able to define the microbes, their genes, and gene products that contribute to the development of a disease, we will only be able to determine the occurrence, course, and outcome of a given disease by spatially aligning and dynamically displaying the expression of all
of the microbial elements to the host response as it develops in real time. Only then will we be able to understand why certain microbes can behave as indolent colonizers one moment and lethal pathogens the next across a wide variety of microbes and clinical conditions.

Dynamic mathematical modeling and simulation offers a promising, and arguably necessary method to capture the complexity of host-pathogen interactions. If a classic descriptive diagram takes a picture of an idea, then dynamic modeling makes movies of ideas. Dynamic computer-based modeling recapitulates interactions within and between microbes, cells, tissues, and organ systems based on information from in vitro experiments of molecules and cells, in vivo animal models of human disease and clinical-level studies. These simulations can incorporate elements of randomness (stochasticity) to capture emergent patterns and behaviors. Ultimately, these simulation methods provide a means to “visualize knowledge” and translate the vast repository of molecular details into a clinical context by guiding drug development, augmenting personalized medicine and coordinating the indication and timing for therapy.

As an example of a modeling paradigm that is already used to study host-microbe systems in this fashion, agent-based modeling is a scalable computational simulation method consisting of “agents” (typically representing cells) that interact in a “virtual world” and behave according to programmed rules extrapolated from laboratory and clinical investigations. The result is a modifiable in silico experimental platform that is capable of incorporating a wide array of measurable variables and dynamic processes to visualize a more complex account of mechanistic detail that more closely approximates the clinical disease entity. Agent-based models have been published for several biological processes including inflammation, immunology and wound healing. More recently, specific models of microbe-mediated disease have emerged as possible tools for deciphering the complex host-pathogen interaction in a dynamic context. In the future, computer-based models incorporating the growing body
of molecular details can potentially serve as test platforms for the discovery and testing of novel compounds affecting all aspects of the host-pathogen interaction. In this setting equal importance is placed on microbial functions and host physiology; capturing the comprehensive dynamics of the entire system requires this approach. As a result, the actions of the simulated microbes would be accounted for, and potentially targeted, with the same degree of detail as is currently applied to the eukaryotic host. Furthermore, not only will mechanistic interventions be evaluated with an unprecedented degree of resolution, but also combinations of interventions could be explored and evaluated in such a way that is currently not feasible. Thus, the development of these computational experimental platforms will facilitate the translation of basic science research into advances in the clinical care of patients.

We have recently witnessed the abandonment of dogma-based therapies to prevent and treat surgical infections, such as the use of bowel preparation for colorectal surgery and the operative treatment of infected pancreatic necrosis to name a few. The importance to both research and clinical practice of having guiding principles such as Koch’s postulates is that they call for readjustment of those principles within a new paradigm of understanding. We believe that the principles put forth in this review will help address the central questions facing surgeons as they attempt to control and manage serious infections which will always be a major threat to patients. The application of molecular Koch’s postulates in a surgical context provides a conceptual framework with which to more rigorously understand our practices and treatment options. Advances in the recognition and identification of microbial sensing and behavior, improved characterization of host environmental cues, and the development of measures to reduce or modulate those cues will guide future research and practice regarding surgical infectious disease.
Figures

Figure 1. Evolution of Koch’s Postulates to incorporate advances in molecular microbiology and biological complexity

Figure 2. A. Environmental information processing by microbes. Microbes sense and respond to cues within the temporal and spatial context of their local microenvironment. The state of the microenvironment is dictated by the populations of microbes, their genes and gene products (microbiome) and the host-derived inflammatory and immune-related genes and gene products (inflammasome). These factors interact through continuous chemical dialogue and collectively constitute the input information for microbes. The processing of information by the microbe is dictated by its genetic repertoire through gene switching (gene regulation), gene swapping (horizontal gene transfer), gene silencing (suppression of gene expression at transcriptional or translational levels), and gene expression (activation of gene expression at transcriptional or translational levels). As a result of the processing of environmental information, the microbe shifts its phenotype to improve fitness to the local conditions, resulting in either pathogenic or non-pathogenic behavior.

B. Interaction of host and bacterial networks. Infectious pathogenesis is dictated by the interaction between complex networks of microbe-microbe, host-microbe, and host-host chemical cross-talk. In response to environmental and host stress, microbes form highly coordinated, multi-cellular networks through intercellular, cross-species and even cross-kingdom signaling pathways, resulting in potent expansion of adaptive response to environmental changes (nutrient scavenging, immune evasion, toxin production, biofilm formation, etc). Similarly, the host is constantly sampling and assessing colonizing organisms and regulates defense mechanisms (mucus barrier, inflammation, clearance) to contain potentially infectious processes. This is accomplished through sophisticated networks of communication between
interface cells (epithelial, endothelial), immune recognition cells (dendritic cells, antigen-presenting cells) and inflammatory mediators (lymphocytes, neutrophils). The host and microbial networks are linked in the interactome, the dynamic micro-environment at the interface between host and microbe (gut, skin, respiratory tract, urinary tract, etc).

References


