CellPress

Opinion

Epigenetics: A New Model for Intracellular Parasite–Host Cell Regulation

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Intracellular protozoan parasites are an extremely important class of pathogens that cause a spectrum of diseases in human and animal hosts. There is a growing body of evidence suggesting that protozoan parasites, like other prokaryotic and viral pathogens, manipulate host cells via epigenetic modifications of the host genome that alter transcription and corresponding signaling pathways. In light of these data, we examine the role of epigenetics in downregulation of host macrophages by *Leishmania* that could potentially lead to a permanent state of inactivation, thus favoring pathogen survival and disease progression.

Leishmania Subverts the Immune Response of the Vertebrate Host

Intracellular protozoan parasites such as *Plasmodium*, *Theileria*, *Toxoplasma*, and *Leishmania* cause of an array of diseases in human and animal hosts. These successful pathogens have evolved sophisticated strategies to manipulate the host response and parasites of the genus *Leishmania*, the causative agents of leishmaniasis, are no exception. Leishmaniases are a global public health concern, especially in resource-poor areas of Africa, Asia, the Americas, and Europe. An estimated 20 million people are affected worldwide, with 1.3 million new cases each year and 20 000–30 000 deaths occurring annually [1]. Transmission of *Leishmania* to the mammalian host occurs during a blood meal by infected sand flies of the genus *Phlebotomus* or *Lutzomyia* [2]. Clinical manifestations of leishmaniasis vary depending on the infecting *Leishmania* species: *Leishmania major* causes primarily a cutaneous form where infected individuals develop characteristic self-healing open sores. By contrast, *Leishmania donovani* and *Leishmania chagasi* infections can lead to a more invasive visceral leishmaniasis, also called kala-azar, that is potentially fatal if untreated [1]. *Leishmania* parasites have a complex, digenetic life cycle, alternating between an extracellular, flagellated promastigote form that develops in the gut of a sand fly and an intracellular, non-motile amastigote form that replicates in the macrophages of its mammalian host [2]. The hallmark of successful intracellular infection of macrophages by *Leishmania* is the inhibition of the activation of the host cell's innate defenses and subsequent prevention of an effective immune response [3]. The overall unresponsiveness of the host macrophage enables *Leishmania* amastigotes to survive and replicate within the macrophage parasitophorous vacuole and, on release, infect naive macrophages, with the end result of leishmaniasis [2]. Multiple mechanisms may contribute to the inhibition of macrophage function induced by intracellular infections [3]. Recent evidence suggests that infection with *Leishmania* causes specific effects on the epigenome of the macrophage host [4]. In light of this evidence, we propose that *Leishmania*-induced epigenetic changes result in permanent downregulation of the host macrophage defense mechanisms, thus favoring parasite survival and disease progression.

Trends

Epigenetic regulation of gene expression is essential for development and differentiation in many systems.

There is a growing body of evidence suggesting that protozoan parasites such as *Leishmania*, *Toxoplasma*, and *Theileria* manipulate host cells via epigenetic modification of host gene expression.

A hallmark of *Leishmania* infection is parasite-induced downregulation and inhibition of the activation of macrophage innate immunity enabling parasite survival and replication.

Based on recent data, a new hypothesis is proposed where intracellular infection of macrophages by *Leishmania* induces epigenetic modifications at the level of DNA methylation of the host cell genome, resulting in permanent downregulation and inhibition of host defense mechanisms to promote the intracellular replication and survival of the pathogen.

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Intracellular *Leishmania* Infection Downregulates Host Macrophage Functions

While macrophages are the major effector cells responsible for the destruction of *Leishmania* and other parasites in mammalian hosts, they are also indispensable for the parasite's survival, replication, and differentiation within the vertebrate host [2]. There is substantial evidence that multiple mechanisms may contribute to the inhibition of macrophage function induced by *Leishmania* infections. Such mechanisms occur at the levels of transcription, translation, and signal transduction [3,5].

Leishmania infection modifies macrophage signal transduction pathways leading to generalized suppression of activation of immune mediators including interferon gamma (IFN-γ), cytokines, chemokines, and proteins involved in antigen presentation [3,5]. Several specific signaling pathways, including Janus-activated kinase (JAK)/signal transducer and activator of transcription 1 (STAT1), calcium-dependent protein kinase C (PKC), mitogen-activated protein kinases, especially extracellular signal-regulated protein kinase (ERK) 1/2, and tyrosine phosphatases, particularly proto-oncogene c homology phosphatase 1 (SHP-1), have been shown to be involved in *Leishmania*-mediated immune suppression [6,7]. Other pathways also contribute to inhibition of macrophage activation following infection, including inhibition of translation through mechanistic target of rapamycin (mTOR) inactivation [8] and modification of the nucleopore complex [9]. In addition, infection by *Leishmania* leads to a decrease in antigen processing due to decreases in expression of transporter associated with antigen processing (TAP) and MHC class I and class II cell surface molecules [10] and modulation of membrane trafficking involving soluble *N*-ethylmaleimide-sensitive factor-activating protein receptor (SNARE) [10]. Cytokines and chemokines play an important role whereby various combinations may either activate or deactivate macrophage function. For example, IFN-γ activates macrophages to kill *Leishmania*; however, prior infection of naïve macrophages by *Leishmania* renders infected cells resistant to IFN-γ activation, thus allowing *Leishmania* to survive and replicate [11]. Therefore, manipulation of the macrophage by *Leishmania* infection leads to evasion of the innate response and to impairment of the ability of the macrophage to stimulate an adaptive immune response. It is the balance between host and parasite factors that controls the activation/deactivation of macrophages and determines the outcome of the parasites within the infected macrophage.

Epigenetic Modulation of Host Cell Function by *Leishmania* and Other Intracellular Pathogens

Epigenetics (epi, 'on top of') involves transcriptional regulation at the chromosome level without modification of genomic sequences and is mediated by three main processes: DNA methylation [12,13], histone modification [14], and noncoding RNA (ncRNA)-associated gene silencing [15,16] (Box 1). In many systems epigenetic regulation leads to terminal differentiation and is one of the main mechanisms involved in embryonic and tissue differentiation [16].

Epigenetics is an emerging area of research for many aspects of infectious disease with particular relevance in the regulation of intracellular infections. Extensive data have shown that DNA viruses induce epigenetic modification of the host genome to enable virus survival and latency, as well as modulation of host cell replication, inflammation, and susceptibility [17]. Similarly, it is well established that prokaryotic pathogens, including several species of intracellular pathogenic bacteria, induce epigenetic modification of host cell genome enabling acute and persistent infections [18,19]. Bacterially induced mechanisms include DNA methylation, histone and chromatin modifications, and regulation of gene expression by ncRNAs and RNA splicing factors [18,19].