The transcriptional analysis of the macrophages’ innate immune response to
Salmonella typhimurium and Legionella pneumophila infection

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December 2010

A thesis submitted to McGill University in partial fulfillment of the requirements for
the
degree of Master of Science
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I- Abstract

Macrophages are the first line of defense against microbial pathogens; they recognize microbial structures and products via surface receptors (Fc, C3b, SR, TLR) and intracellular antigen sensors (NLR family). Engagement of surface receptors results in phagocytosis of the microbe into a specialized vacuole, the phagosome. Through a series of fusogenic events, the phagosome matures into a fully microbicidal phagolysosome that is highly acidic and contains a number of degradative enzymes and toxic molecules that cause destruction of the microbe. 

Salmonella typhimurium (S. typhimurium) and Legionella pneumophila (L. pneumophila) are two pathogenic Gram-negative bacteria that are able to block phagosome maturation. Our hypothesis is that the macrophages’ response to these pathogens contains a core response, which is induced by both pathogens, as well as a pathogen-specific response. We used a genome-wide transcription profiling approach to compare macrophage responses to phagocytosis of S. typhimurium or L. pneumophila at early time points, 2h (T2) and 4h (T4) post-infection (p.i.). The infections were performed on the macrophage-like cell line J774, and RNA isolated from infected and non-infected cells was hybridized to Mouse WG6 Illumina microarrays. Pairwise analysis led to the identification of 159 genes differently regulated compared to Non Infected (NI) samples in response to L. pneumophila infection at T2, 148 genes at T4 and 192 genes differently regulated in response to S. typhimurium at T2, and 402 genes at T4. Comparative analysis identified three groups of genes: 164 (T2) and 347 (T4) “Salmonella typhimurium-specific” genes, 131 (T2) and 99 (T4) “Legionella pneumophila-specific” genes. This analysis also revealed that 28 (T2) and 49 (T4) genes were
differentially expressed in response to both pathogens. A list of 27 genes was validated using quantitative RT-PCR. Networking programs, including STRING or Pathvisio were used to generate 3 interaction networks illustrative of these three groups of genes. Our results clearly show that TNF-α is associated with the macrophage response to both infections, with this gene playing a central role in this pathway. The *Legionella* specific pathway is centered on *Egr1, Fos* and *Jun* whereas the *Salmonella* specific pathway has 3 nodes centered on *Il10, Il6* and *Cенд1*. 
II- Résumé

Les macrophages représentent la première ligne de défense contre les pathogènes intracellulaires. Ils sont capables d’identifier des structures et protéines spécifiques aux bactéries grâce à des récepteurs membranaires, (Fc, C3b, SR and TLR) et à des molécules cytosoliques capables de reconnaître des antigènes sur la surface des bactéries. Le contact entre les récepteurs à la surface des deux protagonistes entraîne la phagocytose du microbe dans un compartiment spécialisé appelé le phagosome. À la suite d’une série d’événements de maturation, le phagosome se développe en un phago-lysosome capable de détruire les microbes phagocytés grâce à leur environnement très acide et la présence d’enzymes dégradatives et de molécules toxiques pour les pathogènes. 

*Salmonella typhimurium* (*S. typhimurium*) et *Legionella pneumophila* (*L. pneumophila*) sont deux bactéries Gram-négatives capables d’éviter la réponse immunitaire innée. Notre hypothèse défend l'idée que la réponse du macrophage à ces deux pathogènes comprend une réponse commune, élicitée par les deux bactéries et une réponse spécifique à chacun de ces pathogènes. Nous avons utilisé une étude transcriptionnelle, à l’échelle du génome, pour comparer les premières réponses à 2h (T2) et 4h (T4) suivant l’infection du macrophage par *S. typhimurium* à celle par *L. pneumophila*. Les infections ont été faites sur des cellules immortalisées, J774 et l’ARN a été isolé puis hybridé sur des micropuces (Illumina MouseWG6). Une comparaison par paire nous a permis d’identifier 159 gènes régulés de manière différente entre les groupes non infectés et ceux infectés par *L. pneumophila* à T2, 148 gènes à T4; similaires 192 gènes à T2 et 402 à T4 étaient différemment régulé par l’infection de *S. typhimurium*. Une analyse
Comparative des résultats de micropuces entre les infections avec ces deux pathogènes nous a permis de générer trois groupes de gènes : 164 (T2) et 347 (T4) gènes sont impliqués dans la réponse du macrophage à l’infection de *S. typhimurium* tandis que 131 (T2) et 99 (T4) gènes sont associés à la réponse à l’infection de *L. pneumophila*. Cette analyse a aussi révélé 28 (T2) and 49 (T4) gènes appartenant à une réponse commune du macrophage à ces deux infections. Une liste de 27 gènes a été validé par amplification en chaîne par polymérase (PCR) et l’utilisation de programmes tels que STRING et Pathvisio nous a permis de créer 3 schémas d’interactions entre les gènes de nos trois groupes. Nos résultats montrent que TNF-α est clairement associé à la réponse du macrophage aux deux bactéries et semble être au centre de la réponse aux infections. La réponse spécifique à *Legionella* est centrée autour de 3 gènes, *Egr1*, *Fos* et *Jun* tandis que la réponse spécifique à *Salmonella* est, elle, centrée sur *IL10*, *Il6* et *Ccnd1*. 
III- Introduction

Infectious diseases are still a major public health problem and a major cause of death worldwide; it is an economic burden in particular for developing countries where access to health care is limited [1]. Infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi. Transmission of infections happens by contact with an infected individual, by ingestion of contaminated food or water or by inhalation of contaminated air [2]. Among all microorganisms, only few can lead to a disease in an otherwise healthy person. Infectious diseases result from the interplay between those few pathogens and circumvention of defense systems of the host they infect. The appearance and severity of diseases resulting from any pathogen depend upon the ability of that pathogen to damage the host as well as the ability of the host to resist the pathogen assault. Pathogens are classified in two categories: primary or opportunistic [3]. Infectious microorganisms are classified as primary pathogens when the infection of a host is a necessary consequence of their needs to reproduce and spread. Opportunistic pathogens are ordinarily in contact with the host and require impairment of host defenses to establish an infection, which may occur as a result of genetic defects or exposure to immunosuppressive drugs [3].

Defining the means of transmission plays an important part in understanding the biology of an infectious agent, and in addressing the disease it causes. Transmission may occur through several different mechanisms. Respiratory tract infections and meningitis are commonly acquired by contact with aerosolized droplets, spread by sneezing, coughing, talking, kissing or even singing [2]. Gastrointestinal tract infections are often acquired by ingesting contaminated
food and water. Sexually transmitted diseases are acquired through contact with bodily fluids, generally as a result of sexual activities [2]. One of the ways to prevent or slow down the transmission of infectious diseases is to understand the different characteristics of various diseases and the molecular and biochemical consequences of the encounter between the pathogen and the host [3].

1- Macrophage innate immune response to bacterial infection

A- Response to bacterial infection

The mechanisms regulating host-pathogen interactions and ultimate appearance of pathology are poorly understood. Cells of the innate immune system use several receptors to detect and signal the presence of unwanted visitors. These signals lead to the initiation of an inflammatory response, which allows the host to contain the infection, and to the activation of the adaptive immune response, the second arm of the immune system [4]. The adaptive immune response has a role in response to an infection and is able to generate unlimited pathogen-specific receptors, but it leads to a delayed response upon pathogen-recognition compared to innate immunity [5]. It usually generates long-lasting immunological memory in contrast with the innate immune system [6]. A strong inflammatory response is usually enough to control bacterial replication while adaptive immune response helps clearing the infection and protects against re-infection with the same or related microbes [7]. The main purpose of an immune response is to resolve the infection and then return to homeostasis; if regulated improperly, the inflammation process can be very detrimental to the host itself. The destructive potential of this response is vital for survival during infection but can also be the
source of collateral damage. Some pathogens have acquired virulence mechanisms and evolved the ability to manipulate the host immune system to their favor.

**B- Role of the immune system**

The immune system is the first line of defense against invading pathogens and it has evolved different ways for their recognition and destruction. Tissue-resident macrophages and dendritic cells are the primary detectors of invading pathogens. Early detection of these intruders is dependent on molecules called pathogen recognition receptors (PRRs) which are able to sense conserved microbial elements called pathogen associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS; a major component of the outer membrane of Gram-negative bacteria), peptidoglycan (PGN; the main component of the cell wall of Gram-positive bacteria), flagellin, and microbial nucleic acids. Two important PRRs families are the Toll-Like Receptors (TLRs) which are the mammalian homologues of Toll, the first Toll receptor identified in fruit fly, and the nucleotide-binding oligomerization domain (NOD) like receptors (NLRs) proteins [8].

**C- TLR and NLR**

TLRs are type I transmembrane proteins characterized by a cytoplasmic domain called TIR domain, due to its homology to interleukin-1 receptor (IL-1R), and an extracellular leucine-rich domain (LRR). The LRR domains are responsible for the recognition of the pathogens through their PAMPs. Thirteen mammalian TLRs have been identified, 10 in humans and 12 in mice with some homologs in
both species [8]. TLRs expression differs with cell types and cellular localization. They can be expressed at the cell surface or intracellularly on different myeloid cells (macrophages, dendritic cells, neutrophils) and on non-myeloid cells (epithelial cells, fibroblast). Their ability to recognize specific ligands confers to the innate immune system some level of specificity. TLR4 is known as the LPS receptor [9], TLR2 recognizes different ligands such as bacterial lipopeptides and lipoteichoic acid (LTA) from Gram-positive bacteria, TLR5 detects a conserved domain on flagellin monomers, the main structural proteins forming the flagella on Gram-negative bacteria, important for their virulence [10]. Ligand binding induces two signaling pathways, one is MyD88 dependent and the other one is MyD88 independent [11]. These two responses are mediated by the usage of specific adaptor molecules recruited to the TIR domains after ligand recognition. Four adaptors have been described: MyD88, TIR-associated protein (TIRAP), TIR domain-containing molecule 1 (TICAM-1) and TIR domain containing molecule 2 (TICAM-2). MyD88 and TIRAP are responsible for the induction of pro-inflammatory genes and TICAM-1 and TICAM-2 for the induction of the interferons (IFNs) [8].

NLRs are intracellular molecules that are involved in the recognition of intracellular PAMPs. NLRs are a family of regulatory cytosolic proteins with a conserved structure: LRRs at the C-terminal, a central NOD (or NACHT) dimerization domain and an effector binding domain at the N-terminal. That last domain is specific to different family members and can be a pyrin domain (PYD), a caspase activation and recruitment domain (CARD) or a baculovirus inhibitor
of apoptosis protein repeat (BIR). This domain classifies NLRs into NALPs, NODs or NAIPs, respectively. *NOD1* and *NOD2* are known to detect PAMPs shared by many pathogens. Their LRRs domains interact with small peptides derived from peptidoglycan (PGN), a major component of bacterial cell wall [12]. Other NLRs have been implicated in the activation of immune response in reaction to pathogens, for example *IPAF* and *NAIP5* are associated with host resistance to *L. pneumophila* [13].

In response to a bacterial infection, cells of the innate immune system, like macrophages, are recruited to the site of infection; they phagocytose the bacteria detected through the TLRs and initiate a conserved signaling cascade resulting in the release of pro-inflammatory cytokines. TLRs engagement by microbial products leads to the activation of *NF-κB* and IFN-regulatory factor (IRF) transcription factors[14]. NLRs detection of the pathogen leads to the activation of the inflammasome, a multiprotein complex involved in the activation of caspase-1, a protease that processes pro-IL-1 into mature active form [15]. Macrophages are also able to kill the bacteria using proteases, antimicrobial peptides, reactive oxygen species (ROS) and reactive nitrogen species (RNS) which denature proteins, disrupt lipids and damage DNA [16]. The functions of TLRs and NLRs reinforce each other at multiple points; for example TLR activation regulates the activity of the inflammasome through induction of the expression of pro-IL-1 and other components [15].

Many bacteria are able to infect macrophages and replicate inside them. These intracellular pathogens, such as *S. typhimurium, L. pneumophila* and
Many scientists have used these bacteria as a tool to study in more details the mechanisms of the immune response [7, 17]. The availability of excellent models of experimental infection in mouse, and the ability to generate mutant mice for a gene of interest has enabled the discovery of specific genes and pathways playing critical roles in macrophage interactions with intracellular microbes.

2- Intracellular pathogens

A- Legionella pneumophila

a- Legionnaires’ disease

Legionnaire’s disease was first described as a large outbreak of severe pneumonia amongst attendees at an American Legion convention in Philadelphia in 1976 [18]. The causative agent was a Gram-negative bacterium that was named Legionella pneumophila. This bacterium is usually acquired by inhaling contaminated aerosol droplets. L. pneumophila is an opportunistic and accidental pathogen of humans. Many disease outbreaks are linked to air-conditioning cooling towers and evaporative condensers which can produce contaminated water droplets that are inhaled by passersby [19]. Legionnaire’s disease is a rare but severe infection: in 1976, 182 persons were affected and 29 died [18]. It usually affects immune-deficient persons, smokers and people with pre-existing pulmonary diseases. It rarely affects young people aged 20 or less [20]. In the United States approximately 12000 cases are reported annually [21]. In Europe the number of cases is evaluated around 10000 to 20000 annually [21]. Fifty species of Legionella have been described, with 24 being associated with human
diseases. At least 15 serogroups have been identified but close to 90% of Legionnaires’ disease cases worldwide are caused by *L. pneumophila* serogroup 1 [22]. *L. bozemanae, L. micdadei*, and *L. longbeachae* are the next most common etiological agents of Legionnaires’ disease and together account for 2-7% of the infection worldwide [22]. In the past 5 years, four *L. pneumophila* serogroup 1 genomes have been sequenced. It has allowed researchers to gain insight into fundamental mechanisms of pathogenesis and pathogen evolution. The different sequenced strains are: Philadelphia-1 derived from the original Philadelphia outbreak; the Paris strain, an endemic strain responsible for around 12% of the cases of Legionnaires’ disease in France; the Lens strain, the causative agent of a large outbreak in France and the Corby strain, a human isolate [7]. The strains share 80% of genes, which constitute the core genome, while around 10% of the genome is strain specific [23]. The core genome contains many of the factors associated with the ability of the bacteria to infect eukaryotic cells and replicate intracellularly and there is a high degree of conservation among virulence-associated genes [24]. Interestingly in *L. pneumophila* genome, there are a great number of genes predicted to encode proteins with amino acid sequences similar to eukaryotic proteins or containing eukaryotic domains [25]. Some of these were found to play a role in host-pathogen interactions and many are translocated into the eukaryotic cells, where they can interfere with pathways through functional mimicry.
b- Manipulation of the host processes by L. pneumophila

*L. pneumophila* is found in natural and human-made water systems where it infects and multiplies in phagocytic protozoa [26]. The increase use of human-made water systems, such as air-conditioning, has led to a greater exposure of humans to *Legionella* and therefore an increase in the incidence of infection. The evolution of virulence traits in *L. pneumophila* is thought to be the result of the pathogen replication in environmental protozoa.

In humans, the bacteria are able to colonize and replicate in alveolar macrophages. In the murine model, researchers have used macrophage cell lines or bone marrow-derived macrophages to study the host-pathogen interaction involved in the infection process.

Different mechanisms have been suggested for the internalization of the pathogen by macrophages. The first one and the more conventional one is phagocytosis, another one, less common is a coiling phagocytosis, but due to its infrequency researchers have questioned its significance [27]. Finally micropinocytosis, which has been observed in bone marrow derived macrophages (BMDMs) also appears to be a less frequent mechanism for *L. pneumophila* uptake [28]. Following internalization by the host cell, bacteria are found in a phagosome that usually matures into a digestive vacuole by associating with the endocytic pathways leading to the acidification of the vacuole and the degradation of the pathogen [29]. The *L. pneumophila* containing vacuole (LCV) avoids fusion with the endocytic pathways and acquires characteristics of the endoplasmic reticulum (ER) [30]. Following phagocytosis, some proteins from the secretory vesicles that
cycle between the ER and Golgi apparatus are recruited to the LCV. Rab1, a small GTPase that recruits factors necessary for the fusion of ER-derived vesicles with the Golgi apparatus, is recruited before any remodeling of the vacuole. Inhibition of Rab1 activity prevents the intracellular replication of *L. pneumophila* [31]. Other molecules like the SNARE Sec22b[31], GTPases Sar1 and Arf1[32] have also been implicated in the regulation of intracellular replication of *L. pneumophila*. The recruitment of GTPases and the control of GTP cyclin have been shown to be dependent on the Dot/Icm system of *L. pneumophila*, which will be described in the next section.[33][34] In addition to cell trafficking, the pathogen is also able to manipulate autophagy, which is an important process for cellular homeostasis in which double-membrane vesicles (autophagosomes) derived from the engulfment of cytoplasmic components and organelles, traffic to lysosomes for degradation [33]. Within permissive BMDMs, *L. pneumophila* seems to activate the autophagy process upon infection; it is thought that the interaction with the autophagic pathway provides the bacteria with a source of nutrients and avoidance of detection by the immune system [34]. However it has been observed that defects in autophagy in *Dictyostelium* does not impair LCV development or *L. pneumophila* replication which leads to the conclusion that it is not a core element of LCV formation [7].

An essential step in the development of infection and disease progression is the ability of intracellular pathogens to exit the host cell once replication has ceased, allowing infection of new host cells. The ability of the bacteria to escape from the replicative vacuole is mediated by the ability to form pores and lyse membranes.
This escape appears to be a regulated process since in the post-exponential phase, the bacteria undergo many phenotypic changes converting it to a more transmissive and motile phenotype [36-37]. In these conditions, *L. pneumophila* is able to induce contact-dependent cell cytotoxicity mediated by the development of pores less than 3 nm in diameter in the host cell membrane [38-39]. On the other hand, two Dot/Icm effectors, LepA and LepB promote non-lytic release from protozoa [40]. Any strains lacking these proteins remain trapped within the replicative vacuole, unable to disseminate and infect new cells [41].

**c- Virulence factors of *L. pneumophila***

Like other intracellular pathogens, *L. pneumophila* possesses virulence determinants important for pathogenicity: LPS, flagella, pili, a type 2 secretion systems (T2SS) and outer membrane proteins [7]. The most important virulence factor, necessary for manipulation of the host cells processes from within an intracellular vacuole, is a type IV secretion system (T4SS) named Dot/Icm, which translocates around 150 proteins, called effectors, into the host cell where they modify different cellular pathways [7]. The Dot/Icm system is required for intracellular replication and the formation of the LCV. It is also involved in invasion [42], inhibition of host cell apoptosis [43] and exit of *L. pneumophila* from host cells [44]. Others pathogens use T4SSs to secrete virulence factors as well, including *Bordetella pertussis*, *Helicobacter pylori* and *Coxiella burnetti*. There are two categories of T4SSs: T4SSa includes the systems that resemble the prototypic *Agrobacterium tumefaciens* Vir system and T4SSb includes the systems with homology to the Transfer (Tra) system of the IncI ColIb-P9
plasmids of *Shigella flexneri* [45]. The Dot/Icm system is a member of the T4SSb category. Recent work has suggested that Dot/Icm components form a multiprotein apparatus that spans the inner and outer membranes of the bacterial cell wall [46]. Cytoplasmic chaperones like IcmS and IcmW bind to effector proteins and facilitate their translocation [47]. Effectors represent close to 10% of the proteome of *L. pneumophila* but functional redundancy has been observed since inactivation of genes encoding for these proteins usually leads only to a modest defect in intracellular replication compare to a mutation in the Dot/Icm apparatus itself [32]. The Dot/Icm effectors target many host cell processes including the regulation of host GTPases, which is controlled through competition with endogenous guanine exchange factors (GEFs), to enable rapid recruitment, redirection and activation of Arf1 and Rab1 to the LCV. These two molecules are involved in the interaction between the ER-derived molecule and the Golgi compartment [48]. RalF is one effector that acts as a specific GEF for Arf1, which normally regulates COPI-coated vesicle formation and thus manipulates vesicular trafficking [49]. Phosphoinositide binding of the LCV has also been shown to be targeted by Dot/Icm effectors. The surface of the LCV is rich in phosphatidylinositol 4-phosphate [PtdIns(4)P] which are usually found on the *trans*-Golgi network and mediate the export of early secretory vesicles from the ER [50]. SidC and SidM are examples of phosphoinositide binding proteins that play a role in regulating the maturation of the LCV [50-51]. Other processes like host proteins translation, induction of stress responses, inhibition of apoptosis and vesicular trafficking are also affected [7].
d- The host response to L. pneumophila infection

Different animal models of L. pneumophila infection have been used to characterize the parameters of host-pathogen interaction, including inbred mice and guinea pigs. The mouse model has been favored by researchers due to the availability of transgenic mutant and transgenic animals to study immune responses and pathogenesis. Inbred strains of mice are resistant to L. pneumophila infection, with the exception of the A/J strain which develops acute lung inflammation [52]. Researchers have been able to identify elements of the immune response that are important for the control of bacterial replication in macrophages ex vivo and in the lung in vivo. The susceptibility of A/J mice has been mapped to the Lgn1 locus on chromosome 13 [53]. More precisely, the gene involved has been identified as the neuronal apoptosis-inhibitory protein 5 (Naip5) also named baculoviral IAP 1 (Birc1) [54] [55].

Naip5 is an intracellular sensor of flagellin that belongs to the NLR family [56]. In macrophages from resistant mouse strains, Naip5 has been shown to activate caspase-1 upon phagocytosis of L. pneumophila, leading to mature IL-β production and an increased fusion of the LCV to the endosomes, leading to bacterial degradation [15]. Ipaf, another intracellular flagellin recognition molecule, has been shown to be essential to restrict L. pneumophila replication [57]. Various studies have identified key components of the innate immune response to L. pneumophila challenges, including interferon gamma (Ifn-γ) [52], Tumor necrosis factor alpha (Tnf-α) [58], IL-12 [59], IL-18 [60] and the cells that produce these cytokines, including macrophages, neutrophils and natural killer
(NK) cells [61]. More recently, the focus has been placed on TLRs, more precisely on the adaptor molecule myeloid differentiation primary response gene 88 (MyD88). It was demonstrated that MyD88 deficient mice infected with *L. pneumophila* have an increased bacterial burden in the lung and decreased survival rates, they develop more severe lung pathology and suffer disseminated bacterial infection in the spleen compared to wild-type (WT) animals [62]. Apart from activation of the inflammasome, *L. pneumophila* infection of macrophages stimulates cytokine activity in a Dot/Icm-dependent manner; mitogen activated protein kinase (MAPK) signaling is induced in response to the Dot/Icm system in infected macrophages [63]. Flagellin has also been shown to be important for virulence since the host is more susceptible to infection by flagellin-deficient *L. pneumophila*. Indeed a flagellin deficient strain is able to survive longer in macrophages and after 24h of infection, the CFUs are higher for the mutant compared to a WT *L. pneumophila* strain [64].

It has been suggested that an impairment in the IFN-γ response may also increase susceptibility to the disease [65]. Clearly an early and robust inflammatory response appears to be critical to limit the infection. Correlation of human TLR polymorphisms with the development of disease has been observed, for example, a polymorphism in the *TLR5* gene leading to a premature stop codon, occurs in 10% of the population, and is associated with a significant increased risk of Legionnaires’ disease [66]. These results support the finding that, in the mouse model, recognition of flagellin is important for restriction of the infection [57].
**B- Salmonella Typhimurium**

**a- Salmonellosis**

*Salmonella* can cause typhoid fever and gastroenteritis in humans and is a major threat to human health. It is a serious public health problem in developing countries with 17–21 million cases of typhoid fever annually resulting in 600,000 deaths in endemic areas [67]. *Salmonella* is a Gram negative facultative intracellular bacterium and is divided in two distinct species: *Salmonella bongori*, a commensal of cold blooded animals rarely involved in human infections and *Salmonella enterica*, a major human pathogen, which contains over 2000 serovars [68]. *Salmonella enterica* serovar Typhi and Paratyphi cause typhoid fever, a systemic disease characterized by fever, intestinal perforation and hemorrhage, enlargement of the mesenteric lymph node, spleen and liver [69]. The disease is endemic in Asia, Africa and South America [67]. The infection is usually cleared after 4 months in the absence of complication although asymptomatic carriage and shedding of the bacteria can continue in some individuals for a year or longer [70]. *Salmonella enterica* serovars Enteritidis (*S. enteritidis*) and Typhimurium (*S. typhimurium*) belong to the serogroup B, they are capable of infecting a broad range of warm and cold blooded hosts. In humans, *S. typhimurium* and *S. enteritidis* usually cause a localized infection, gastroenteritis, characterized by diarrhea, abdominal pain, nausea, vomiting and fever. The acute enteritis is characterized by mucosal edema and inflammation mostly in the large intestine with recruitment of polymorphonuclear leukocytes (PMN) [71]. *S. enteritidis* is the most frequent cause of bacterial food-borne infection in North America. An
estimated 1.3 billion cases of intestinal disease have been reported with 3 million deaths worldwide [72]. Since S. typhi is restricted to humans, S. typhimurium has been used as a murine model of typhoid fever pathogenesis, in which it mimics the systemic infection and the long-term persistence observed in human S.typhi infection [73].

b- **Manipulation of the host by S. typhimurium**

Different models have been used to study typhoid fever and gastroenteritis. The most widely used animal is the mouse because it offers genetic mutants that permit the study of specific genes or pathways [17]. The pathology associated with S. typhimurium infection in mice closely resembles that of S. typhi in humans even though it is not a perfect model since it is known that some of the virulence determinants are not conserved in both strains. Mice infected with S. typhimurium show a disseminated infection and bacterial replication in the liver and spleen where large granulomatous lesions develop around infected macrophages [17].

Orally ingested S. typhimurium cross the intestinal barrier by 3 mechanisms: i) invasion of specialized cells, termed M-cells, situated in the Peyer’s patches (PP), ii) active invasion of enterocytes and iii) uptake by intestinal dendritic cells (DCs) [17]. Once the bacteria cross the mucosal epithelia, they encounter cells of the gut-associated lymphoid tissue including DCs, macrophages, B and T cells [74]. The bacteria enter the host circulation and then reach the Mesenteric Lymph Nodes (MLNs), spleen and liver where they can replicate within phagocytic cells.
High level of replication and subsequent release in the blood stream ultimately leads to sepsis in susceptible mice.

*S. typhimurium* can also infect livestock leading to gastroenteritis with similar clinical manifestations to those observed in human infection. A mouse model for enterocolitis has been developed, which displays a mix of the typhoid fever and colitis symptoms [75].

**c- Virulence factors of *S. typhimurium***

*S. typhimurium* possesses virulence determinants that enable it to invade, persist, and replicate within eukaryotic cells by subverting host cell processes. A significant number of virulence factors are clustered on the virulence plasmid or within large regions (15 to 40 kb) of the chromosome called *Salmonella* pathogenicity islands (SPI). The two larger SPIs in *S. typhimurium*, SPI-1 and SPI-2, each encode a type III secretion system (T3SS) with structural homology to each other and to the T3SSs of other known pathogens. The two T3SSs are differentially expressed and have distinct roles during infection. Similarly to T4SS, they are used by the bacteria to inject proteins inside the host cells that will act as mediators of cell invasion and modifications contributing to intracellular growth [73]. SPI-1 mediates invasion of host cells and pro-inflammatory response whereas SPI-2 is required for survival and replication inside macrophages and is therefore responsible for systemic progression of the infection [76].

SPI-1 is present in all serovars of both *S. enterica* and *S. bongori* [77] and seems to be important for the intestinal phase of *Salmonella* infection, mostly the initial
steps of active invasion of epithelial cells and the inflammatory cascade that ensues. The majority of the SPI-1 genes are expressed under conditions that are similar to the intestinal environment and are repressed once Salmonella colonizes an intracellular compartment [78]. These genes are controlled by 5 regulators, HilA, HilC, HilD, InvF and SprB [17]. HilA play an essential role and its deletion is phenotypically similar to a SPI-1 deletion. A two components system, PhoP/Q plays a major role in SPI-1 and also SPI-2 regulation and regulates genes in response to extracellular cation levels [79].

SPI-2 is only present in S. enterica. It is extremely important for intracellular replication and is able to translocate effectors involved in the modification of the Salmonella containing vacuole (SCV), and inhibition of lysosome fusion, allowing intracellular growth of the bacteria [80]. SPI-2 mutants are severely attenuated for virulence in the mouse typhoid model and fail to proliferate in internal organs [81]. They also have a reduced survival in macrophages, probably due to the failure to form the SCV [82]. SPI-2 is also known to mediate inhibition of the recruitment of oxidase-containing vesicles and iNOS to the SCV, thus preventing oxidative degradation of the pathogen [83-84]. The two-component regulatory system SsrA/B is responsible for the regulation of SPI-2 genes. The proteins translocated by the T3SS apparatus are called the effectors proteins. Several effectors proteins have been identified; one of the most studied is SifA, which is essential for SCV integrity and Salmonella replication [85]. Recently, another SPI-2 effector, SseL, was identified and was implicated in modulation of the host inflammatory response in vivo [86].
Other important virulence factors include the fimbriae, which are structures present on the bacterial cell wall allowing interaction with the cells, and the flagella, a tail-like structure of the bacteria that enables its motility, necessary for the bacteria to actively infect new cells [73]. *Salmonella*’s flagellin is comprised of 494 amino acids and distinct domains have been described. Both the amino- and carboxy-terminus are well conserved among *Salmonella* serovars, while the central portion displays more diversity, one particular region being termed the “hypervariable region” [87]. That central region is exposed on the outside of the filament, which explains why the antibody responses tend to be targeted to this region [88]. Infection with *Salmonella* strains lacking a functional flagellin have demonstrated an obligatory role for the flagella in bacterial adhesion to epithelial surfaces, colonization, biofilm formation, and invasion of host tissues [87].

*d- The host response to S. typhimurium infection*

Susceptibility to *S. typhimurium* in mice is determined by virulence factors expressed by bacteria as well as by the host genetic determinants [89]. The host response is complex and under the influence of many genetic loci. Many genes conferring susceptibility to the infection have been characterized, such as *TLR4*, which detect LPS and is responsible for most of the mouse response after infection with *Salmonella* [90] and pyruvate kinase, which affects RBC turnover and iron homeostasis [91]. The most important susceptibility determinant is the Natural resistance-associated macrophage protein 1 (*Nramp1*) also known as *Slc11a1* [92]. The susceptibility of many inbred mice strains has been associated to a single mutation of amino acid 169 in the protein, which substitutes a glycine
by an aspartic acid leading to impaired folding [93]. Nramp1 is a hydrophobic protein that possesses 12 transmembrane domains and acts as a divalent cation transporter [94]. The protein is expressed in the spleen, the liver and macrophages [95]. The mechanism by which Nramp1 controls intracellular replication of the bacteria is still controversial, but it may have a role in the modulation of the divalent cations content of the phagosome either by depriving intracellular bacteria from essential cations leading to reduced growth and virulence or by increasing the intracellular Fe$^{2+}$ to generate, with oxidative molecules, hydroxyl radicals that kill the bacteria [96]. Nramp1 seems to have a role in the maturation of the SCV since in Nramp1 deficient macrophages, the SCV fails to acquire mannose 6 phosphate receptor (M6PR) a protein that regulates the delivery of a subset of lysosomal enzymes from the trans-Golgi network to the prelysosomal compartment [97]. A role for Nramp1 in priming the immune system has also been suggested, as it has been shown that Nramp1 is able to facilitate the innate host defense mechanisms in macrophages, such as the synthesis of ROS and NOS, as well as that of proinflammatory cytokines [98].

The course of the Salmonella infection in the mouse typhoid model has been divided into 4 phases: the first one is the rapid clearance of the bacteria from the bloodstream, followed by an exponential replication of the surviving intracellular bacteria that has reached phagocytic cells like macrophages or dendritic cells. The second phase is influenced by the Nramp1 status of the host as well as ROS production levels [99]. The third phase is initiated by the activation of the innate immune system and is characterized by the production of several pro-
inflammatory cytokines such as TNFα, IFNγ and IL-12 which leads to the suppression of the bacterial growth and a plateau phase in systemic bacterial burden. This phase ends with activation of the adaptive immune system, which clears the bacteria and resolves the infection. In some cases, the bacteria can stay dormant in the host cells and a change or a deficiency in the immune status can lead to a relapse of the infection [99].

3- Aim and hypothesis of the project

A- Similitude and differences between Salmonella and Legionella infections

The diseases caused by Salmonella and Legionella and the routes of infection they use are not similar. Salmonellosis usually leads to a systemic infection beginning in the gastrointestinal track and disseminating to the rest of the organs via the bloodstream whereas Legionellosis leads to a mucosal infection restricted to the area of the lungs. However, L. pneumophila and S. typhimurium are both intracellular pathogens that colonize phagocytic cells like macrophages and replicate in a modified vacuole (LCV or SCV). As previously explained, they are able to subvert macrophage defenses and dampen the innate immune response by reducing cytokine production. For both pathogens, extracellular recognition is possible through interaction with the TLRs; as mentioned earlier, LPS is recognized extracellularly by TLR4 and leads to the activation of a cascade of innate immune responses; at the intracellular level, both infections lead to the activation of the inflammasome, leading again to the activation of many innate immune pathways and the regulation of pro-inflammatory and anti-inflammatory
cytokines in order to assure a timely destruction of pathogens. In both infection models, genomic determinants play a role in the outcome of the infection. These similarities led us to hypothesize that there might be a common “core” response of the macrophages to these pathogens but also a pathogen-specific response. To obtain a global view of the macrophages’ responses to \textit{S. typhimurium} and \textit{L. pneumophila} infections, we decided to monitor gene transcription in these cells under different conditions and following infection.

\textbf{B- Technological approaches}

Extensive amount of work has been done on these 2 pathogens; many groups have used different approaches to better understand the effect of these bacteria on their host and the immune responses elicited by macrophages and other immune cells to control the infections. But the exact mechanism underlying the host-pathogen relationship is still not completely understood. In our case, we were interested in studying the effects of the infection at a genome wide level. This is feasible using two different techniques: the sequence based approach, RNA sequencing (RNA-seq) or the hybridization approach, using microarrays.

Hybridization to microarrays containing a complete compendium of all genes transcripts can be used to study transcriptional responses of a given animal or cell type. It allows rapid comprehensive transcriptome analysis of any cell type, including response to external stimuli such as infections in the case of macrophages [100].
RNA-seq is still under development but has many advantages over the other techniques; unlike hybridization-based approaches, RNA-Seq is not limited to detecting transcripts that correspond to known genomic sequences; it has very low, if any, background signal because DNA sequences can be unambiguously mapped to unique regions of the genome. Also, RNA-Seq has been shown to be highly accurate for quantifying expression levels. RNA-seq has some important challenges: it involves several manipulations of the RNA during the production of cDNA libraries, which can complicate its use in profiling transcripts. Larger RNA molecules must be fragmented into smaller pieces (200–500 bp) to be compatible with most deep-sequencing technologies. Common fragmentation methods include RNA fragmentation (RNA hydrolysis or nebulization) and cDNA fragmentation (DNase I treatment or sonication). Each of these methods creates a different bias in the outcome. Another important issue is the sequence coverage, or the percentage of transcripts surveyed, which has implications for costs. Greater coverage requires more sequencing depth and is more expensive [101].

We used a microarray approach to monitor gene expression in the macrophage cell line J774 in response to *L. pneumophila* and *S. typhimurium* infections, early after infection (at 2h and 4h). We have been able to identify a common response of the cells to both infections and a specific response to each bacterium.
IV- Materials and Methods

1- Cell line culture

The J774 cell line was cultured in Dulbecco's modified Eagle's medium (DMEM) (Sigma) containing 10% heat-inactivated fetal bovine serum (HI-FBS) at 37 °C in a humidified atmosphere containing 5% CO₂. Cells were cultured to confluence and were then passaged to expand the culture. Cells were harvested by scraping and were plated at 10⁷ cells per 150 mm cell cultures dishes (for RNA extraction) or at 10⁶ cells per well in 12-well plates (for CFU determination) in DMEM containing 10% HI-FBS and 100 μg/ml of thymidine (Sigma) for L. pneumophilla infection and in DMEM containing 10% HI-FBS for S. typhimurium infection. J774 cells were cultured for 16hrs prior to infection.

2- Salmonella and Legionella infections

A- L. pneumophila infection

L. pneumophila Philadelphia-1 strain Lp02, a thymidine auxotroph derivative of strain Lp01, was a kind gift from Craig Roy (Yale University School of Medicine, New Haven, CT). The Lp02 strain was cultured to stationary phase in N-(2-acetamido)-2-aminoethanesulfonic acid (ACES) (Sigma)-buffered yeast extract broth supplemented with 100 μg/ml of thymidine. The culture was centrifuged and the pellet re-suspended in DMEM supplemented with 10% FBS and 100 μg/ml of thymidine to infect J774 macrophages. J774 cells were exposed to L. pneumophila at a multiplicity of infection (MOI) of 10:1 (bacteria to macrophages) for 1 h at 37°C to allow phagocytosis. The cells were then washed
with warm DMEM, the time point 0 was collected and the remaining cells were incubated for an additional 2 and 4 hours in DMEM supplemented with 10% HI-FBS and 100 μg/ml of thymidine. Bacterial replication is expressed as the log increase in the number of CFU determined by lysis of macrophages with distilled water and plating of the cell lysates onto BCYE agar plates.

**B- *S. typhimurium* infection**

*Salmonella enterica serovar* Typhimurium 14028 was provided by Dr Danielle Malo (Complex trait group, McGill University, Montreal). *S. typhimurium* was grown overnight in 5 ml Tryptic Soy Broth (TSB). The next day 50 ml TSB was inoculated with 2 ml of overnight culture and grown at 37 ºC until stationary phase. The inoculum was centrifuged and the pellet was re-suspended in DMEM supplemented with 10% FBS to infect J774 macrophages at an MOI of 10:1 for 1h at 37ºC to allow phagocytosis. The cells were then washed with warm 1X PBS, the time 0 was then collected and the remaining cells were incubated for an additional 2 and 4 hours in DMEM supplemented with 10% FBS and 100 μg/ml gentamicin to prevent extracellular replication. After one hour, the gentamicin concentration was decreased to 10 μg/ml gentamicin. Bacterial replication is expressed as the log increase in the number of CFU determined by lysis of macrophages with PBS-1%Triton X-100 and plating of the cell lysates onto TSB agar plates.
3- RNA extraction

Total cellular RNA was extracted from J774 cells using TRIzol reagent (Invitrogen) according to the manufacturer's recommendations. Macrophages were harvested in 5ml of TRIzol reagent. The samples were incubated for 5 min at 20°C, followed by chloroform extraction. The aqueous phase was removed and nucleic acids were precipitated with isopropanol. The pellet was washed with 75% ethanol and dissolved in RNase-free water treated with 0.1% diethlypyrocarbamate (DEPC water). The integrity of each of the RNA preparations was verified by electrophoresis on 1% formaldehyde-containing agarose gel.

4- Microarray analysis

Total cellular RNA from uninfected macrophage controls and L. pneumophilla and S. typhimurium infected macrophages, at 2 hours post infection and 4 hours post infection, were used for transcriptional profiling. The RNA samples were hybridized to Illumina expression Beads Array (Mouse-6 v2), according to the manufacturer's recommendations. Four arrays were hybridized for the uninfected and 2 hours post infection samples and 3 arrays for the 4 hours post infection samples. The data were log transformed and normalized to the mean. Data analysis was performed using the GeneSifter microarray data analysis program (www.genesifter.net). Differential expression was tested by performing pairwise analysis with a t-test, P value ≤ 0.05, fold change ≥ 2, and Benjamini and Hochsberg correction. The Heat Maps were generated using the program Multiple Experiment Viewer (MeV 4.6) [102]. The Venn diagrams were
generated using 3Venn applet software [103]. Interaction network maps were
generated with STRING and were then re-drawn in Pathvisio in order to associate
each gene with their appropriate expression value. STRING is a data base of
predicted and known interactions that are derived from four different sources:
genomic context, previous knowledge obtained by high throughput experiments,
co expression results or literature derived information. All the interaction data
obtained from these sources are quantitatively integrated allowing the creation of
an interaction map/network. STRING was used to analyze our 3 lists of genes (S.
typhimurium or L. pneumophila specific and the common response lists of gene)
to determine the possible interactions and create networks. T2 and T4 lists were
pooled for this analysis. The analysis was performed within the Mus musculus
organisms’ category, using the interactive view and the default parameters except
for the require confidence which was increased to the highest confidence.

5- Semi-quantitative and quantitative RT-PCR
For semi-quantitative reverse transcription (RT)-PCR, 3 μg of each RNA sample
was converted to cDNA with reverse transcriptase (Moloney murine leukemia
virus reverse transcriptase; Invitrogen) in a 20-μl reverse transcription reaction
mixture, as previously described [104]. The reaction was then diluted in DEPC
water in a 1:5 ratio. 3 μl of the reverse transcription reaction mixture was used for
Taq DNA polymerase (Invitrogen)-mediated PCR amplification. Amplicons were
resolved on 1% agarose gel analyzed under UV light and were transferred to
GeneScreen Plus membranes (Dupont, NEN Research Products). After transfer,
DNA was UV cross-linked and pre-hybridized for at least 4 h at 65°C in a
solution containing 10% dextran sulfate, 1% sodium dodecyl sulfate (SDS), and 1 M NaCl with 200 μg ml\(^{-1}\) of salmon sperm DNA. Hybridization was then performed overnight at 65°C with an [\(\alpha^{32}\)P]dATP-labeled specific DNA fragment (100,000 cpm/ml of buffer) corresponding to each target gene. After incubation, the membrane was washed twice with 2× SSC-0.1% SDS (15 min per wash, 42°C), once with 2× SSC-0.5% SDS (30 min, 65°C), and once with 0.5× SSC-0.5% SDS (30 min, 65°C) (1× SSC is 0.15 M NaCl plus 0.015 M sodium citrate). The signal was quantified using a phosphorimager.

For the quantitative RT-PCR (qPCR), independent RNA samples \((n = 3)\) from the same experimental group were pooled and the reverse transcription was performed as described above. The reaction was then diluted in DEPC water in a 1:10 ratio. 2 microliters of the reverse transcription reaction mixture was used for SYBR Green (Quiagen) PCR amplification in a 7500 Real time PCR system from Applied Biosystem. The amplification plots were then analyzed using the software 7500 system SDS from Applied Biosystems. The quantification method used is the comparative \(C_t\) method, which involves comparing the \(C_t\) values of the samples of interest to the control (NI) [105]. The \(C_t\) values of both the control and the samples of interest are normalized to an appropriate endogenous housekeeping gene (L32).
V- Figures and Tables

1-Figure1: Characterization of the infections: bacterial load

J774 macrophages were infected at an MOI of 10:1 with *S. typhimurium* (A) or *L. pneumophila* (B). The CFU were determined at 0, 2 and 4 hours post infection (T0, T2 and T4) as described in the previous chapter. This experiment was performed in triplicate and the results represent the average of the three replicates for each time points and for each bacterial infection.
2- Figure 2: Characterization of the infections: semi quantitative PCR

A

Beta actin

Phosphomager intensity

cycles

St

Lp

B

Tnf alpha

Phosphomager intensity

cycles

C

Il1 beta

Phosphomager intensity

cycles
Semi quantitative PCR was performed to monitor the expression of genes expected to be induced in response to infection. The PCR was performed for each sample at 3 different cycles in the logarithmic phase of amplification for both pathogens infections. β-actin was use as an internal control (A). Tnf-α (B), Il-1β (C), Il-6 (D) and Il-12p40 (E) are genes known to be regulated by both *L. pneumophila* and *S. typhimurium* infections. The expression level of our genes of interest was quantified by phosphoimager and the radioactive hybridization scans are shown for each gene.
The microarray expression data of the 27 genes chosen for validation (Table 2) and the q-PCR expression results are plotted alongside for *L. pneumophila* at T2 (A) and T4 (B). Shown is the mean of 3 replicates. MA: Microarray expression results; QPCR: quantitative PCR expression results.
Figure 4: Real time q-PCR validation for *S. typhimurium*.

The microarray expression data of the 27 genes chosen for validation (Table 2) and the q-PCR expression results are plotted alongside for *S. typhimurium* at T2 (A) and T4 (B). Shown is the mean of 3 replicates. MA: Microarray expression results; QPCR: quantitative PCR expression results.
A pool of 3 RNA replicates from *L. pneumophila* and *S. typhimurium* infections at T2 and T4 time point were hybridized on Illumina MouseWG-6 v2.0 expression beadchip. A pairwise analysis was performed to compare T2 and T4 of each infection to the NI sample. A Venn diagram was made to compare the results of the *S. typhimurium* infection to the *L. pneumophila* infection; the diameter of the circles is proportional to the number of genes differently regulated in each categories. The comparison was made with the results at T2 (A) and the results at T4 (B). Lp, *L. pneumophila*; St, *S. typhimurium*.
6-Figure 6: Heat maps representing the list of differently regulated genes in the 3 groups

The genes were classified in 3 groups: the Salmonella specific genes, the Legionella specific genes and the genes affected by both infection. These genes are classified according to their expression data at T2 (A) and at T4 (B). The boxes identify the samples and time point of interest. Lp, L. pneumophila; St, S. typhimurium
7- Figure 7: pathways involved in the innate immune response of the macrophages to *Salmonella typhimurium*

Using STRING network program, a pathway was generated with the list of genes modulated in response to *Salmonella* infection. The pathways obtained in STRING were redrawn in PathVisio2 and the appropriate expression data were superimposed on the pathways.

Pathway and expression data of the common response and the *Salmonella* specific response at T2 (A) and at T4 (B) are illustrated. Generally, the expression data is similar for both time points, but when a box displays two different colors, it signifies that the expression data was different between T2 (bottom of the box) and T4 (top of the box). The arrows correspond to actions such as activation or inhibition and simple lines correspond to interaction according to STRING database results.

With respect to uninfected expression levels, genes that are down-regulated (≤ 0.4-fold) are shown in green, up-regulated genes (≥ 2 to 15-fold) are coloured in a range of yellow to orange, and genes that are highly up-regulated (≥ 15-fold) are displayed in red.
8- Figure 8: pathways involved in the innate immune response of the macrophages to *L. pneumophila*

Using STRING network program, a pathway was generated with the list of genes modulated in response to *Legionella* infection. The pathways obtained in STRING were redrawn in PathViso2 and the appropriate expression data were superimposed on the pathways.

Generally, the expression data is similar for both time points, but when a box displays two different colors, it signifies that the expression data was different between T2 (bottom of the box) and T4 (top of the box). The arrows correspond to actions such as activation or inhibition and simple lines correspond to interaction according to STRING database results.

With respect to uninfected expression levels, genes that are down-regulated (≤ 0.4-fold) are shown in green, up-regulated genes (≥ 2 to 15-fold) are coloured in a range of yellow to orange, and genes that are highly up-regulated (≥ 15-fold) are displayed in red.
9-Figure 9: Macrophage response to *S. typhimurium* and *L. pneumophila*

Qualitative representation of the macrophage response to both infections, where each group was assigned a number and a corresponding colour: genes in common (-1, green), *Legionella* specific genes (0, yellow) and *Salmonella* specific genes (1, red) and these numbers were associated to a color code that allows visualization of all the genes on a same pathway. The arrows correspond to actions such as activation or inhibition and simple lines correspond to interaction according to STRING database results. When a box displays two different colors, it signifies that there is a difference in the classification of the gene depending on the time point (T2 (bottom of the box) and T4 (top of the box)).
### Table 1: Number of genes differently regulated by *S. typhimurium* and *L. pneumophila* infections

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<tr>
<td>NI vs St2h</td>
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<td>NI vs St4h</td>
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## 11- Table 2: Microarray expression data of the 27 genes validated

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\(^a\) microarray expression data of the 27 genes validated by qPCR (Fold change I/NI).

\(^b\) Each gene was tested in NI, T2 and T4 conditions for both bacterial infections and validation was confirmed if the trend in all conditions were respected. (*) corresponds to a gene validated in all condition, (~) corresponds to a gene that has not been validated in a least one condition. Validation was performed in triplicate. (See Figures 3 and 4).
Table 3: Top 10 differently regulated genes following *L. pneumophila* and *S. typhimurium* infections

<table>
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<tr>
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**Table 4: Top 5 KEGG pathways affected by *L. pneumophila* and *S. typhimurium* infections.**

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\(^a\) corresponds to the number of genes assigned to this pathway in the entire microarray data.
VI- Results

1- Characterization of the infection

The effects of intracellular parasitism by S. typhimurium and L. pneumophila on transcriptional response in macrophages were studied. To reduce experimental variations, we implemented a standardized procedure to harmonize bacterial loads in macrophages infected with S. typhimurium or L. pneumophila. In both cases, J774 macrophage-like cells were infected at a multiplicity of infection (MOI) of 10:1. The bacterial load was assessed by Colony Forming Unit (CFU) at each time point (Figure 1). No significant changes were observed at the CFU level during the 4-hour S. typhimurium infection but a small decrease is observed after 4h in the case of the L. pneumophila infection. The CFUs level after S. typhimurium infection were 10 fold more that the CFUs after L. pneumophila infection regardless of the time point. This could be explained by the difference in the virulence properties of the bacteria, S. typhimurium being able to actively invade macrophages, while L. pneumophila enters by macrophage-dependent phagocytosis. Increasing the MOI for L. pneumophila infection to 100:1 only resulted in increased toxicity to the macrophages, as determined by cell loss. An MOI of 10 was deemed to be the optimal condition to ensure a maximum level of infection of a single cell without inducing toxicity.

To verify that J774 macrophages respond to bacterial infection as expected from the literature, five genes which RNA expression is known to be induced in this condition were selected: Tnf-α (Figure 2B), Il1-β (Figure 2C), Il6 (Figure 2D) and Il12p40 (Figure 2E). β-actin was used as an internal control and its expression
does not change in the condition tested (Figure 2A). Semi-quantitative PCR was done to evaluate the expression level of each gene in RNA samples prepared at NI, T0, T2 and T4 time points. All genes were induced by both \textit{L. pneumophila} and \textit{S. typhimurium} infection. No changes were observed at T0 for \textit{Tnf-α} and \textit{Il1-β} in \textit{L. pneumophila} infected samples whereas an increase in expression was detected in \textit{S. typhimurium} infected samples, compared to NI. However, a greater induction was observed at T2 and T4 in all infected samples. (Figure 2 B and C) For \textit{Il6} and \textit{Il12p40}, no change is observed at T0 for both infections but the expression is increased at T2 and T4 in \textit{S. typhimurium} infected samples. In the \textit{L. pneumophila} infected samples, the levels of induction is very low for both genes but an increase can be clearly observed at T4 for \textit{Il6}. (Figure 2 D and E) From these preliminary results, it is already possible to see that the transcriptional response of macrophages to these two pathogens has common and specific features. For example \textit{Il12p40} shows an increase in expression at T2 and T4, compared to NI, for cells infected with \textit{S. typhimurium} that is not observed in the case of \textit{L. pneumophila} infection. Similarly, an induction is seen for \textit{Il1β} in response to both infections, but is greater in the case of the \textit{S. typhimurium} infection. These results not only confirm that macrophages were indeed infected by each pathogen, but also show that the macrophages react to \textit{S. typhimurium} and \textit{L. pneumophila} by activating certain pathways. Therefore we proceeded to a genome wide approach to characterize cellular responses activated by infection with these two pathogens.
2- Microarray results

A- Macrophages response to *S. typhimurium* and *L. pneumophila* infection

To better understand early transcriptional response of macrophages to intracellular infections, we used transcriptional profiling. Three macrophage RNA samples obtained at NI, T2 and T4 following *S. typhimurium* and *L. pneumophila* infections were obtained, pooled and hybridized to Illumina beads arrays. Four arrays were hybridized for the NI and T2 samples and three arrays for the T4 samples. The results were analyzed using the GeneSifter analysis program as described in the Material and Methods section, and to identify genes which expression is regulated in response to each infection.

We performed pairwise analyses individually comparing NI to either T2 or T4, and then extracted the number of genes that were differently regulated by either or both infections (t-test, P value < 0.05, fold change ≥ 2, Benjamini and Hochsberg correction). At T2, 159 genes were differently regulated by *L. pneumophila* compared to NI and 192 by *S. typhimurium* compared to NI. Similarly at T4, 148 genes and 396 genes were differently regulated by *L. pneumophila* and *S. typhimurium* infections, respectively. (Table 1)

B- Validation of microarray results by qPCR

We used quantitative PCR (qPCR) to validate transcript profiling obtained by microarray. A total of twenty-seven genes selected from all conditions were tested. These corresponded to *L. pneumophila* infected cells at T2 and T4 (Figure 3) and *S. typhimurium* infected cells at T2 and T4 (Figure 4). A summary of qPCR results is presented in Table 2. Globally, 77% of the genes tested shared a
similar trend by both qPCR and transcript profiling. This conserved trend was seen for genes from all genes lists and for different effects (up-regulation, down-regulation). Therefore, we concluded that results from microarray experiments were reliable.

C- Comparison between the transcript profiles of S. typhimurium and L. pneumophila infected macrophages

To compare the macrophages’ response to S. typhimurium and L. pneumophila infections, we focused the analysis on the differences and similarities between the transcription profiles obtained for each infection, and carried out a pairwise analysis. These analyses identified a list of 131 L. pneumophila specific genes, 164 S. typhimurium specific genes and 28 genes in common at T2 (Figure 5 A). For T4, we identified 99 L. pneumophila specific genes, 347 S. typhimurium specific genes and 49 genes in common. (Figure 5 B) A Heat Map representing the expression of all the genes in each list was created, where up-regulated and down-regulated genes are clustered separately. In Figure 6 (panel A) the Heat Map was made with the list of genes found to be differently regulated a T2 post infection, but the expression data of both time points are shown. Likewise, panel B was made with the list of genes differentially regulated at T4 post infection. (Figure 6) The top10 genes up- or down-regulated are displayed in Table 3. A good overlap was observed between the gene lists obtained at T2 and T4 post-infection and this for each bacterial infection (Table 3).

A Gene Ontology analysis based on the KEGG pathways was performed on each of the gene lists generated. The 5 most represented pathways for each group are
displayed in Table 4. For the *L. pneumophila* specific genes, we observed an over representation of the genes involved in Systemic lupus erythematosus (autoimmune condition) with 41 genes differentially expressed in this group; the MAPK signaling pathway is also well represented with 9 genes differently expressed. Regarding genes specifically regulated by *S. typhimurium* infection, 24 genes are involved in cytokine-cytokine receptor interaction, and 16 in the chemokine signaling pathways. Pathways corresponding to Systemic lupus erythematosus (12), cytokine-cytokine receptor interaction are also prominent in the gene list corresponding to genes which expression was affected by both infections (9), and Toll-like receptor signaling pathway (6) were also prominently represented in the list of genes which expression in macrophages is regulated by both infections.

Using the program STRING and Pathvisio, we generated two pathways that summarize our transcription profile findings: “The macrophage innate immune response to *S. typhimurium* infection” (Figure 7) and “The macrophage innate immune response to *L. pneumophila*” (Figure 8) whose are based on all genes whose expression is regulated by each infection (specific and common, together). To allow a better visualization of the different pathways and the interconnections between the common and the specific responses, a qualitative number and color was assigned to each group of genes; (Figure 9) the *Legionella* specific genes (0) (yellow), the *Salmonella* specific genes (1) (red) and genes in common to both infections (-1) (green).
The network is centered on the common response genes, *Tnfa* and *Il-1β*. The genes associated with each infection are often linked even if they are not specific for the response to the same bacterial challenge, which shows that the macrophages are activating the same biological pathways but through different genes. The network is more complex in the case of *S. typhimurium* due to the greater number of genes differently regulated which probably means that the responses to *L. pneumophila* infection either elicit a less robust response or is delayed in time, or that the infection stimulus was lower in the case of *Legionella*. 
VII- Discussion

The goal of this project was to use transcriptional profiling to study the response of macrophages to infection with different, antigenically unrelated, intracellular pathogens. For this, we compared the early transcriptional responses of J774 cells to infection with either *S. typhimurium* or *L. pneumophila*. In these studies, we wanted to distinguish the transcriptional responses that are elicited in common by both infections, from those that are pathogen-specific. Our analyses have indeed identified both bacterium-specific responses and a common “core” response that is triggered by infection with either *S. typhimurium* or *L. pneumophila* (Figure 5 and 6).

This common response is comprised of 28 genes regulated at 2 h p.i. and 49 genes regulated at 4 h p.i. Several genes found in these lists have been previously associated with innate immune response to bacterial infection including the critical caspase-1 substrate Interleukin 1beta (*I1-β*). Pro-IL-1b is cleaved by caspase-1 to *IL-1b* in response to activation of inflammasome platforms, such as infection with intracellular bacteria, and caspase-1 mutant mice are susceptible to infection with *L. pneumophila* [106]. Increased expression of Saa3 has also been reported as occurring in response to inflammatory stimuli [107].

Pathway analysis indicates that the common response pathway is anchored to the pro-inflammatory molecule *Tnf-a*, a cytokine secreted by macrophages and that is involved in the regulation of a wide range of biological processes in response to inflammatory or infectious insults, including pro-inflammatory cytokine production, cell proliferation, differentiation, apoptosis, lipid metabolism, and
coagulation [108]. *Tnf-α* has been implicated in a variety of diseases, including autoimmune diseases, insulin resistance, and cancer [108]. It is also known that infection with *S. typhimurium* and *L. pneumophila* stimulates the rapid production of *TNF-α* *in vivo* [109], which is thought to play a critical protective role during infection. A recent study has shown that *TNF-α* might also affect expression of *S. typhimurium* T3SS effectors, such as SipA, gogB, and spvB. *Salmonella* exposed to TNF-α before the infection, display increased internalization, with concomitant increased activity of JNK pathway with enhanced p-JNK and p-c-Jun in the host cells [109]. *TNF-α* is also required for protection against Salmonellosis in the murine model *in vivo* [110]. Similarly, in *Legionella* infection, *TNF-α* is required for macrophage resistance to infection and for restriction of intracellular bacterial replication [111].

There are 132 and 99 genes differentially expressed specifically in response to *L. pneumophila* infection, at T2 and T4, respectively. Many of these genes are associated with immune response including, Ier3 that functions in the protection of cells from *TNFα*-induced apoptosis [108]. Several histone genes are also found in this list of genes, which raised the question of the role of histones in response to *L. pneumophila* infection. Histones play a broad role in regulating transcription and modulation of their level of expression by intracellular pathogens may be an intermediate step in overall transcriptional response. For example, it has been observed that stimulation of macrophages with LPS leads to the phosphorylation of histones H3 and H4, an important intermediate step in the activation of *CD40* gene transcription [112].
The *Legionella* specific pathway is centered on *Egr1*, *Fos* and *Jun*. *Egr1* encodes a protein that belongs to the EGR family of C2H2-type zinc-finger proteins. It is a nuclear protein that functions as a transcriptional regulator. The products of the target genes it activates are required for differentiation and induction of mitosis [108]. In addition, *Egr1* has been implicated in the regulation of *TNF-α* through the ERK and JNK MAPK pathways [113]. *Fos* encodes a leucine zipper protein that can dimerize with proteins of the Jun family, thereby forming the transcription factor complex AP-1. As such, the Fos protein has been implicated as a regulator of cell proliferation, differentiation, and transformation[108]. In some cases, expression of the *Fos* gene has been associated with regulation of apoptotic cell death [114]. Finally, *Jun* is the putative transforming gene of avian sarcoma virus 17. It encodes a protein highly similar to the viral protein and interacts directly with specific target DNA sequences to regulate gene expression. Jun and Fos seem to interact in their regulation of apoptotic cell death [114]. It has been previously proposed that intracellular survival of *L. pneumophila* involves modulation of apoptosis and autophagy in infected cells [115-116].

We detected 164 genes regulated in a *Salmonella*-specific fashion at T2 and 347 genes at T4. Several of these genes have been previously associated with innate immune response, including *Ccl4*, a chemokine that is induced after *S. typhimurium*-derived endotoxin treatments [117]. *Gbp1*, *Gbp2* and *Gbp3* are guanylate binding protein (Gbp) which expression is known to be induced by interferon [108]. Pathway analysis indicates that the *Salmonella* specific pathway(s) has multiple centers and clusters, but the most obvious is *Il10, Il6* and
Cend1. Il10 is an essential immunoregulator in the intestinal tract and has pleiotropic effects in immunoregulation and inflammation; it down-regulates the expression of Th1 cytokines and co stimulatory molecules in macrophages [108]. It also enhances B cell survival, proliferation, and antibody production. This cytokine can block NF-kappa B activity, and is involved in the regulation of the JAK-STAT signaling pathway [108]. Il10 acts as an anti-inflammatory cytokine to limit the immune response to pathogens and thereby prevents damage to the host [118]. Il6 is a cytokine involved in inflammation and the maturation of B cells [108]. The protein is primarily produced at sites of acute and chronic inflammation, where it is secreted into the serum and induces an inflammatory response by binding to interleukin 6 receptor alpha [108]. This gene is implicated in a wide variety of inflammation-associated disease states, including susceptibility to diabetes mellitus and systemic juvenile rheumatoid arthritis [108]. Finally Cend1 belongs to the highly conserved cyclin family, whose members are characterized by a dramatic periodicity in protein abundance throughout the cell cycle [108]. Different cyclins exhibit distinct expression and degradation patterns which contribute to the temporal coordination of each mitotic event. Mutation, amplification and overexpression of this gene, which alters cell cycle progression, are observed frequently in a variety of tumors and may contribute to tumorigenesis [108]. The role of Cend1 in regulating cell cycle or cell replication in response to S. typhimurium infection remains unclear.

The next step in our analyses would be to investigate the pathogen virulence determinants that modulate the “core” or pathogen-specific transcriptional
response of macrophages to infection. Indeed, *S. typhimurium* and *L. pneumophila* possess a series of genes, proteins and biochemical pathways known as virulence factors, that are both essential for intracellular survival and that modify host response to infection. These include flagellin, a large number of effector proteins transported by type 3 and type 4 secretion systems, as well as other proteins encoded by pathogenicity islands in the microbial genome [119-120]. Therefore, the use of mutant strains of bacteria, such as secretion system (T3SS and T4SS) or flagella mutants could provide insight into the effect of virulence factors on the regulation of the host response to the infection. Comparison of transcript profiles from J774 macrophages infected with Δfla and flif bacterial mutants, the flagellin mutant or dotA and ssaR, the secretion system mutant for *L.pneumophila* and *S.typhimurium* respectively, may identify those genes and pathways that are specifically modulated in response to virulence.

It would also be very interesting to conduct similar studies with additional intracellular bacteria, such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*. Such parallel experiments may further sharpen the identity of the “core” response to intracellular infection, while identifying pathogen-specific effects.

The relevance of the genes and proteins identified here in macrophages in response to intracellular infection needs to be further validated one gene at a time. This can be achieved by creating a loss-of-function mutation in the gene and testing its effect on microbial replication in macrophages derived from such mutant animals. However, this can be done more systematically and more
efficiently using RNA silencing. Such validation is required to determine which of the genes detected have a biological or biochemical importance in the innate immune response to bacterial infection.
VIII- Conclusion

*Salmonella typhimurium* and *Legionella pneumophila* are two intracellular pathogens responsible for two infectious diseases that are still major health problems both in developed countries and developing countries. As for many other diseases there is still a lack in our understanding of the interaction between the host and the bacterial intruders. Understanding the mechanisms of the infection and the innate immune response orchestrated by the first line of defense of the host, the macrophages, could allow development of new targets to treat these diseases. Our study is the first example of a comparison of the immune response of a same host to two different bacteria, and show that there are a common response and specific responses that we need to be aware of and that could be important in developing a general approach to the treatment of these infections. We have identified genes that are part of the common response to gram-negative intracellular bacteria and genes that are part of a specific response of the macrophage to either *S. typhimurium* or *L. pneumophila*. Additional studies with other bacteria and functional validation of the genes identified are necessary to broaden the picture of the host-pathogen interaction.
**IX- Acknowledgements**

First and foremost I would like to thank my supervisor, Philippe Gros, for his help, encouragement and patience during the course of my studies in his Laboratory. He pushed me to develop scientific skills that will be very important for the rest of my life. He provided me with a great environment to learn and good advice that I will do my best to follow.

I want to thank Anne Fortier, my former “boss” in the lab when I joined as an undergrad student; she taught me everything about the project and the life of a researcher. I am also grateful to Jean François Marquis who helped me a lot with technical issues about the microarray results and without whom it would have taken longer to understand all this data. Finally, a special thanks to Sébastien Faucher who came to the lab very recently but was of tremendous help in the writing of this thesis, he helped me correct it and gave me important guidelines.

I also want to thank past and present member of the lab for their help, specially, Irena Radovanovic, Alexandra Iliescu, Sandra Salem, Michel Gravel, Charles Meunier and Jean François Marquis for their good advice and friendship and for making these two past years such a good human experience.

Finally I need to thank my family and friends for their love and support during all these years of studying, for their encouragement and love even when I was too busy or too stressed or too tired. They were my only “support system” and without them I would not have been able to do it.
X - References

21. Dr. Robert Geursen (Rédaacteur en Chef), P.H., Bill Kirkness, Philippe Loewenstein, and D.J.-M.M. Steve Mees, Marie-Claire Pickaert (Coordinatrice).


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### XI-Appendix

**Whole gene lists**

**FC: fold change I/NI**

**Genes in common 2h**

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natural killer tumor recognition sequence

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