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CXCL8 Regulation and Function in HIV Infections and Potential Treatment Strategies

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1. Introduction

Interleukin-8 (CXCL8) is a chemokine that was originally identified as a key factor in neutrophil recruitment and activation. Numerous cell types produce CXCL8, including immune cells, mucosal epithelial cells, endothelial cells and smooth muscle cells (Garcia-Vicuna et al., 2004). CXCL8 is one of the important inflammatory mediators responsible for the recruitment of neutrophils and T-cells to the site of infection, therefore it is an attractive target for therapy against diseases that affect immune cells such as HIV. HIV directly targets the host's immune system and thus reduces the ability of the innate and adaptive immune system to fight disease. As a chemokine, CXCL8 is a potential target for controling HIV infection by reducing the migration of T-cells to the site of infection. It is therefore necessary to identify the signaling pathways involved in CXCL8 regulation in order to develop viable CXCL8 based treatment strategies. In line with this, we have recent shown that CXCL8 activation in Jurkat T-cells is not primarily under the control of NFκB, but that the AP-1 signaling pathway appears to be central for the regulation of CXCL8 (Khalaf et al., 2010). An understanding of the regulation and function of cytokines and chemokines, while complex, remains important for the development of new strategies in the development of HIV treatments. It is interesting to note that several lactobacilli strains are able to modulate CXCL8 expression and release (Anukam et al., 2009; Zhang et al., 2005). Disturbance of the lactobacilli flora in the vaginal tract has been shown to increase the risk of infections and acquisition of HIV type 1 (Taha et al., 1998). Several studies have shown that treatment with certain *Lactobacillus* species and strains have positive effects on women with HIV infections and have been successful in trials to counteract vaginal infections (Hummelen et al., 2010; Spear et al., 2007).

In the present chapter we give a background to CXCL8 regulation and function as well as its involvement in HIV etiology. We also provide an overview of the available information on the possible uses of *Lactobacillus* species in treatment of infections with special emphasis on HIV. In addition, the effects obtained by using lactobacilli treatment together with expression of adhesion inhibitors will be discussed. The aim is to give the reader an overview of the role of CXCL8 in HIV infections and combine this with information on how lactobacilli treatment influences the chemokine levels and evaluate these systems potential in the treatment of HIV patients.

1.1 Inflammatory responses

Pro-inflammatory cytokines, such as TNF, IL-1 and IL-6, as well as the chemokine CXCL8 promote inflammation, whereas anti-inflammatory cytokines, including IL-4, IL-10 and IL-13, suppress the activity of pro-inflammatory cytokines (Dinarello, 2000). Gene-expression and release of cytokines, such as TNF, IL-1 and IL-6, and cell adhesion molecules, including ICAM-1, P selectin, and E selectin, are indicators of induced inflammatory responses (Pearson et al., 2003). NF-κB has been proposed as the main transcriptional regulator of cytokine expression, adhesion factors and anti-apoptotic factors (McKay & Cidlowski, 1999). It has been suggested that inflammatory cytokines, such as TNF, are involved in the induction of reactive oxygen intermediates (O_2^-) that cause DNA damage (Shoji et al., 1995). Recent observations have shown that elevated levels of IL-6 and C-reactive protein are associated with the development of atherosclerosis and type II diabetes (Libby et al., 2002). Elevated cytokine levels are also associated with cellular senescence and may be involved in telomere shortening and continuous cell divisions (Itahana et al., 2001).

1.2 T-cell derived inflammatory responses

Optimal T-cell activation is achieved following antigen binding to the T-cell receptor (TCR), together with co-stimulatory signals followed by cytokine expression (Gonzalo et al., 2001). T-cells produce a broad range of pro- and anti-inflammatory cytokines, including IL-2, IL-6, IL-10 and TNF, in response to infections (Opal & DePalo, 2000). IL-10 is another important anti-inflammatory cytokine expressed by activated T-cells, providing control of intestinal inflammatory responses, but is also important for normal T-cell function (Asseman et al., 1999). Chemokine expression (CXCL8) by $CD8^+$ T-cells is crucial in immune responses by inducing cytokines, such as TNF and IFN-γ by $CD4^+$ cells, and antibody secretion by B-cells (Kim et al., 1998). Recent findings provide evidence indicating expression of several types of Toll-like receptors (TLRs), including TLR4, on T-cells (Caramalho et al., 2003). These results demonstrate a specific role of T-cells in the induction of inflammatory responses by direct recognition of antigens, independent of antigen-presenting cells.

1.3 Epithelial cell derived inflammatory responses

Wounds, chemical irritation or infection may cause inflammation of the epithelial surface. Acute inflammation induces expression of pro-inflammatory cytokines and chemokines that attract immune cells, such as neutrophils, followed by the production of anti-inflammatory cytokines thereby initiating the healing process (Philip et al., 2004). The balance between pro- and anti-inflammatory cytokines determines the severity of an infection. However, prolonged inflammatory responses are prevented by the expression of IL-1ra, glucocorticoids and IL-10, which also improves cell survival (Berg et al., 1995; van der Poll et al., 1997; Walley et al., 1996). Lipopolysaccharides (LPS) are well-known bacterial toxins and potent inducers of inflammatory responses. It has been suggested that epithelial cells are refractory to LPS since they do not express surface CD14, an important signaling protein that functions by docking the LPS/LBP (Lipid binding protein)- complex with TLR4 to initiate intracellular signaling cascades (Svanborg et al., 1999). However, in the presence of serum cells, epithelial cells respond to LPS, demonstrating the presence of a second soluble form of CD14 (sCD14) (Noel et al., 1995; Riedel et al., 2006). Furthermore, CD14-independent pathways are also present in epithelial cells that can be triggered by substances such as peptidoglycan and result in the release of pro-inflammatory cytokines (Sato et al.,

2003). While inflammatory responses are mainly induced through signals transduced via TLRs on epithelial cell surface, there is evidence indicating involvement of other membrane receptors, including Dectin-1, in the enhancement of inflammatory responses (Gantner et al., 2003).

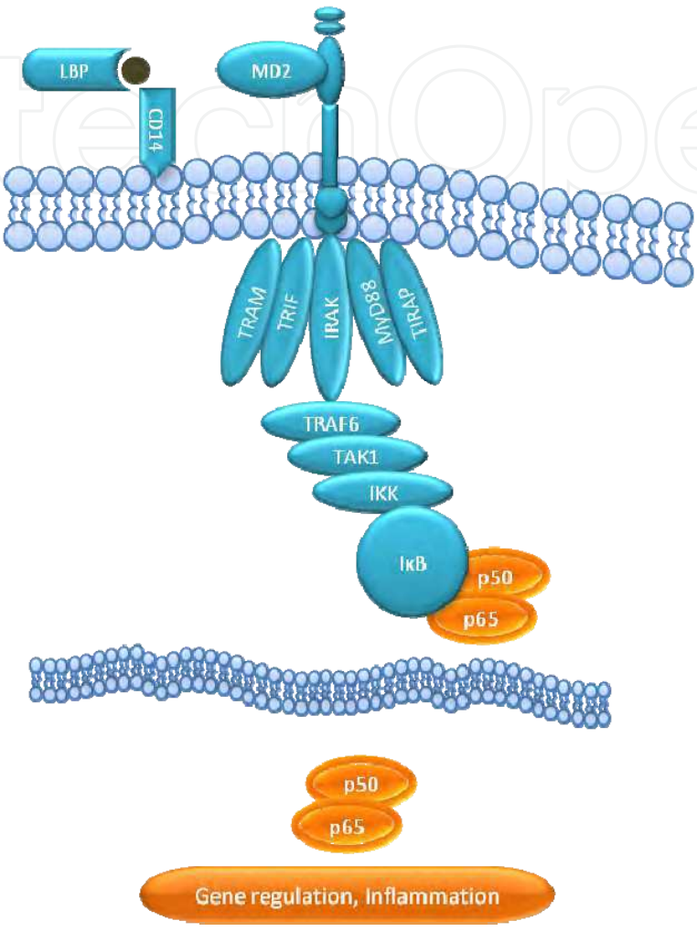

Fig. 1. Inflammation induced by LPS, which binds to TLR4 and signals for MyD88 activation that in turn starts a phosphorylation cascade leading to NF-κB activation and nuclear translocation.

1.4 NF-κB and MAPK signaling pathways

Recognition of toxins by epithelial- and immune cells occurs via TLRs that activate specific intracellular signaling pathways and result in the transcription of essential proteins for survival. Currently, more than 10 TLRs have been identified and recognize; among others, zymosan (TLR1/TLR2), LPS-LTA (TLR4-TLR2/TLR6) and dsRNA (TLR3) (Xu et al., 2001). NF-κB has a central role in the induction of inflammatory responses by regulating a wide range of genes. Several stress factors can activate NF-κB, including bacterial toxins, cytokines, reactive oxygen species and UV light. Bacterial toxins, such as LPS and peptidoglycan, activate NF-κB via TLRs whereas cytokines, TNF, IL-1, signal via TNF-R1 and IL-1R on the membrane surface (Dinarello, 2000). LPS activates NF-κB following

binding to a LPS-binding protein, which facilitates LPS binding to CD14. Once bound to CD14, the LPS-binding protein dissociates, and the LPS-CD14 complex associates with TLR4 with the help of the extracellular protein MD2. The binding of LPS-CD14 complex leads to the activation and binding of a cytoplasmic signaling molecule called myeloid differentiation factor 88 (MyD88). Binding of MyD88 leads to the activation of interleukin-1-receptor-associated kinase (IRAK), which phosphorylates TNF-receptor-associated factor (TRAF) 6. TRAF6 leads to the activation of TGF-beta activated kinase (TAK) 1, which activates NF-κB-inducible kinase (NIK). IκB kinase (IKK), activated by NIK, phosphorylates the inhibitory protein IκB followed by subsequent degradation in the proteasome. This leads to NF-κB activation, which translocates into the nucleus and initiates transcription of a wide range of inflammatory genes (Fig. 1) (Ali & Mann, 2004).

An additional important signaling pathway involved in the induction of cytokines and inflammation is the mitogen-activated protein kinase (MAPK) pathway. Several stress factors can induce the activation of MAPK pathway, however only pro-inflammatory cytokines and growth factors can induce inflammation, apoptosis or differentiation through either p38 MAPK or c-Jun NH_2-terminal kinase (JNK). There are three major groups of MAPKs; p38 Map kinase family, extracellular signal-regulated kinase (Erk) family and JNK family (McCarroll et al., 2003). A series of phosphorylation steps are the key events leading to MAPK activation and gene-expression (Faure et al., 1994). Furthermore, activation of the Raf/MAPK pathway has been shown to stimulate transcription of, among others, cytokines through AP-1, NF-IL6 and NF-κB (Bruder & Kovesdi, 1997).

Since T-cells lack TLRs, antigens are recognized by the TCR with the help of co-stimulatory receptors, such as CD28. This results in the activation of resting T-cells and a signaling cascade that activates phospholipase C (PLC) and cleavage of phosphatidylinositol bis-phosphate (PIP2) to inositol (1,4,5)-trisphosphate (IP3) and diacylglycerol (DAG) (Teixeira et al., 2003). IP3 mobilize Ca^{2+} from intracellular stores and together with DAG activates PKC (Gajewski et al., 1994; Werlen et al., 1998). In addition, Ca^{2+} also activates calcineurin/calmodulin and RasGRP, which is a Ras activator and is directly connected to the MAPK pathway (Dower et al., 2000). Recent reports have revealed the importance of three additional intracellular proteins, namely CARMA1, Bcl10 and MALT1 (CBM) in the induction of NF-κB (Scharschmidt et al., 2004). Down regulation of Bcl10 was shown to result in inhibition of NF-κB, transduced via TCR/CD28 and PKC. It was suggested that Bcl10 is initially activated by TCR/PKC but further activation (>1h) promotes its degradation. Furthermore, deletion of any component of the CBM complex impairs antigen receptor activation of NF-κB (Gaide et al., 2002; Narayan et al., 2006). CARMA1 has been shown to be required for NF-κB activation through Akt signaling, in cooperation with PKC following short-term exposure (30min) of Jurkat T-cells with PMA (Narayan et al., 2006). These studies indicate that PKC is crucial for NF-κB activation, following short-term exposure; from signals transduced via TCR and co-stimulatory receptors, such as CD28, and that the CBM complex proteins play a key role in these signaling processes (Fig. 2).

NF-κB is an important transcription factor complex involved in almost every aspect of cell regulation including apoptosis, differentiation, proliferation and initiation of immune responses (Barnes & Adcock, 1997; Makarov, 2000; Tergaonkar, 2006). NF-κB is an attractive therapeutic target since it is constitutively active in many human malignancies (Dolcet et al., 2005).

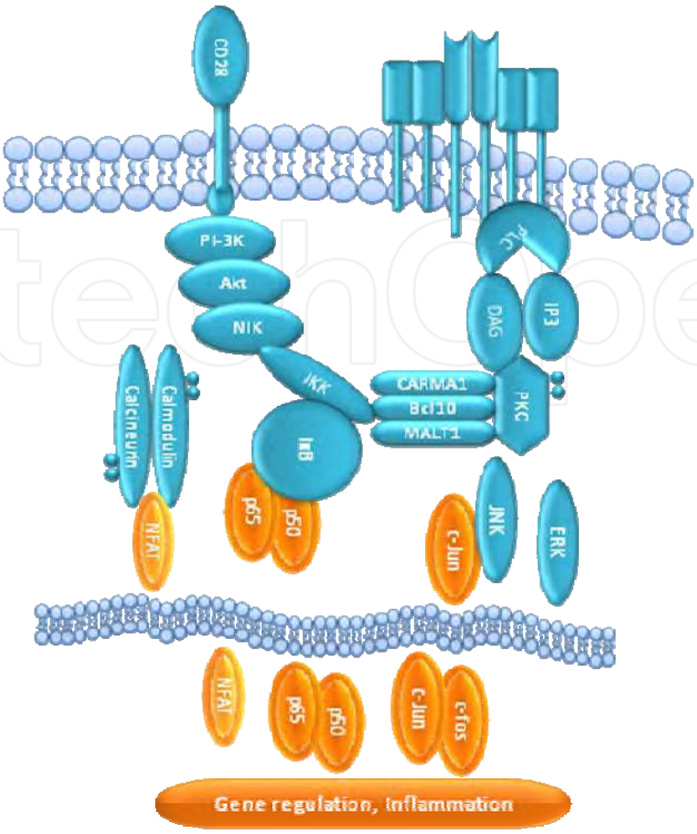

Fig. 2. T-cells recognize antigens via TCR and co-stimulatory receptors (CD28), leading to a downstream signaling cascade involving PKC activation and several transcription factors including NF-κB, AP-1 and NFAT.

2. CXCL8 regulation and signal transduction

In order to understand how CXCL8 contributes to the etiology of HIV, it is important to characterize the cellular signal transduction pathways regulating CXCL8. There are over 50 chemokines identified and almost 18 chemokine receptors have been characterized (Alfano & Poli, 2005). Chemokines are divided into four categories according to the location of two cysteine residues at the N-terminal region. These include C, CC, CXC and CX_3C chemokines (Zlotnik & Yoshie, 2000). Chemokine receptors have been designated the same nomenclature as for their respective chemokine. Besides several immune cells, many other cell types have been described to express chemokine receptors, including endothelial cells, fibroblasts and smooth muscle cells (Garcia-Vicuna et al., 2004). This indicates that chemokines are not only implicated in the regulation of cell trafficking but also in cell proliferation and gene regulation (Wong & Fish, 2003).

Several chemokines share the same receptor but possess different binding affinities to each one. We have previously shown an association between IL-6 release and NF-κB activity while CXCL8 release was more closely correlated with activator protein (AP)-1 activity (Khalaf et al., 2010). Blocking NF-κB activation resulted in a complete inhibition of IL-6 while the CXCL8 levels remained elevated as shown both at the protein and mRNA levels.

Our results indicate that in Jurkat T-cells, IL-6 is regulated through NF-κB while CXCL8 regulation is independent of NF-κB and is closely associated with AP-1 activation. The interplay between immune cells and the expression levels of different cytokines/chemokines is an important factor for consideration.

The gram-negative derived endotoxin, LPS, is a known factor reported to induce CXCL8 expression and release. However, pre-treatment with anti-inflammatory cytokines, including IL-4, IL-10 and TGF-β1, resulted in a significant reduction in CXCL8 expression (Ehrlich et al., 1998). Thus, the balance between pro- and anti-inflammatory cytokines is a determinant factor for immune cell activation as well as the expression levels of cytokines and chemokines released by different cells. Maintaining this balance is therefore of great importance, however there is a need to improve our understanding about the regulatory mechanisms controlling the expression of inflammatory mediators and their effect(s) on different immune cells.

The main regulators of *cxcl8* gene expression are NF-κB and the MAP kinases JNK, ERK and p38 leading to the assembly and activation of the transcription factor AP-1. NF-κB is required for CXCL8 release in most cell types, while optimal induction is achieved following binding of additional transcription factor including MAP kinases and C/EBP (Hoffmann et al., 2002). However, the ratio of activation between NF-κB to MAPK and other transcription factors in this regulatory mechanism seems to differ depending on the pressure caused by a specific stress factor and cell type. In airway epithelial cells NF-κB, ERK and JNK were found to be essential for TNF-induced CXCL8 expression, while p38 acted as a posttranscriptional regulator (Li et al., 2002). Even though p38 is not required for *cxcl8* gene expression, it plays a major role in CXCL8 release by stabilizing its mRNA through protein kinase-2 (Hoffmann et al., 2002). A simplified representation of the signaling pathways involved in CXCL8 expression and regulation is shown in figure 3. Furthermore, reactive oxygen intermediates (ROI) are important regulators of cytokine and chemokine expression and has been shown to mediate a dose-dependent CXCL8 expression (DeForge et al., 1993). They further demonstrated that the effect of these potent immune regulators could be almost completely abolished by applying the OH-radical scavenger DMSO, which reduced CXCL8 expression by 90%.

There are two well-characterized receptors for CXCL8, namely CXC chemokine receptor (CXCR)-1 and -2. CXCL8 binds to these receptors with high affinity (Bertini et al., 2004), while CXCR1 is specific for CXCL8, (NAP)-2 and granulocyte chemotactic protein (GCP)-2, CXCR2 can bind additional chemokines, including CXCL1, 2, 3, 5, 6 and 7 (Acosta et al., 2008). Despite their structural similarities, these receptors possess different biological effects through distinct signaling pathways (Gabellini et al., 2009).

Signals transduced through CXCR1 stimulate neutrophil migration through epithelial layers, while CXCR2 signaling promotes angiogenesis (Sturm et al., 2005). The intracellular protein Bcl-10 has been proposed to play a critical role in the signaling pathway leading to CXCL8 expression and its enhancement of angiogenesis through CXCR2 (Karl et al., 2005). Both NF-κB and C/EBP have been reported to be downstream targets of activation in the CXCR2 signaling cascade, ultimately leading to CXCL8 expression, creating a positive feedback loop (Acosta & Gil, 2009). This positive feedback loop leading to neutrophil activation and migration is regulated by internalization of CXCR1 and CXCR2 upon ligand binding. Furthermore, a second regulatory mechanism of CXCL8 receptor expression involves metalloproteinases as important regulatory factors (Khandaker et al., 1999). They

demonstrated a significant reduction of CXCR1 and CXCR2 following exposure of neutrophils with LPS or TNF that was shown to act through activation of serine proteinases. This may indicate that a mechanism used by microorganisms to evade the immune system is by reducing neutrophil migration towards the infected site. CXCR1 was further shown to be expressed on cytotoxic $CD8^+$ effector T-cells, indicating the vital physiological role of CXCL8 in recruiting lymphocytes and therefore acting as an important link between innate and adaptive immunity (Takata et al., 2004).

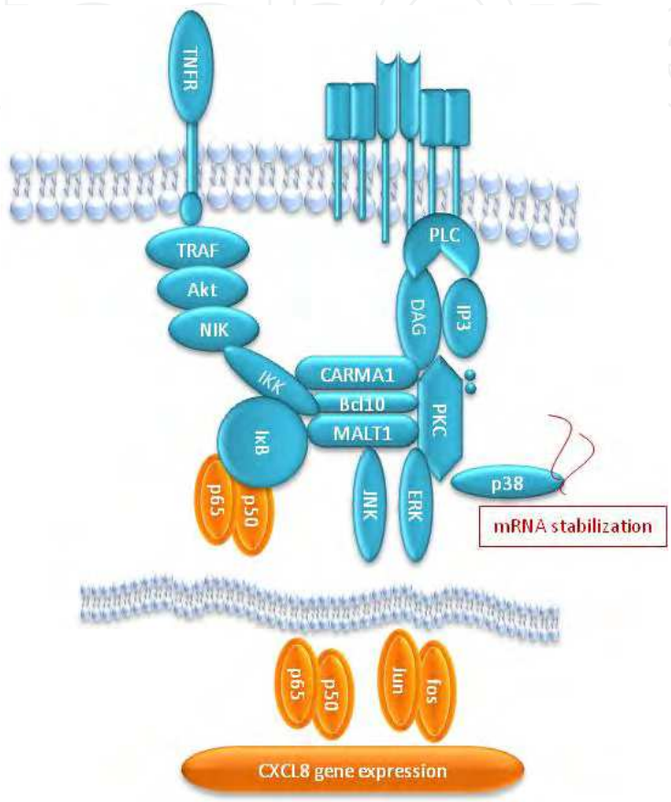

Fig. 3. Intracellular signaling cascade leading to *cxcl8* gene expression. NF-κB (p50, p65) and AP-1 (jun, fos) are the main regulators at the transcriptional level, while p38 serves to stabilize the mRNA molecules.

3. Targeting CXCL8 in HIV treatment strategies

CXCL8 has been implicated in many cellular responses, such as HIV pathogenesis, angiogenesis and cell growth and survival. HIV-infected individuals have elevated CXCL8 levels that, due to the potent chemo-attractant characteristics of CXCL8, can result in the recruitment of target cells, leading to a progressive infection and HIV-1 replication (Ott et al., 1998). However, it has also been suggested that CXCL8 is involved in decreased replication of HIV-1 during the early stages of infection (Rollenhagen & Asin, 2010). In addition, CXCL8 can act as a potent anti-apoptotic agent, inducing the expression of pro-survival proteins, including Bcl-2 and Bcl-x_L (Li et al., 2003). While the role of CXCL8 remains complex it remains an interesting candidate as a suitable therapeutic target in HIV treatment.

Cellular HIV infection involves interactions between glycoprotein gp120, CD4 and CC/CXC receptors (Suresh & Wanchu, 2006). It is therefore possible that an HIV infection can be interrupted and the progression of an established infection can be delayed by targeting CC and/or CXC chemokine receptors. There are two well characterized chemokine receptors by which HIV can bind, enter and infect monocytes, microglia and T-lymphocytes, namely CCR5 and CXCR4 (Ghafouri et al., 2006). CXCL8 dependent activation of CXCR1 has also been suggested to result in inhibited HIV infection and entry into cells (Richardson et al., 2003). Richardson and colleagues showed that CXCR1 activation and internalization resulted in a cross-phosphorylation and internalization of CCR5. Furthermore, C-terminal mutation of CXCR1 internalized both CCR5 and CXCR4 and thus inhibited HIV-1 infection and entry. Furthermore, since HIV-1 competes with CCL5 and CXCL8 for the chemokine receptor DARC (duffy antigen receptor for chemokines) the serum levels of these chemokines may affect the progression of HIV by binding to their respective receptors (He et al., 2008). HIV-1 binding to DARC was also shown to affect chemokine-induced inflammation.

Even though CXCL8 expression is impaired in HIV-infected cells, pro-inflammatory cytokines such as TNF can induce CXCL8 production and expression from other immune cells. It was recently demonstrated that HIV-infected macrophages secrete TNF and IL-1β that in turn act on astrocytes to induce CXCL8 production (Zheng et al., 2008). CXCL8 production was mediated through the MAPK-associated pathways, including p38, c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinases (ERK1/2). This inflammatory process plays an important role in the pathogenesis of HIV-associated dementia. Reduction of CXCL8 production can therefore be used to control immune cell migration into the central nervous system, which will reduce the overall inflammatory responses at this site. In addition, CXCL8 is co-localize with CD68/CD40 cells, and CD40 receptor expression on microglial cells act as potent inducers of CXCL8 expression, through AP-1 and NF-κB, following ligation of its ligand CD40L, which is expressed on monocytes and T-lymphocytes (D'Aversa et al., 2008). Taken together, these studies show the importance of understanding the regulatory mechanisms leading to chemokine expression in T-cells and other immune cells in order to find a suitable target to control HIV replication and progression.

Antiretroviral drugs that target different structural properties in HIV have failed to eradicate the virus but rather suppressed its spreading and pathogenesis. These difficulties have been due to the variability and ability of HIV to internalize without being detected, followed by reactivation (Archer et al., 2009). These drugs are therefore applied in a combination to inhibit several steps of the viral life cycle, including proteases to inhibit maturation, reverse transcription inhibitors and inhibitors for HIV integration into the genome (Arhel & Kirchhoff, 2010). Other difficulties include drug-drug interactions and long-term toxicities (Tilton & Doms, 2010). However, as chemokine levels are severely altered in HIV infected individuals and are involved in HIV replication this has led to an interest in applying this knowledge to controling HIV infections (Llano & Esté, 2005). Alternative treatment methods have been developed, targeting host proteins/receptors that are used by the virus to enter and infect a cell, such as maraviroc, which is a CCR5 antagonist (Swenson et al., 2011). As viruses are divided into CCR5- and CXCR4-dependent (Pilcher et al., 2004), it is important to accurately determine this mechanism before applying a specific treatment to successfully reduce/inhibit HIV spread and pathogenesis. However,

although an initial virus infection is CCR5-dependent, a large subset will switch to using CXCR4 as a co-receptor. This is a major concern since maraviroc has little or no effect on CXCR4-dependent viruses (Kuritzkes, 2011). The interplay between different immune cells during an established HIV infection remains important to understand. Determination of cytokine expression by specific cells and the effect that these inflammatory mediators have on other cells to produce chemokines is also important. Further investigations are needed to evaluate the patterns of immune cell activation and cytokine/chemokine regulation in order to find suitable therapeutic targets.

4. Probiotic *Lactobacillus* as an alternative HIV treatment strategy

Lactobacillus spp are part of the healthy human microbiota, found primarily in the gastrointestinal and vaginal tracts. Certain *Lactobacillus* spp have been identified as health promoting probiotic bacteria by inhibiting pathogen colonization and modulating the immune response in the host (reviewed in Reid et al., 2003). Evidence of immune modulating properties exhibited by certain lactobacilli strains has been shown through their ability to alter cytokine expression in tissue cells infected by pathogens, *in vitro* and *in vivo*, and thus helping maintain homeostasis (Anukam et al., 2009; Frick et al., 2007; Moorthy et al., 2010; Nandakumar et al., 2009; van Hemert et al., 2010; Zhang et al., 2005). Altered cytokine responses, including TNF, NF-κB, IL-6, IL-1β, CXCL8, IL-10 and IL-12, are dependent on cell type (human mucosal epithelial cells, human mononuclear cells, T-cells, dendritic cells etc) and *Lactobacillus* species and strain (Nandakumar et al., 2009; van Hemert et al., 2010). From these reports, probiotic lactobacilli demonstrate a clear potential for both development of new strategies to reduce the risk of HIV infection and combat AIDS progression through their anti-infective and immune-modulating properties.

Vaginal infections such as bacterial vaginosis (BV) and candidiasis have been correlated with an increased risk of HIV infection (Sha et al., 2005; St John et al., 2007). BV and candidiasis are characterized by microbiota that is comprised of a range of anaerobic bacteria or *Candida albicans*, respectively, while deficient in lactobacilli (Sha et al., 2005). Furthermore, women already infected with HIV that lacked vaginal lactobacilli and had BV or candidiasis had higher levels of HIV shedding in the genital tract (Coleman et al., 2007; Spinillo et al., 2005). Increased HIV transcripts in vaginal cells and viral shedding increases the risk of HIV transmission. Furthermore, vaginal secretions from women with BV increased HIV expression in chronically infected monocyte cell line *in vitro*, while secretions from women without BV had no effect on HIV expression (Spear et al., 2007). This is believed to be due to the higher levels of proinflammatory cytokines primarily those that function through NF-κB (Al-Harthi et al., 1998). *C. albicans* infections increase vaginal CXCL8 levels and neutrophil presence while higher levels of vaginal lactobacilli reduced CXCL8 levels and other pro-inflammatory cytokines (Spear et al., 2008). CXCL8 is a potent chemokine that recruits neutrophils to the site of infections, thus by reducing chemokine levels, the target cells for HIV infection are limited. Using lactobacilli to modulate the CXCL8 levels and other pro-inflammatory signals may thus reduce the risk of HIV infection and reduce viral replication.

Certain *Lactobacillus* spp have been shown to reduce pro-inflammatory cytokine release from stimulated cells. The probiotic *Lactobacillus rhamnosus* GG reduced the *cxcl8* expression and CXCL8 and CCL11 secretion in TNF or IL-1β - stimulated human intestinal epithelial cells

(Caco-2bbe) by blocking NF-κB activation and nuclear translocation (Donato et al., 2010). In the same study, related bacteria *Lactobacillus farciminis* and *Lactobacillus plantarum* RO403 did not alter the CXCL8 or CCL11 levels in the stimulated cells. Others reported that *L. plantarum* 299v showed differential influence on expression and secretion of CXCL8 in HT-29 colonic epithelial cells that were treated with TNF. *L. plantarum* 299v enhanced the *cxcl8* mRNA above that of TNF treatment alone while decreasing CXCL8 secretion from HT-29 cells (McCracken et al., 2002). The *L. plantarum* 299v alone did not induce CXCL8. This is especially interesting since CXCL8 has been shown to decreases transcription of RS-Tropic HIV-1 in peripheral blood lymphocytes and decreases replication in ectocervical tissue explants (Rollenhagen & Asin, 2010; Tiemessen et al., 2000). However, another study had reported that increased levels of CXCL8 stimulated HIV-1 replication in T lymphocytes and macrophages, and this could be significantly inhibited using CXCL8 antibodies or blocking CXCR1 and CXCR2 receptors (Lane et al., 2001). High levels of secreted CXCL8 have been associated with chronic infections in HIV infected persons, thus recruiting and exposing the target cells for HIV infection. Modulation of CXCL8 suggests a potential role for certain strains of lactobacilli in reducing the risk for HIV infection and disease progression.

5. Genetically modified lactobacilli for HIV treatment

Commensal *Lactobacillus* spp from the gastrointestinal and vaginal tract have been considered safe and thus have been used to develop genetically engineered lactobacilli as potential live antiviral-fusion delivery systems. Several investigators have genetically engineered a human isolate of *Lactobacillus jensenii* to secrete fusion inhibitors that target necessary receptors for HIV infection with the aim of being used as a vaginal topical treatment. Chang and colleagues have genetically engineered *L. jensenii* to produce a two-domain CD4 protein that bound the HIV-1 gp120 moderately inhibiting HIV binding and entry into Hela cells expressing CD4-CXCR4 *in vitro* (Chang et al., 2003). Similarly, other fusion inhibitors have been successfully expressed from *L. jensenii* such as the anti-HIV-1 chemokine RANTES and a mutated CCR5 antagonist that showed inhibition of infecting T-cells and macrophages in a concentration dependent manner (Vangelista et al., 2010). A recent patent has been filed for genetically engineered *L. reuteri* RC-14 to be used in treatment of HIV and AIDS after infection by secreting fusion inhibitors in the gastrointestinal tract to reduce or slow the progression of AIDS (Lemke 2010; Patent #US 2010/0143305 A1). One report showed that *L. rhamnosus* GR-1 and *L reuteri* RC-14 did not naturally have the ability to alter RANTES in yeast-infected epithelial cells and *L. rhamnosus* GG did not induce the expression of CCL5 (Martinez et al., 2009; Nandakumar et al., 2009). However, to the authors' knowledge, there has been no systematic evaluation of lactobacilli for inducing HIV-1 fusion inhibitors in cell. The combination of genetically engineered lactobacilli strains to express fusion inhibitor molecules, including CXCR1 and 2 and CXCL8 modulation may further reduce HIV infection and AIDS progression.

6. Conclusions

It is clear that cytokines and chemokines are important factors in HIV infection and disease progression, making them plausible targets for anti-HIV therapy and to slow the progression to AIDS. CXCL8 is an important factor to consider in HIV therapy, as it is responsible for the recruitment of neutorphils and T-cells to the site of infection. As HIV

targets immune cells and thereby interferes with the innate immune systems, it is of interest to develop methods to block or reduce the ability of HIV to infect immune cells. Therefore, in order to develop viable CXCL8 based treatment strategies it is important to identify the signaling pathways involved in CXCL8 regulation as well as to determine the function of CXCL8 and its receptors in different physiological responses.

Certain lactobacilli have been shown to have immune modulating abilities. There is a clear potential for using probiotic lactobacilli to counter infections, including HIV, as they have both anti-infective and immune-modulating properties. From this aspect, the ideal probiotic *Lactobacillus* species/strain for therapeutic use is one that increases intracellular CXCL8, while maintains a low level of secreted pro-inflammatory cytokines, such as NF-kB, TNF, CXCL8 and IL-6, that promote HIV replication and recruit HIV-target cells. Combining the health promoting properties of lactobacilli with modulation of *cxcl8* expression and release can be of great importance in fighting HIV infections.

7. Acknowledgement

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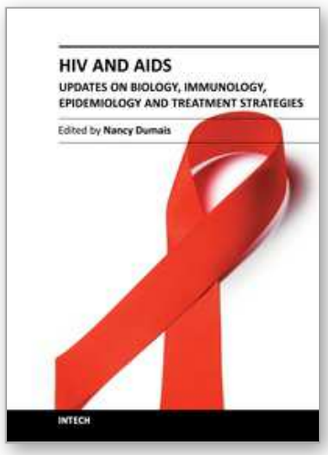

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The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, â€œFrom the laboratory to the clinic,â€ and the second part, â€œFrom the clinic to the patients,â€ represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

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