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Innate, Adaptive and Intrinsic Immunity in Human Immunodeficiency Virus Infection

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ABSTRACT

The first line of defence of the innate immune system functions by recognizing highly conserved sets of molecular structures specific to the microbes, termed pathogen-associated molecular patterns, or PAMPs via the germ line-encoded receptors Pattern-Recognition Receptors (PRRs). In addition to the innate immune system, the vertebrates have also evolved a second line of defence termed adaptive immune system, which uses a diverse set of somatically rearranged receptors T-Cell Receptors (TCRs) and B Cell Receptors (BCRs), which have the inherent ability to effectively recognise diverse antigens. The innate and adaptive immune systems are functionally tied in with the intrinsic immunity, which comprises of endogenous antiviral factors. Thus, this effective response to diverse microbial infections, including HIV, requires a coordinated interaction at several functional levels between innate, adaptive and intrinsic immune systems. This review provides a snapshot of roles played by the innate, adaptive and the intrinsic immune systems during HIV-infection, along with discussing recent developments highlighting the genomic basis of these responses and their regulation by micro-RNA (miRNAs).

Keywords: Innate Immune System, Adaptive Immune System, TLRs, Endogenous Anti-Viral Factors

1. INTRODUCTION

1.1. HIV Epidemiology

The discovery of the Human Immunodeficiency Virus (HIV) in 1983 by Barre-Sinoussi *et al*. (1983) led to the understanding of the causative agent of Acquired Immunodeficiency Syndrome (AIDS)-a disease which gradually decreases the levels of CD4+T cells and impairs the host's immune system and predisposing the host to opportunistic diseases and cancers. This virus has caused 25 million deaths since then (Wainberg and Jeang, 2008). Currently, there are 33.3 million people living with HIV globally 2010 UNAIDS global report.

1.2. Transmission and Clinical Manifestation of HIV Disease

HIV targets and infects human immune cells. The primary target of HIV is the CD4+ T cells and mature macrophages (Matsuda *et al*., 1995) and the HIV-1 transmission occurs through the mucosal tissues, which leads to the infection of these CD4+CCR5+ T cells (Weiss, 2001). Cells which do not express the surface CD4 marker are usually not susceptible to HIV infection. During the early infection the host is unable to mount a successful rapid immune response via the production of neutralizing antibodies or cytotoxic lymphocytes. Innate immune system, which acts independent of prior encounter with a pathogen, plays a major part in clearing the virus.

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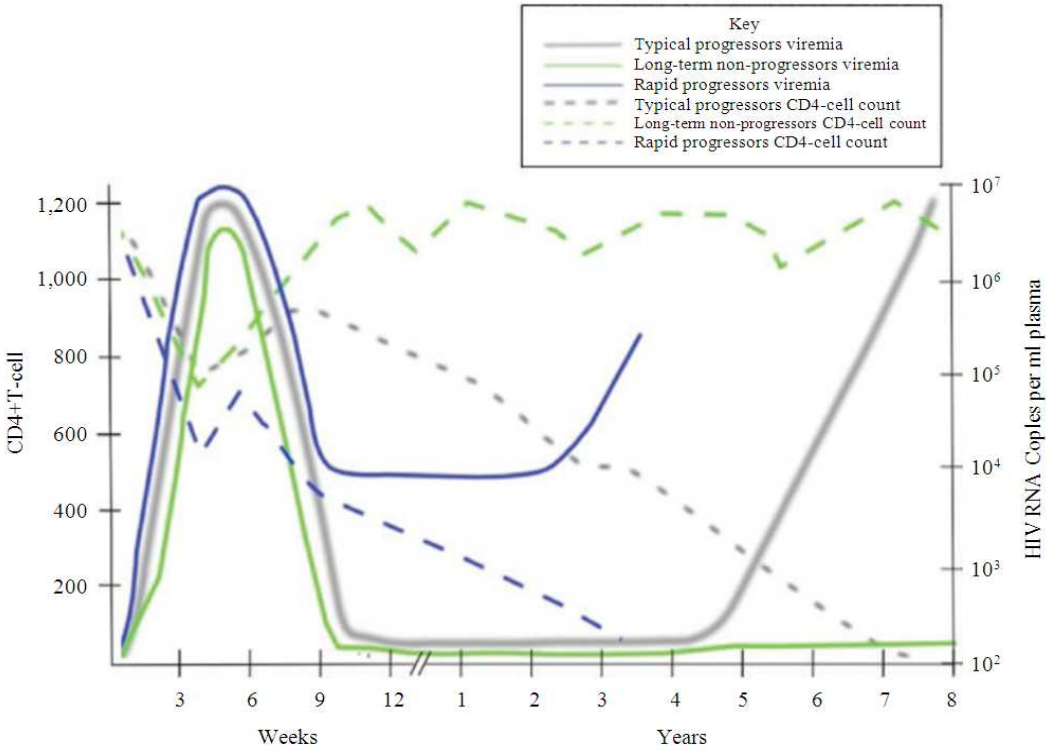

Fig. 1. Profiles of HIV disease stages in relation to plasma viremia and CD4+ T cell counts. Comparison of HIV Disease groups-typical progressor, rapid progressors and Long-term nonprogressors (Poropatich and Sullivan, 2011)

The initial barriers encountered by invading HIV include the epithelial layer, vaginal pH and mucous are quite effective in thwarting HIV infection. However exposure of these barriers results in the production of pro-inflammatory cytokines, that recruits dendritic cells, macrophages and lymphocytes into the infection site, thereby providing target cells for the virus (Sivro *et al*., 2010).

The progression of HIV to AIDS is determined by the host and viral factors. Gradual loss of CD4+ cell population along with increasing of plasma viremia eventually lead to AIDS, the final stage of HIV infection (Saksena *et al*., 2007). This progressive failure of host immunological functions leads to opportunistic infections, such as pneumonia or tuberculosis, which eventually lead to AIDS. Although AIDS usually develops within 8-10 years in therapy naïve patients, the treatment with Highly Active Antiretroviral Therapy (HAART) slows disease progression with which quality of life has dramatically improved for HIV patients (Saksena *et al*., 2007).

The progression of HIV disease has been categorized into 3 different groups: (1) Rapid Progressors (RP), who typically progress to AIDS within 3-5 years showing rapid decline of CD4+T cell counts in concomitance with increasing plasma viremia. (2) Slow-Progressors (SP), who show gradual CD4+ T cell decline over 10-15 years and increasing plasma viremia and (3) Elite Controllers (EC) or Long-term non-progressors, who are infected for 20 years or more, maintain >500 CD4+ T cells per ml blood, below detectable levels of plasma viremia and remain therapy naïve for the entire duration of infection (Saksena *et al*., 2007; Poropatich and Sullivan, 2011) (**Fig. 1**). A subset of LTNP's, known as Elite Controllers (EC's) or elite suppressors, which comprise about less than 1% of the total HIV population and remain an interesting area of investigation, as they hold clues to HIV cure (Saksena *et al*., 2007).

2. HOST'S INNATE IMMUNITY AND HIV PATHOGENESIS

The human immune system is divided into two main arms: Innate immunity which forms a rapid, "less" specific immune response and the more specific, robust adaptive immune system.

Table 1. Breakdown of host defences against HIV

Innate Immunity				Adaptive immunity		
Cellular	Extracellular	Intracellular	Memory	Systemic	Cellular	Mucosal
DC, Mφ, γδcells Receptors PRR, Mannose Binding lectins, TLR(1-10), NLR Conserved ligands: PAMPS, DAMPS	Complement, cytokines, chemokines. α-defensins, SLP-1, Trapin2, Serpine proteases.	APOBEC3G, F, Trim5α, Murr1, Tetherin	Natural killer cells	Neutralizing Antibodies, CCR5, HLA HSP	T cells CD4+, CD8+ Bcells	CCR5, CCR7, CD45RO/RA

Innate immune system is the host defence system, which has evolved to recognise patterns that are conserved in nature and are present in large groups of microorganisms such as LPS, peptidoglycan, double-stranded RNA (Alfano and Polia, 2005). It is now widely accepted that the key to resistance to HIV infection and its progression lies within the host immune system that consists of innate and adaptive immune components (Reviewed in Arriaga *et al*., 2006; Saksena *et al*., 2007; Zaunders *et al*., 2004). Innate immunity controls HIV and other infections through a rapid host response (Ganesh *et al*., 2003), which involves intracellular signalling pathway activated by pattern recognition receptors on the surface of variety of cells, most of them antigen-presenting cells (dendritic cells, monocytes and macrophages). The innate immune system is classified into three major sections cellular, extracellular and intracellular components (**Table 1**). The cellular comonent of the innate immune system comprises of Toll-Like Receptors (TLRs), different cell types including Dendritic Cells (DC), macrophages, natural killer cells and several soluble factors such as complement components, defensins, mannose binding lectins, interferons, cytokines and chemokines and have evolved to provide early and rapid responses to pathogens (Lehner *et al*., 2011; Eger and Unutmaz, 2005). As some of these components of innate immunity overlap, it is important to emphasize that DCs, monocytes and macrophages can also play a role in both innate and adaptive immunity as antigen presenting cells.

2.1. Role of Toll Like Receptors (TLRs), Mannose Binding Receptors, Dendritic and NK Cells in the Control of HIV Viremia and in Non-Progression of HIV Disease

TLRs are type I transmembrane proteins (also known as pattern-recognition receptors) that function as homodimers or heterodimers and are essential architectural components of the innate immune system. Currently, there are 10 known functional human TLR's (Lester *et al*., 2008) and upon stimulation TLRs activate signal transduction pathways, which induce dendritic cell maturation and cytokine production (Ricci *et al*., 2010). TLR3, TLR7, TLR8 and TLR9 have been shown to have anti viral properties. Especially TLR7 and 8 which are activated via stimulation of single-stranded RNA from HIV (Barton, 2007; Biasin *et al*., 2010; Mogensen *et al*., 2010). It is known that specific Single Nucleotide Polymorphisms (SNPs) in several TLR genes regulate the risk of bacterial and viral infections and polymorphisms in TLR-8 and TLR-9 are associated with the disease progression of HIV (Bochud *et al*., 2007; Oh *et al*., 2008). In the study by Oh *et al*. (2008) of the German cohort of HIV-positive patients, it was showed that A1G polymorphism in TLR8 gene was associated with the restriction of progression of HIV disease, which occurs via decreasing the activation of NF-Kβ (a known activator of HIV 1 replication) and increasing the production of TNF-α, IL-10, PGE2 and LTB4 cytokines which are potent suppressors of viral infections including HIV-1 (Oh *et al*., 2008). In contrast, the SNP's 1635A/G and 1174G/A in TLR9 were associated with rapid disease progression, high viral load and low levels a CD4+ T cell counts as was shown by Bochud *et al*. (2007) on a Swiss cohort. These studies suggest that the activation of NF-Kβ induces the transcription factor that promotes activation of the HIV-1 Long Terminal Repeat (LTR), thereby promoting HIV replication and subsequent disease progression. In a similar study done

on a cohort of children born to HIV-1 positive mothers, it was found that children carrying c.4-44G >A and c.1635A >G SNP haplotypes in the TLR 9 gene was associated with a significantly increased risk of mother-to-child transmission (Ricci *et al*., 2010), whereas the SNP c.4-44GG in TLR9 was associated with slower disease progression in HIV-1-infected adults (Ricci *et al*., 2010).

Late stage chronic HIV infection has a profound effect on the TLR expression. TLR 7/8/9 have been shown to induce a strong pro-inflammatory/anti microbial response and in late stages of HIV infection and the TLRs appear to be linked to impairment in virus-specific T cells and T cell exhaustion (Sivro *et al*., 2010). In a study conducted by Lester *et al*. (2008) on 200 therapy naive late stage HIV patients of the Nairobi cohort, it was observed that mRNA expression levels for TLR6, 7 and 8 levels were significantly increased in subjects with chronic HIV-1 infection and this increase in expression of these TLR's was even more prominent in patients with advanced HIV infection. Moreover, patients with advanced HIV infection also displayed TLR2, 3 and 4 mRNA expression levels. Thus the increased expression of circulating TLRs bear significant correlation with HIV progression, which possibly occurs via the activation of the host's immune system.

2.2. Genomic Basis of TLR Responses in HIV-Infected Primary Monocytes and Their Relationship with HIV Disease Progression and Non-Progression

Little is known about the genomic basis of TLR responses during HIV infection. With the advent of microarray, miRNA and next generation sequencing technologies, we are seeing a more indepth picture of such responses in HIV patients.

Recently, (Wu *et al*., 2012) have shown a genome-wide transcriptome analysis of *ex-vivo*-derived monocytes from HIV+ patients at different stages of plasma viremia (HIV patients with and without viremia while on HAART and HIV+ aviremic, therapy naïve Long-Term Non-Progressors-LTNP). There was overall down-regulation of TLR signalling pathway in the viremic groups when compared to HIV+ LTNPs manifested by the decreased TLR expression with subsequent tuning down of MAPK, NF-κB, JAK-STAT, IRF signalling cascades and the reduced cytokine production. This reflected the deficiencies in the innate immune response of monocytes in viremic patients. To our knowledge, this is the report showing the simultaneous tuning down of all four signalling cascades integrated within the TLR pathway during HIV disease progression.

Receptors of the innate immune system are crucial in the first-line defence against foreign microbes and are important for modulating the adaptive immune response. TLRs represent an important category of such pathogen-recognition receptors. Monocytes have been shown to express TLR-2 and TLR-4 and the stimulation of these receptors induces the activation of NFκB, with subsequent production of inflammatory cytokines and chemokines (Heggelund *et al*., 2004). Heggelund *et al*. (2004) have demonstrated that there is increase in TLR-2 expression on monocytes during HIV infection. Supporting these studies, the stimulation of Peripheral Blood Mononuclear Cells (PBMC's) with HIV-1 envgp120, significant increase in TLR-2 was observed suggesting a possible link between HIV-1 infection and TLR-2 expression, which ties in well with the biological studies discussed in the previous section. Previously, it has been suggested that the altered TLR expression and a deficient TLR2/4 signalling through ERK may cause the decreased production of TNF-α, in alveolar macrophages, which was associated with HIV disease progression (Nicol *et al*., 2008). In the study performed by Wu *et al*. (2012) the detection of the down-regulation of the enrichment genes along the MAPK branch not only fully supported the previous observations on altered expressions of TLR2/4, ERK/MAPK3 and TNF-α, but also extended the previous postulation to a clear view of the disturbed MAPK signalling cascade integrated within TLR pathway during disease progression, which revealed the comprehensive link underlying the observed discrete changes in gene expression. Further, the decrease in cytokine production has also been observed in the TLR signalling pathway, which was further manifested by the down-regulation of the cytokine-cytokine receptor interaction pathway in the viremic groups compared against the LTNPs. One of the most pronounced changes in this pathway was the significant and systematic down-regulation of genes encoding proinflammatory cytokines including IL-1β, IL-6, IL-8, TNF-α and the receptor CSF1R in the viremic groups. On the other hand, the anti-inflammatory cytokines such as TGF-β, IL-4, L-10 and IL-13 did not show any significant changes between viremic and the LTNP group (Wu *et al*., 2012). This selective reduction in proinflammatory cytokines during disease progression was consistent with the previous report that the frequencies of monocytes producing proinflammatory cytokines (IL1β, IL-6 and TNFα) was diminished in patients with viremia during the time off therapy

compared to the time on therapy with effective control of viral replication (Tilton *et al*., 2006).

Though it is not clear how HIV achieves the global down-regulation of the TLR pathway, previous studies have documented the interactions between HIV accessory proteins and components associated with the innate immune signalling, such as the interactions between nef and MKP-1, between Vpu and βTrCP (Tachado *et al*., 2005; Leulier *et al*., 2003). Similarly, the global down-regulation of the TLR pathway could be achieved through HIV actively inhibiting/suppressing immune signalling and/or passively evading pattern recognition of monocytes.

2.3. Mannose-Binding Lectin (MBL)

MBL is an acute phase, multimeric protein (with six 96 kDa subunits) of hepatic origin and belongs to the family of collectins (Eisen *et al*., 2008; Garred *et al*., 1997). MBL acts as a pattern recognition molecule and binds to carbohydrate structures of invading pathogens. By doing so MBL not only opsonises the microbe but also activates the complement system. It has been previously described that low serum concentrations of MBL are associated with defect in opsonisation of microbes (Garred *et al*., 1997). In HIV infection, MBL is known to bind to envelope viral protein subunits gp120 and gp41. Both these proteins have oligosaccharide side chains of high-mannose type; gp120 in particular is highly glycosylated, with a high proportion of mannose-containing oligosaccharides (Eisen *et al*., 2008). MBL-HIV interaction enhances opsonisation and initiate viral killing (Eisen *et al*., 2008). Three variant alleles in the MBL genes (B, C and D) have been shown to be associated with lower MBL serum level by Garred *et al*. (1997), who observed that HIV patients who are homozygous to three variant alleles are at higher risk of HIV infection due to increased susceptibility to co-infections, hence a higher rate of disease progression in HIV-infected patients.

2.3.1. Dendritic Cells and Antigen Presentation in HIV Disease

Along with monocytes and macrophages, the Dendritic Cells (DCs) are professional antigen presenting cells which act as an important link between the innate and adaptive immunity (Krambovitis and Spandidos, 2006). Transmission of the predominant HIV-1 R5 variants to T cells is mediated by infected monocyte-derived macrophages and HIV also harbors the ability to tamper with antigen presentation, which gets severely impaired during HIV infection at different stages of plasma viremia. DCs secrete soluble immune factors which have anti HIV activity (Alfano and Polia, 2005). Based on the beta integrin CD11c, this cell type is further divided into two groups myeloid CD11c+ DCs (mDCs) which are precursors of Langerhan cells and plasmacytoid DCs (pDCs). Both subsets specialize in virus detection and will activate the host innate and adaptive immunity during viral infection (Donaghy *et al*., 2001). mDCs produce cytokines such as Interleukin12 (IL12), IL15 and IL18. Cytokines such as IL12 are crucial for the activation of CD4+ T cell subset, which in turn activate the Cytotoxic T Lymphocyte (CTL), clearing the virus-infected cells. pDCs produce more type I Interferons (IFNs) in response to HIV and are known to stimulate mDCs and activate NK cells (Altfeld *et al*., 2011). Upon virus detection in the peripheral tissue sites, the activated DC uptake the virus and migrate to the draining lymph nodes. In lymph nodes virus is presented to the cellular adaptive immune components, which then activates the CD4+ T and Natural Killer cells (NK cells). HIV gp 120 is known to interact with Four types of C-type lectin receptors on DC, DC-SIGN, langerin, the mannose receptor (also known as CD206) and an unidentified trypsin-resistant C-type lectin3 (Wu and Kewalramani, 2006; Turville *et al*., 2001). The interaction of gp120 and DC-SIGN facilitates the phagocytosis of the whole virus into DC early endosomal compartments where degradation of the viruses does not occur, enabling intact virus to come into contact with CD4+ cells (Altfeld *et al*., 2011).

Epithelial DCs express myeloid markers and intercept invading pathogens in the periphery and then migrate to the secondary lymphoid tissue where they present peptides to antigen-specific T cells thereby inducing pathogen-specific T cell responses. Donaghy *et al*. (2001) showed that there is considerable loss of these two DC subsets during HIV infection and their numbers remain low throughout the course of disease. This correlates with viral load in patients. Further, the antigen presentation by monocyte-derived dendritic cells partially restores impaired antigen specific CD4+T cell responses associated with HIV-1 infection (Donaghy *et al*., 2001).

Thus there is a belief emanating from these studies that immunization strategies, which target dendritic cells and other antigen presenting cells such as monocyte and macrophages may offer significant advantages in the ability to stimulate HIV-specific protective immune responses (Newton *et al*., 2006). This novel therapeutic vaccination strategy can become feasible, if a pool of such antigen presenting cells against HIV can be

induced. It has long been believed that the key to control of HIV replication is immune restoration, especially HIV-specific immunity, which is lost soon after the initial infection. This immunity remains perfectly restored in many long surviving, therapy naïve HIV-infected non-progressors and elite controllers, which can provide clues to components of protective immunity in HIV+ individuals.

2.3.2. Natural Killer Cells (NK Cells)

NK cells make up to 15% of peripheral blood lymphocytes and play a major role in innate immunity, in addition to acting as a bridge with the adaptive immune system by interacting with T cells and DCs. There are two subsets of NK cells, CD56dim subset making up the majority (~90%) of human NK cells which express high levels of the Fcγ receptor III (CD16) and CD56bright subset is CD16- or CD16dim (Eger and Unutmaz, 2005). NK cells express a vast array of cell surface inhibitory and activating receptors (Stratov *et al*., 2008). These cells recognize the virally-infected cells by down regulating levels of Major Histocompatibility Complex (MHC) class I molecules (Eger and Unutmaz, 2005). They are also known to secrete antiviral, proinflammatory cytokines such as gamma interferon (IFNγ) interleukin-1 (IL-1), tumour necrosis factor alpha (TNFα, granulocyte-macrophage colony-stimulating factor and degranulated perforin and granzyme B (**Table 2**) (Stratov *et al*., 2008). Vieillard *et al*. (2010) observed that NK cells from both viremic and non-viremic LTNPs produced significantly higher levels of IFNγ than progressors and healthy uninfected subjects.

NK cells play an important role in controlling HIV infection even though, to date, no HIV-specific receptors have been observed on NK cells (Altfeld *et al*., 2011). In the absence of such receptors, it is believed that this function is carried out by inhibitory and activating signals delivered to the NK cells via the cross talk with the infected cells. It is known that inhibitory receptor, highly polymorphic Killer cell Immunoglobulin like Receptors (KIRs), which bind to classical MHC class I molecules and CD94-NKG2A receptor, which in turn binds to non-classical MHC molecule HLAe are believed to play a role in this (Altfeld *et al*., 2011). NK cells from LTNPs are known to have abnormal phenotype compared with both HIV-1-infected viremic subjects and uninfected subjects (Poropatich and Sullivan, 2011). HIV protein Nef is known to down regulate expression of HLA-A and HLA-B, but not HLA-c or HLAe in infected cells and by doing so it prevents NK cell activation in HIV-infected subjects (Altfeld *et al*., 2011; Alter and Altfeld, 2008). Interaction between HLA-Bw480I alleles (i.e., HLAB57) and KIR3DL1 are known to produce a robust cytotoxic cell response. Martin *et al*. (2001) found that not only was the absence of HLA-B Bw4-80Ile alleles, KIR3DS1 significantly associated with more rapid progression to AIDS, the co-expression if KIR3DS1 and HLABw480I alleles was associated with slow progression of HIV disease (**Fig. 2**).

2.4. Role of γδ T Cells in Innate and Adaptive Immunity During HIV Infection

Although the γδ T cells qualify for a full review in the context of HIV infection, this review discusses only the significant features of these cell types, which guide innate immunity.

How the responses of γδ T cells come into play remains poorly understood. The facets of complex behaviour of γδ T cells and the current dogma suggests these cells as first line of defence, 'regulatory cells and a possible bridge' between innate and adaptive immune responses during viral infections (Holtmeier and Kabelitz, 2005). The γδ T cells actually form an entire lymphocyte system that develops under the control of other leukocytes, in the thymus and in the periphery. Mature γδ T cells are highly functional and obey rules at the subset level in carrying out direct and indirect effects on tissues, immune cells and on pathogens in mounting host responses to them. One side of the γδ T cells functions like the components of adaptive immunity, especially in the way they rearrange TCR genes leading to functional diversity and in developing a memory phenotype. On the other hand, the various subsets of γδ T cells can also be cross into innate immunity (Born *et al*., 2006) especially under circumstances where a restricted TCR being used as a pattern recognition receptor (Morita *et al*., 2000).

Table 2. Shows the soluble factors secreted DC, pDc and NK cells and their effect on HIV replication (Alfano and Polia, 2005)

	Innate immune effectors
Cell type	Secreted factors
DC	IL-2, IL-10, IL-12, IL-18, TNF-α,CCL3,CCL4 & CXCL1
PDC	IFN-α,IL-12 & IL-15
NK	IFN-γ,FasL,TRAIL,CCL1,CCL3, CCL4,CCL5 & CCL22
NKT	TNF-α, IFN-γ,IL-4, IL-10 & IL-13
γδ Tcells	TNF-α, IFN-γ,IL-6, CCL3, CCL4 & CCL5
Basophils and Neutrophils	TNF-α & IL-4

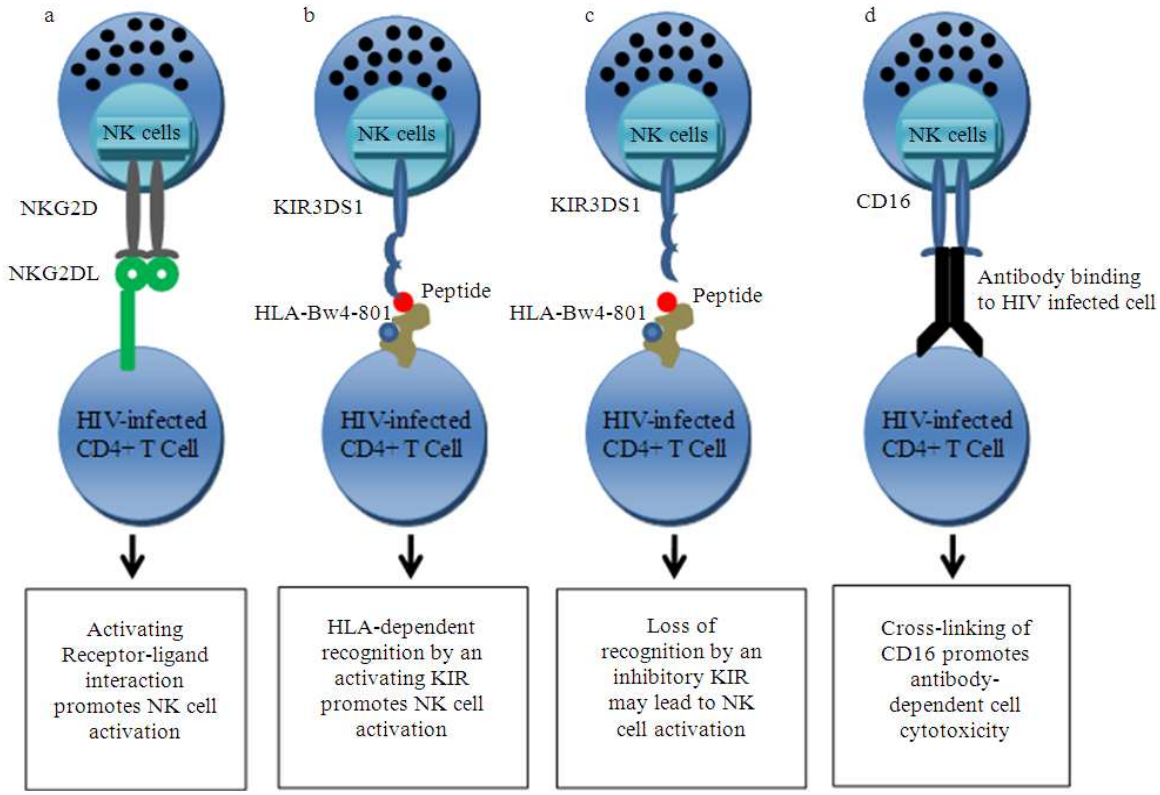

Fig. 2. NK cell-mediated recognition of HIV-1-infected cells. Interaction of inhibitory receptor KIRs and activating receptors NKG2D, are depicted. Adapted and modified from Altfeld *et al*. (2011)

In the context of HIV, recent research has shown that Vγ9/Vδ2 T cells are involved in phagocytosis, a function known to be exclusive to innate myeloid lineage cells neutrophils, monocytes and dendritic cells (Wu *et al*., 2009). Innate, as part of a rapid lymphoid stress surveillance system, is known to play a central role in host responses to many infectious agents. In particular, Vγ9Vδ2 T-cells are able to quickly respond to danger signals without the need for classical major histocompatibility complex presentation and may act as a bridge between innate and acquired arms of immune response, being able to kill infected/transformed cells, release antimicrobial soluble factors and increase the deployment of other innate and acquired responses. T-lymphocytes expressing the gamma delta T-Cell Receptor (TCR) comprise a small proportion (1-5%) of circulating CD3 (+) T-lymphocytes. While T-cells expressing a V delta 2V gamma 9-encoded TCR dominate among peripheral blood gamma delta T-lymphocytes in healthy individuals, considerable alterations in the gamma delta TCR repertoire is a feature commonly seen in HIV-infected persons. These changes are a consequence of selective preservation and more frequently a moderate expansion of V delta 1-expressing cells and along with the depletion of V delta 2-expressing cells (Kabelitz and Wesch, 2006). Many experimental evidences suggest a direct role of circulating Vγ9Vδ2 T-cells during HIV disease. They may exert a direct anti-HIV role by secreting chemokines competing for HIV entry co-receptors, as well as other soluble antiviral factors and by killing infected cells by cytotoxic natural killer cell-like mechanisms.

3. HIV DISEASE AND INTRINSIC IMMUNITY

Over the course of human evolution, constant exposure to a wide variety of viral pathogens has enabled us form antiviral host factors also called "host restriction" factors, which interfere with different stages of the virus life cycle. Even though they are a part of the innate immune system these restriction" factors appear to act in a more rapid manner to provide much faster

defence. There are three main subclasses of intracellular restriction factors, comprising of APOBEC3G : Which induces lethal hyper mutations in the retroviral genome; Tripartite motif protein 5 (Trim5 alpha): Proteins, which impede the incoming retroviral capsid and Tetherin, which hinders the release of newly formed virions (Sauter *et al*., 2010). Extracellular proteins comprise of Defensins, which are small natural endogenous cysteine rich cationic peptides with high anti-HIV1 activity.

The recognition of intrinsic immunity as a potent anti-viral defence mechanism is a recent discovery and is not yet discussed in most immunology courses or texts. Though the extent of protective intrinsic immunity still remains largely unknown, it is believed that the intrinsic immunity may very well constitute a third branch of the traditionally bipartite immune system. Intrinsic immunity comprises of cell-mediated or anti-viral defence mechanisms, which are initiated as a consequence of proteins genetically encoded, which preferentially can target eukaryotic retroviruses and facilitate the halting of the viruses in quick time. Unlike adaptive and innate immunity effectors, the intrinsic immune proteins are expressed at a constant level, thereby allowing viral infections to resolve quickly. Since eukaryotic organisms have been exposed to viral infections for many millennia, the intrinsic immunity always remains active and has evolved to block viral infections. The development of the innate and adaptive immune system truly reflects the evolutionary significance of combating viral infection.

3.1. Relationship of Intrinsic Immunity to the Immune System

Although Intrinsic Immunity combines the two traditional branches of the immune system-adaptive and innate immunity-it is distinct in its mechanism of action from the traditional branches. Innate immunity senses viral infection using Toll-Like Receptors (TLRs), or pattern recognition receptors, which sense Pathogen-Associated Molecular Patterns (PAMPs), in turn triggering the expression of non-specific antiviral proteins (Bieniasz, 2004). By contrast, the intrinsic immune proteins are specific in recognition of the virus and mechanistically specific in causing attenuation of virus. Like innate immunity, the intrinsic immunity does not react any differently upon re-infection by the same pathogen. Furthermore, like adaptive immunity, intrinsic immunity is also specifically made to target a type or class of pathogens, most notably retroviruses. In case of retroviral infections, adaptive and innate immunity permit the sensing of the virus for the immune system to be turned on, which can take time, but because the intrinsic immune proteins are constitutively expressed they are able to shut down infection viral infections following viral entry into the host. This is particularly vital in HIV or retroviral infections because these viruses have the ability to integrate into the host genome as provirus.

3.2. Role of Extracellular and Intracellular Host Antiviral Intrinsic Factors

3.2.1. Intracellular Factors

3.2.2. TRIM5α (Tripartite Interaction Motif Five, Splice Variant Alpha)

TRIM5α is a Ring domain-E3 ubiquitin ligase, which blocks retroviral infections in mammals. It is known to bind to HIV-1 capsid during the post viral entry phase and inhibit viral replication by inducing premature uncoating (Pertel *et al*., 2011). TRIM5α also has a role in signal transduction and is known promote the innate immune signalling (Pertel *et al*., 2011). Along with ubiquitin-conjugating enzyme UBC13-UEV1A, Trim5α catalyses the TAK1 kinase complex and stimulate AP-1 and NFkB signalling ultimately increasing the expression of specific genes involved in innate immunity (Pertel *et al*., 2011; Aiken and Joyce, 2011). Due to above two reasons Trim5α is known to hinder the HIV-1 viral replication even though it is unable to bind to the HIV-1 in humans efficiently (Manen *et al*., 2008). Manen *et al*. (2008) analyzed 327 HIV-1 patients with Trim5α polymorphisms- H43Y and R136Q, respectively and looked at potential differences in clinical progression of HIV patients. They found Trim5α to be associated with reduced HIV disease progression. In addition it was observed patients carrying the R136Q polymorphism had robust immune response towards CXCR4 tropic HIV-1 infection.

TRIM5α is one of the most studied intrinsic immune proteins due to its connection with human HIV and Simian Immunodeficiency Virus (SIV). The rhesus monkey TRIM5α variant is able to recognize and prevent HIV infection, whereas the human TRIM5α protein can prevent SIV infection, but the human TRIM5α is not as effective as seen in simian counterparts, who bear an evolutionary advantage in restricting SIV and adaptation to SIV. This variation helps explain why HIV and SIV infect humans and monkeys, respectively and probably reflects a previous epidemic of what we now call HIV among ancestors of current rhesus monkey populations (Stremlau *et al*., 2004).

3.2.3. APOBEC3G (Apolipoprotein Editing Complex 3 G)

This is another intrinsic immune protein, which interferes with HIV infection. APOBEC3G is a cytidine deaminase against single stranded DNA which introduces transversion mutations into the HIV genome during reverse transcription by randomly changing cytidine base pairs into uracil. Though this will not necessarily stop viral integration, the resulting progeny viral genomes are too riddled with mutations to be viable. In addition a low-molecular-mass APOBEC3G may induce post-entry restriction of HIV replication in resting primary CD4+T cells and monocytes (Jin *et al*., 2007).

APOBEC3G expression is disrupted by the HIV Vif protein which induces its degradation through the ubiquitin/proteasome system. If a HIVΔvif deletion mutant is created it will be able to infect a cell, but will produce non-viable progeny virus due to the action of APOBEC3G (Sheehy *et al*., 2002).

Other intrinsic immune proteins have been discovered which block Murine Leukaemia Virus (MLV), Herpes Simplex Virus (HSV) and Human Cytomegalovirus (HCMV). In many cases, such as that of APOBEC3G above, viruses have evolved mechanisms for disrupting the actions of these proteins. Another example is the cellular protein Daxx, which silences viral promoters but is degraded by an active HCMV protein early in infection (Saffert and Kalejta, 2006).

High levels of APOBEC3G mRNA expression levels in PBMCs is associated with decreased HIV-1 progression to AIDS and lower levels of APOBEC3G mRNA expression was associated with higher rate of disease progression. In a study done by Vazquez-Perez *et al*. (2009) observing the APOBEC3G mRNA expression levels in PBMCs HIV-1-infected individuals at different disease stages, it was found that higher mRNA expression linked with higher CD4+ T-cell counts and lower HIV-1 viral loads. Similarly higher APOBEC3G mRNA expression was detected in slow progressors who were infected for more than 3 years and were therapy naive even when compared to both progressors and uninfected healthy controls (Vazquez-Perez *et al*., 2009).

3.2.4. Tetherin

Tetherin (also named BST-2, CD317 and HM1.24) recently identified restriction factor in human cells, which can block the release of many enveloped viruses, such as retroviruses including HIV Tetherin is a type II single-pass transmembrane protein, which is highly expressed in plasmacytoid dendritic and differentiated B cells. When induced by IFN, Tetherin blocks the release of HIV-1 and other enveloped viral particles from infected cells (Neil *et al*., 2008) HIV seems to overcome this protective effect by Vpu, a HIV-1 accessory protein, which is essential to virion exocytosis from infected cells by degradation and via cell surface downregulation of tetherin (Mansouri *et al*., 2009; Perez-Caballero *et al*., 2009).

3.2.5. Murr1

Murr1 is a highly conserved 190-amino-acid protein that plays a role in copper metabolism. (Ganesh *et al*., 2003) have shown that Murr1 is able to inhibit HIV replication in un stimulated CD4+T cells. Murr1 was detected in primary resting CD4+T cells and is thought to interfere with activation of the transcription factor NFkB by inhibiting the degradation of IkBa (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha). IkBa prevents NFkB from migrating to the nucleus especially upon the stimulation of proinflammatory cytokine TNF α, which in turn hinders the replication of HIV (Ganesh *et al*., 2003).

3.3. Extracellular Factors

3.3.1. Defensins

Defensins are small natural endogenous cysteine rich cationic peptides with high anti-HIV1 activity (Lama and Planelles, 2007). Mammalian defensins are classified into alpha-, beta- and theta defensins according to structural characteristics (Rodrıguez-Garcıa *et al*., 2010). In human's α-defensins and β- defensins are shown to produce anti HIV1 activity (Rodrıguez-Garcıa *et al*., 2010). There are 6 varieties of α-defensins or Human Neutrophil Peptides (HNP), of which HNP 1-3 are primarily produced by neutrophils (Lama and Planelles, 2007).

α-defensins are known to block HIV-1 entry at several steps. Apart from membrane disruption of HIV1 by binding to glycoproteins and down regulating the expression CD4 α-defensins 1-3 display multiple immune stimulatory activities such as chemo attraction of naive T cells and immature dendritic cells and induction of cytokine and chemokine production (Rodrıguez-Garcıa *et al*., 2010; Lama and Planelles, 2007).

In a study done by Rodrıguez-Garcıa *et al*. (2010), it was shown that the immature DCs from elite controllers, produced higher levels of α-defensins 1-3 compared with normal HIV progressors. This study also showed a positive correlation between high secretion levels of α-defensins 1-3 by immature dendritic CD4 T cell counts (Rodrıguez-Garcıa *et al*., 2010). Together, these studies

suggest the protective mechanism of α-defensins may be due to the damage to the virions before internalization by immature DCs, thereby favouring efficient viral processing and presentation to HIV-specific CD4+T cells (Rodrıguez-Garcıa *et al*., 2010).

There are six known β-defensins in humans mainly in epithelial cells, β-defensins have a similar mechanism of action to α-defensins 1-3 and are known to viral entry of both X4- and R5-tropic HIV-1 strains (Lama and Planelles, 2007). β-defensins 2 and 3 are also associated with down-modulation of CXCR4, but not CCR5, receptors on T cells (Lama and Planelles, 2007).

4. ADAPTIVE IMMUNITY

4.1. CD4+ Tells

Multiple roles played by CD4+ T cells during virus infection make them one of the most effective immune cells in dealing with the invading virus (Kannanganat *et al*., 2007). The cytotoxic potential of antiviral CD4+T cells is critical for maintaining the homeostasis of the CD8+ T cells and antibody producing B cells. It is known that many cytokines such as IFNɣ, IL-2 and Tumour Necrosis Factor alpha (TNFα) are produced by CD4+Tcells (Kannanganat *et al*., 2007). In fact one of the first indicators of T-cell exhaustion, which leads to impaired function of CD8+T cells are progressive loss of IL-2 production followed by the loss of TNFα production (Kannanganat *et al*., 2007). Therefore, the loss of function of CD4+T cells due to infections, such as seen HIV/AIDS is largely responsible for impairment of anti-viral immunity in the HIV-infected host.

In relation to long-term non-progressors, the function of CD4+ T cells in HIV-1 infection is unclear. However Dyer *et al*. (2008) observed that a robust and sustained proliferation of HIV p24 antigen- specific CD4+ and CD8+ T cells (IFN-ɣ response) was associated with the control of viremia and retention of LTNP status in a cohort of 13 LTNP's. The loss or absence of p24 response was observed among the individuals who became viremic (Dyer *et al*., 2008). The study also observed a decrease in Gag-specific Cytotoxic T Lymphocyte (CTL) response to be associated with increase viremia.

Compared with rapid progressors, LTNP's expressed high levels of IL-2, IFNɣ, IL7 and CCR7 in CD4+ T-cells (Poropatich and Sullivan, 2011; Potter *et al*., 2009). The long-term maintenance of immune memory in LTNP's may be due to autocrine IL-2 secretion, which maintains the self-renewal of CD4+ memory cells. Similarly higher expression of CCR7 in CD4+ memory cells may allow these cells to recirculate into secondary lymphoid organs, where renewal is initiated (Potter *et al*., 2009).

4.2. CD8+ Tells

CD8+ T cells (Cytotoxic T Cells or CTL) mount a protective immunity against HIV-infected cells via initiating cytolytic killing infected cells or by secreting antiviral cytokines (Zloza *et al*., 2009). Loss or dysregulation of CD8+ T cells was found to be associated with disease progression. It is also found that CTL response towards the p24 subunit of the Gag protein was the dominant form of immunity in HIV controllers (Zuniga *et al*., 2006). CTL from LTNPs are shown to have poly-functional responses compared to HIV+ rapid progressors. It was found that Gag-specific CD8+ T cells of LTNPs expressed four to five antiviral immune functions (degranulation, IFNɣ, MIP-1β, tumour necrosis factor α and IL-2) simultaneously when compared against progressors, which produced no more than three functions at one time (Betts *et al*., 2006).

Migueles *et al*. (2002) have shown that CD8+T cells from LTNP divided robustly when stimulated by HIV-infected cells compared to progressors. Similarly greater secretion of effector molecules such as perforin and serine protease granzyme B was observed in CD8+T cells from LTNPs. Perforin forms pores in the CD4+T cell membrane, which facilitates granzyme B to enter the cell and induce apoptosis (Migueles *et al*., 2002; Migueles and Connors, 2010). Similarly, the CD8+T cells from LTNPs show increased secretion of IFNɣ and IL-2 and low levels of anti-inflammatory cytokine IL-4 secretion (Poropatich and Sullivan, 2011).

Recently, a study conducted by Chen *et al*. (2012) showed that in addition to the protective alleles the potent CD8 clonotypes played a major role in the protection against the disease progression. This protective ability of these alleles are enhanced or directly linked to the clonal selection of more potent CD8+T cell clonotypes during the infection. This TCR rearrangement altered the effect of the protective alleles on the disease outcome.

4.3. TH17 T Cells

Subset of CD4+ T helper cells, Th17 cells, appears to be critical for regulating gut mucosal immune responses against extracellular microbial pathogens and may serve as a link between innate and adaptive immune responses. During chronic HIV infection along with CD4+T cells this TH17 subset is depleted from the gut mucosa. Reduction in Th17 level has been associated

with increased permeability of mucosal barrier in the digestive tract resulting in continuous leaking of microbial products into the bloodstream and sustain chronic immune activation aiding HIV pathogenesis (Mavigner *et al*., 2012; Klatt and Brenchley, 2010).

A study by Salgado *et al*. (2011) has shown that Long Term Non Progressors (LTNP) to have increased levels of TH17 subset compared to normal progressors with HIV disease. Also the level of Th17 in LTNPs were on par with healthy donors. Therefore TH17 plays a protective important role by preventing the microbial translocation and the subsequent systemic immune activation (Salgado *et al*., 2011).

4.4. FOXP3

Forkhead box P3 (FoxP3) is a transcription factor which is highly expressed in CD4+CD25hi T-cells, a cellular subset of T cells necessary development and function of regulatory T-cells (Tregs) (Fontenot *et al*., 2003; Cao *et al*., 2009). In mouse and human models lack of functional of FOXP3 has lead to autoimmune and inflammatory diseases while over expression has shown to induce CD4+ Treg cell-mediated immune suppression (Fontenot *et al*., 2003, Khattri *et al*., 2003; Cao *et al*., 2009).Tregs play a role in the dynamics of immune activation during HIV-1 infection (Cao *et al*., 2009). FoxP3 has shown inhibit NFAT (key regulator of T cell activation and anergy) and NFkβ proteins, thereby preventing the activation of number of cytokine genes such as IL-2 (Wu *et al*., 2006; Selliah *et al*., 2008). T regs display relative resistance to the HIV infection by decreasing the binding of NFAT2 to the HIV-1 LTR (Selliah *et al*., 2008). Recent studies have shown Tregs to play an immune suppressive role during the HIV infection thereby playing a role in disease progression. Similar studies have also shown cytotoxic T cell responses to be suppressed by (Kinter *et al*., 2009).

4.5. Cytokines and Chemokines

Cytokines and Chemokines are regulatory proteins of the immune system and bring the two arms of host immune system (the innate and the adaptive immune systems) to full circle. Role of these immune regulatory proteins in context to HIV progression is not fully understood.

4.5.1. HIV Coreceptors

The natural chemokine ligands for HIV-1 co-receptors, CCR5 and CXCR4 are known either act as competitive inhibitors of HIV-1 infection or to down regulate the expression of these co- receptors on the CD4+ cell surface, thereby associating with control of HIV1 disease progression (Gallo *et al*., 1999; Mikhail *et al*., 2003). The natural ligand for CCR5 are macrophage inflammatory protein 1α and 1β (MIP-1α and MIP-1β), human CC Chemokine Ligand 3 Like 1 gene (CCL3L1) and RANTES and the only ligand CXCR4 is SDF-1 (Gallo *et al*., 1999). CD8+ T cells and macrophages secrete most of the above chemokines while RANTES is known to be secreted by platelets (Gallo *et al*., 1999; Kornbluth *et al*., 1998).

4.5.2. β Chemokines

β Chemokines have been associated with increased resistance CCR5 strains of HIV-1 infection and slow disease progression (Mahajan *et al*., 2010).

4.5.3. MIP-1α/CCL3 and MIP-1b/CCL4

These chemokines are known to down regulate HIV-1 infection by decreasing the cell surface expression of CCR5 (Poropatich and Sullivan, 2011). Saha *et al*. (1998) has showed that significantly higher amounts of MIP-1α were secreted from CD4+ T cells from LTNPs compared with AIDS patients who don't produce any. A similar study done by Garzino-Demo *et al*. (1999) has shown MIP-1b/CCL4 to have the same effect as MIP-1α/CCL3. MIP-1b/CCL4 only binds to CCR5, therefore this molecule may have significant role in competitive binding (Garzino-Demo *et al*., 1999). Upon stimulation with the HIV protein p24 antigen, increased levels for both MIP-1α and MIP-1β were detected in HIV patients with no AIDS, whereas this effect was not observed in patients with AIDS (Garzino-Demo *et al*., 1999).

4.5.4. CCL3L1/MIP-1aP. CCL3L1

Like other β Chemokines, CCL3L1 plays an important role in blocking CCR5 tropic HIV infection. High copy number of CCL3L1 appears to be associated with slower HIV-1 disease progression, while the low copy number of CCL3L1 was associated with accelerated disease progression (Gonzalez *et al*., 2005).

4.5.5. RANTES/CCL5

Increased secretion of RANTES is associated with control of R5 tropic HIV-1 infection (Garzino-Demo *et al*., 1999).

4.5.6. SDF1 (CXCL12). Stromal Cell-Derived Factor 1

SDF1 is the only natural ligand for CXCR4 and is known to down regulate the cell surface expression of

CXCR4 on T lymphocytes, thereby reducing the X4 tropic HIV infection (Mahajan *et al*., 2010). The X4 strain of HIV-1 is associated with rapid disease progression, therefore constant blocking of CXCR4 by SDF1 may inhibit the switching of less pathogenic CCR5 strain to CXCR4 strain, thereby hindering the disease progression (Mahajan *et al*., 2010).

4.5.7. Cytokines

High expression of cytokines IL-10 and IL-4 are associated with rapid disease progression (Mahajan *et al*., 2010). IL-10-5'-592A allele is associated with increased production of cytokines IL-10. The presence of this allele IL-10-5'-592A is associated with rapid disease. IL-10 is a known anti inflammatory cytokine and higher expression of IL-10 may promote viral persistence by inactivation of effector immune mechanisms (Mahajan *et al*., 2010). Decreased levels of IL-10 or a blockade of the IL-10 pathway may associate with enhanced T cell immune responses and rapid elimination of virus due to the development of antiviral memory T cell responses (Mahajan *et al*., 2010). LTNPs have shown to have decreased expression levels of IL-10 and this may contribute to delayed progression of HIV-1 disease in this group (Mahajan *et al*., 2010).

IL-4 is known to modulate the expression of the HIV-1 co-receptors, CCR5 and CXCR4, it is believed that modulation can alter the mechanism of viral entry. Compared to rapid progressors, LTNPs have significantly lower expression levels of IL-4. IL-4–589T allele polymorphism is associated with decreased production of IL-4 and is known to protect against HIV-1 disease progression (Mahajan *et al*., 2010).

5. MICRO-RNAS AND THEIR ROLE IN INNATE AND ADAPTIVE IMMUNITY: EVIDENCE FOR A DIRECT ROLE OF MIRNA IN HUMAN IMMUNITY

Mi-RNAs, a class of endogenous small noncoding RNAs of approximately 22 nucleotides in length, are dubbed as the prime mediators of these biological processes (Lim *et al*., 2003). miRNAs are emerging as the master key regulators of not only the gene expression, but also of human immune system and of innumerable biological processes. Although the advancement of our knowledge in this area of research has been mainly focused on cellular development and differentiation, the role of miRNAs in both innate and adaptive immune responses and in antiviral defence is being much appreciated currently. As a result, there is enormous amount of interest in not only understanding the role of these small molecules in disease development and viral pathogenesis, but also their use as biomarkers and in therapeutics.

Overwhelming evidence suggests a direct connectivity between miRNA and the immune responses in humans. For instance, the role of miRNAs in cell-mediated immunity is evidenced by Dicer conditional knockout mice harbouring T-cell deficiencies (Muljo *et al*., 2005). In this context, it is important to state that both Interferon-alpha and Interferon-beta have been described in modulating expression of several different miRNAs (Schaley *et al*., 2006). In support of this, miR-146a/b has been shown to be up regulated in response to TLR2, 4 and 5 ligands in concert with NF-kB (Taganov *et al*., 2006), along with its involvement in translational regulation of Tumour Necrosis Factor (TNF) receptor (Taganov *et al*., 2006), thereby suggesting them as negative regulators of the innate immune system.

Previous studies have shown that complex transcriptional programmes regulating the expression and function of a variety of growth factors, CD antigens, transcriptional factors and intracellular signalling molecules, harbor an intrinsic role in maintaining the balance and functional intactness of the human immune system. Although there is far greater activity in the field of miRNA, yet not much is known about their role in post-transcriptional regulation of gene expression and the role of miRNAs in the development of the immune system. MiRNAs are known to regulate gene expression post-transcriptionally by affecting the degradation and translation of target mRNAs. Single miRNA can bind to several hundred to several thousand mRNA targets and these molecules bear both positive and negative correlation with their cognate mRNA targets (Lodish *et al*., 2008).

Host miRNAs are dysregulated by viruses and both DNA and RNA viruses have been found to encode and express miRNAs in the infected host, demonstrating the importance of the role of host and virus-encoded miRNAs in host-virus interactions. Virus-encoded miRNAs bear complimentarily with host mRNAs, as host-encoded miRNA bear complimentarily with viral genes. This is an important process, which guides pathogenic events of host-virus interactions during viral infections and disease progression. Although the role and functions of virally-encoded miRNAs are still unclear, recent analysis of target genes suggests their probable role in immune modulation and evasion by directly targeting pro-apoptotic genes and controlling viral

latency, encouraging viral persistence in the host (Boss and Renne, 2010). Although controversial, several host antiviral miRNAs have been described for different viruses. In case of HIV several endogenous miRNAs are known to play a significant role in HIV latency (Huang *et al*., 2007). Huang *et al*. (2007) found that the 3' ends of HIV-1 messenger RNAs are targeted by a cluster of cellular miRNAs including miR-28, miR-125b, miR-150, miR-223 and miR-382, which only they found to be enriched in resting CD4+ T cells as compared to activated CD4+ T cells, but other studies have failed to confirm. Specific inhibitors of these miRNAs substantially counteracted their effects on the target mRNAs , thereby confirming their role in viral latency and persistence. Moreover, several miRNAs also play a significant role in HIV suppression (miR-28, miR-125b, miR-150, miR-223 and miR-382), which possibly occurs through the incorporation of miRNA into the RISC complex (Pedersen *et al*., 2007; Lecellier *et al*., 2005).

6. CONCLUSION

The relationship between innate, adaptive and intrinsic immunity during HIV infection remain poorly understood. Although these immune systems are not elaborate, yet the central questions- how HIV evades immune recognition and can establish latent sanctuaries for its future survival, remain unanswered. Therefore, an integrative approach to understanding interactions between both innate and adaptive immunity is a prerequisite in not only understanding HIV immunopathogenesis, but also in using various natural elements of these immune activities in the development of new strategies for treatment to benefit HIV patients.

Genomics is a new and rapidly developing field and a considerable effort is needed in not only keeping pace with the findings, but also in assimilating and synthesising accurate and meaningful functional annotation of various functions relevant to the immune system. Although a number of miRNAs have been reported for specific cellular and immune activities in humans, it is becoming apparent that the immune system utilizes multiple miRNAs for functional guidance and it is this balance which defines the fine tuning and execution of well guided immune response to a pathogenic challenge. Therefore, we need an improved, clear and in-depth understanding of how miRNAs interact with their cognate genes in regulating gene expression and how multiple miRNAs collaborate in inflammatory responses or during an infectious process. A clear understanding of miRNA-mRNA functional networks, which together optimise immune responses is needed. Second, we know to some extent the relevance of cellular miRNAs, but a great deal of work is needed at the level of extracellular miRNAs found in different tissue fluids, where miRNAs exist in highly enriched state. It is believed that the extracellular miRNAs may function in an analogous manner to secreted cytokines and, therefore may have an important role in immune responses and in the development of new generation of biomarkers in measuring and validating specific immune responses in humans. Although with the advent of several new high-throughput technologies in genomics (mRNA, miRNA, epigenome and next generation sequencing) and proteomics have emerged, what is now needed is to understand how different tiers in human genome guide innate, adaptive and antiviral immune responses. Thus, understanding the genomic basis of innate and adaptive immune responses will definitely assist in the development of promising new approaches to treating human inflammatory disorders and infectious diseases, such as AIDS.

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