Cell. Mol. Biol. 58 (1): 31-43
Published on December 22, 2012
DOI 10.1170/T918

Cellular & Molecular Biology
http://www.cellmolbiol.com

TYROSINE KINASES AS ESSENTIAL CELLULAR COFACTORS AND POTENTIAL THERAPEUTIC TARGETS FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION

F. BERTOLETTI, E. CRESPAN AND G. MAGA✉

Institute of Molecular Genetics, IGM-CNR, via Abbiategrasso 207, I-27100 Pavia, Italy

Abstract

The Human Immunodeficiency Virus (HIV) is the cause of the AIDS disease. To date, more than 30 million people worldwide are infected with HIV-1, which causes two millions deaths each year. The pandemic is still ongoing, with three million new infections every year. Even though the current arsenal of anti-HIV drugs is composed of more than twenty different molecules, it became clear that the chemotherapeutic approach will not be able to cure AIDS, at least in its current form. It is essential, in order to develop more effective ways of treating this disease, to better understand the interplay of HIV with its cellular host, in fact HIV-1 is an obligatory intracellular parasite that takes advantage of the host cell metabolism for its own replication. HIV-1 takes control of virtually every aspect of cell metabolism by changing the functional properties of key signaling cellular proteins, thus triggering virus-specific signal transduction pathways. In this review, we will summarize the current knowledge about the role(s) of cellular tyrosine kinases in HIV infection and their potential therapeutic exploitation.

Key words: HIV-1, tyrosine kinase, Vif, Nef.

Article information

Received on May 14, 2012
Accepted on July 9, 2012

✉ **Corresponding author**
Tel: +39 0382 546354
Fax: +39 0382 422286
E-mail: maga@igm.cnr.it

HIV and AIDS: an everlasting problem

The Acquired Immunodeficiency Syndrome (AIDS) emerged in the human population in 1981 as an outbreak of *Pneumocystis carinii* atypical pneumonia among homosexual men in the USA even if this syndrome was present in Africa for many decades earlier. To date, more than 30 million people worldwide are infected with HIV-1, which causes two millions deaths each year. The pandemic is still ongoing, with three million new infections every year. The Human Immunodeficiency Virus (HIV) is the cause of the AIDS disease. HIV is a retrovirus that is transmitted by sexual contact, injection of infected blood or blood-derived products (33). HIV exists in two serotypes, HIV-1 and HIV-2. The majority of the infections in the world are caused by HIV-1, whereas HIV-2 is mainly associated to smaller epidemics in West Africa and has a lower transmission efficacy.

AIDS is characterized by a progressive depletion of CD4+ helper T-cells, that allows opportunistic infections, including pulmonary tuberculosis (a frequent complication) and a variety of bacterial, viral, or parasitic infections, as well as cancer such as non-Hodgkin B cell lymphomas or Kaposi sarcoma (33). As all viruses, HIV-1 is an obligatory intracellular parasite that takes advantage of the host cell metabolism for its own replication. Due to the worldwide dimensions of the AIDS epidemic, HIV-1 has been the focus of intense research in the last 30 years, which allowed the uncovering of the extraordinary complexity of its interactions with the host cell. An early outcome of these studies was the development, about twenty years ago, of a chemotherapeutic approach, named highly active antiretroviral therapy HAART, based on the combination of three antiretroviral drugs, targeting different viral proteins. The HAART approach substantially decreased the number of AIDS-related deaths and currently allows to keep the epidemic under control, at least in western countries, where this highly expensive therapy is available. However, HAART is not able to eradicate the infection; in addition, it is a lifelong therapy since its interruption is invariably followed by viral relapse in the patients. A consequence of this fact is the exacerbation of drug side effects, requiring continuous adjustments of the individual therapies and often causing a poor compliance of the treated individuals. On top of that, prolonged therapy favors the selection of viral drug resistant variants that cause the failure of first line therapies. Thus, even though the current arsenal of anti-HIV drugs is composed of more than twenty different molecules, it became clear that the chemotherapeutic approach will not be able to cure AIDS, at least in its current form. It is essential; in order to develop more effective ways of treating this disease, to better understand the interplay of HIV with its cellular host.

A short overview of the HIV-1 life cycle

CD4+T cells of the monocyte/macrophage lineage are the main target of HIV-1. HIV needs both the CD4 receptor and a chemokine receptor for entering the target cells. These chemokine receptors are CCR5 (a β-chemokine receptor) and CXCR4 (an α-chemokine receptor) (69). Attachment and entry of HIV-1 is mediated by the viral envelope glycoprotein Env (13). Env is a 160 kDa glycoprotein that is cleaved into a gp120 external subunit and a gp41 transmembrane subunit that together form trimeric spikes on the surface of the virion. The 9.5 kb molecule of single-stranded positive sense RNA encodes also for other two important structural virus proteins: Gag and Pol. Furthermore the RNA genome encodes the regulatory proteins Tat and Rev, and accessory proteins Nef, Vif, Vpr and Vpu (33).

Following entry into the cytosol the viral enzyme reverse transcriptase converts the RNA genome into double-

stranded DNA. A high-molecular weight structure, known as the pre-integration complex, translocates the newly synthesized viral DNA into the nucleus (10, 24, 34, 103, 113). A second viral enzyme, the integrase, is responsible for the integration of the viral DNA in the chromosome of the host cell. At this point the proviral DNA directs the transcription of viral RNAs, thanks to the action of the early genes Tat and Rev. These RNAs are transported in the cytoplasm where translation of viral proteins takes place. Env is processed in the endoplasmic reticulum and Golgi apparatus and is inserted in the cell cytoplasmic membrane. The Gag and Pol polyproteins and the two single stranded copies of full length viral RNA are then transported at the inner face of the plasma membrane to direct the assembly of new viral particles, which bud from the cell acquiring the viral envelope containing Env. Concomitantly with the release of new viral particle, the viral protease cleaves the Gag and Pol polyprotein precursors, triggering the formation of the mature virion.

At this point the replication cycle of the virus is complete, and a new cycle of infection can be started from the mature virus particle (104).

Being an obligate intracellular pathogen, HIV-1 relies for its replication on several host factors. Over 1000 candidate host factors have been implicated in HIV-1 infection by a large scale siRNA and shRNA screens (5, 7, 12, 56, 57, 80, 87, 118, 123). This number is disproportionately higher than the number of proteins encoded by the viral genome (fifteen). However, these studies also revealed that the ability of HIV-1 to take control of virtually every aspect of cell metabolism through a limited number of its own proteins is made possible by the ability of the virus to directly modulate, through direct protein-protein interactions, key cellular proteins representing functional nodes at the intersection of diverse intracellular pathways. In such a way, by changing the functional properties of a limited number of proteins, HIV-1 triggers virus-specific signal transduction pathways which, in turn, profoundly affect the cellular metabolism.

Tyrosine kinases in HIV infection: novel antiretroviral targets?

Among the most important signal transduction components of the cellular metabolic pathways are the protein tyrosine kinases. The protein tyrosine kinases (TKs) are enzymes that catalyze the transfer of a phosphoryl group to tyrosine residues in protein substrates, using primarily ATP as the phosphate donor. In this large family there are, in the human genome, 58 receptor kinases (RTKs) and 32 non-receptor kinases (NRTKs). TKs regulate different aspects of the cellular metabolism: cell to cell communication, cellular growth, differentiation, motility, adhesion and death (91). TKs also play significant roles in many diseases like cancer and diabetes and they have also been linked to a variety of congenital syndromes (90).

RTKs and NRTKs are characterized by a different structural organization that reflects their different functions. RTKs are the main transducers of extracellular signals, due to their ability to be activated by the binding of specific protein ligands. The majority of RTKs in the absence of their ligand is monomeric and consists of a single polypeptide chain, with a central transmembrane domain, that separates the extracellular portion from the intracellular one. The catalytic activity is found in the cytoplasmic portion, while the extracellular portion binds the specific polypeptide ligands that are responsible for TK activation. The extracellular region contains a diverse array of discrete globular domains (Ig-like domains, fibronectin type III-like domains, cysteine-rich domains and EGF-like domains), whereas the cytoplasmic domain is simpler and consists of a tyrosine kinase catalytic domain and a carboxyl-terminal region (48).

Most of NRTKs are localized in the cytoplasm (some of them are anchored to the inner face of the cell membrane through amino terminal modifications) and, as their name implies, they lack receptor-like features such a transmembrane-spanning region and an extracellular ligand-binding domain (79). In addition to their tyrosine kinase domain, they also have domains that mediate protein-protein, protein-lipid and protein-DNA interaction (48). Several studies indicated important roles of these enzymes for HIV-1 replication, however, the details of their action within the viral life cycle are, at best, still imperfectly understood (Figure 1).

Understanding the interplay among these enzymes and viral replication might offer new venues for HIV-1 chemotherapy. In fact, a strategy being pursued in order to overcome the problem of drug resistance is to target cellular factors of the host cell that interact with the virus during the infection. Since cellular proteins are much less prone to mutation, this could be a winning strategy for developing drugs to combat HIV (and other pathogens) avoiding, or at least substantially delaying, drug resistance. Tyrosine kinases are attractive targets, since they are already being studied as chemotherapeutic targets for the treatment of cancer and a significant amount of knowledge about their structure, functions and possible strategies to develop specific inhibitors is already available. Moreover, several tyrosine kinase inhibitors are already used in the clinics for the treatment of diverse malignancies and more are in advanced clinical trials. Thus, the discovery, among cellular tyrosine kinases, of a potential candidate for the treatment of HIV-1 infection, might very rapidly lead to the development of novel drugs.

In this review, we will summarize the current knowledge about the role(s) of cellular tyrosine kinases in HIV infection. The discussed tyrosine kinases, their biological functions and their proposed roles in HIV-1 replication are listed in Table 1.

Non-receptor tyrosine kinases

The Src family

The Src protein tyrosine kinase family (SFK) is composed of non-receptorial, cytoplasmic tyrosine kinases capable of communicating with a large number of different receptors (107). Eight members of non receptor tyrosine kinases are currently classified as SFK members: Src, Fyn, Yes, Lyn, Fgr, Hck, Lck, Blk. The first three are ubiquitously expressed, while there is a tissue-specific expression for the other five members (36). SFK family members have molecular weights between 52 and 56 kDa and are composed of six distinct functional regions: the Src homologous SH4 domain, the unique region (which is the N-terminal end), the SH3 domain, the SH2 domain, the catalytic domain (SH1), and a short negative regulatory tail (107).

The SH4 domain has a sequence of 15 amino-acids that contains signals for lipid modification of SFKs (107), while

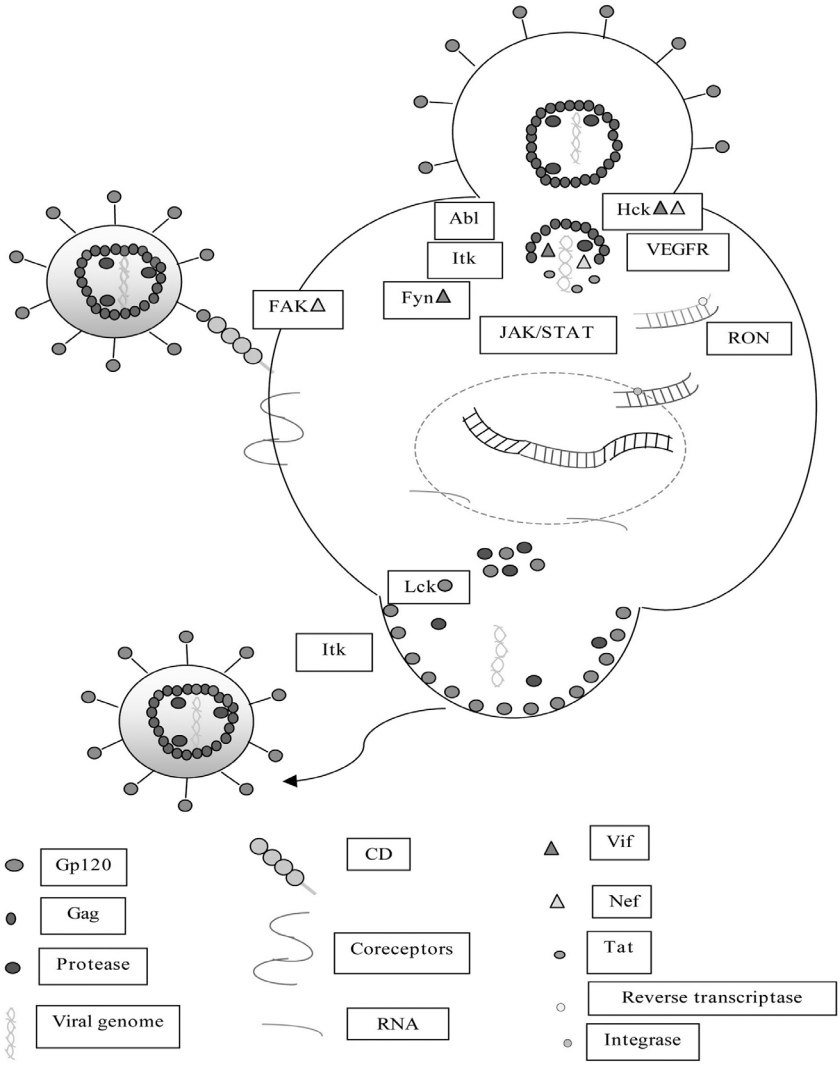

Figure 1. Tyrosine kinases are involved in different stages of the HIV-1 life cycle. Schematic representation of the HIV-1 life cycle from entry to budding. The various tyrosine kinases involved in HIV-1 infection are indicated at each stage of the viral life cycle along with the respective viral interactors.

the unique domain is responsible for the association of SFKs to the inner face of the plasma membranes. The SH3 domain is a protein-protein interaction motif, responsible for recognizing the proline-rich consensus sequence PxxP. The SH2 domain recognizes proteins with phosphorylated tyrosines within the consensus sequence pYEEI. The catalytic site resides in the SH1 domain, where is also present a kinase-activation loop containing a specific tyrosine (activating tyrosine, YA) that can be autophosphorylated leading to fully active kinase (36).

The SFKs are found in the cell in two different functional states, active or inactive, corresponding to particular protein conformations. The inactive conformation is maintained by specific intramolecular inhibitory interactions: the SH3 domain binds to a polyproline type II helical motif located in the linker between the SH2 and SH1 domains, this binding is stabilized by the interaction of a phosphorylated tyrosine located in the C-terminal tail (tail tyrosine, YT) with the SH2 domain. The active conformation is assumed by protein following dephosphorylation of YT, which in turn, promotes the release of the linker domain from SH3, exposing the active site and enabling autophosphorylation of the YA residue. The balance between the active and inactive forms of SFKs in the cell is regulated through phosphorylation of YT and dephosphorylation of YA that are mediated by the C-terminal Src kinase (Csk) and C-terminal Src homologous kinase (CHK), and various protein phosphatases, respectively (78, 102, 109).

SFKs and HIV

Many members of the SFK are involved in the HIV-1 infection.

Hematopoietic cell kinase, Hck

The expression of Hck is mainly present in promonocytic cells, including monocyte-derived macrophages, where it mediates relevant functions such as induction of cytokine production triggered by bacterial lipopolysaccharide, FcγRI receptor signaling, phagocytosis, and cell spreading (22, 66, 72). Hck is the first cellular protein that has been identified as interacting with the auxiliary HIV-1 protein Vif (44). In the C-terminal domain of Vif is localized a proline-rich motif (PPLP) that can interact whit the SH3 domain of the tyrosine kinases and adaptor proteins. Hassaine et al. (44) demonstrated that Vif binds preferentially to the SH3 domain of the tyrosine kinase Hck and not significantly to other SH3 domains of the members of SFK and of adaptor proteins.

It has been demonstrated that in absence of Vif, T cells were less permissive for HIV-1 replication. Moreover, when Vif was lacking and Hck was expressed, release of HIV-1 viral particles was strongly inhibited and virion in-

Table 1. Human Tyrosine kinases involved in HIV-1 infection.

Tyrosine Kinase	Physiological functions	HIV-1 related functions
Hck	Mediates induction of cytokine production, neutrophils migration and degranulation	- Inhibited by Vif - Activated by Nef
Fyn	Control of cell growth	- Interacts with Vif - Phosphorylates APOBEC3G
Lck	Selection and maturation of developing T-cells in the thymus and in mature T-cells function	- Binds Gag during virus assembly - Has a role during viral packaging - Involved in Nef signaling
Abl	Role in morphogenesis and F-actin dynamics, survival and cell growth	- Phosphorylates Wave 2 complex
Itk	Role in T-cell proliferation and differentiation	- Is required for actin polarization and activation of Rac and gp120 induced actin rearrangement. - Stimulates virion assembly and release - Increases intracellular Ca^{2+}
Fak	Influence proliferation, migration attachment and survival of cells	- Phosphorylated when is recruited on the plasma membrane by gp 120,induces apoptosis - Competes with Nef
RON	Regulates macrophage function and inflammation	- Inhibits virus transcription
VEGFR	Vasculogenesis and angiogenesis	- Mediates Tat signaling
JAK/STAT	Involved in signaling pathways mainly activated by cytokines	- Inhibits HIV replication in monocytes

fectivity was reduced. This Hck-dependent inhibition was overcome by the presence of Vif. Douaisi et al. (21) demonstrated that the autophosphorylation of Hck was dramatically reduced by Vif, causing a decrease of the active form of Hck concurrently with an increased expression of Vif.

Nef is an accessory gene unique to the primary lentiviruses HIV-1, HIV-2 and SIV. Nef manipulates HIV-infected cells by altering a variety of protein sorting and signal transduction pathways like T cell receptor (TCR) signal transduction pathway (38) and Hck regulation. Nef binds Hck, increasing its catalytic activity and promoting viral growth (52). Nef interacts with the Hck SH3 domain via its polyproline motif and this interaction was proposed to upregulate the Hck kinase activity by displacing the intramolecular SH3/linker domain interaction characteristic of the inactive form of Hck. The HIV-1 protein Vif is also important to counteract the cellular antiviral cytidine deaminase APOBEC3G (93). During the viral assembly of HIV-1, in the absence of the Vif protein APOBEC3G is packaged in the virions (71) and, upon infection of cell by the virus, catalyzes the cytosine deamination of the single-stranded DNA intermediates which are formed during the reverse transcription step, blocking viral replication (43, 60, 70, 122).

The antiviral factor Vif limits the APOBEC3G packaging into virions by targeting the deaminase to ubiquitin-dependent degradation by the proteasome (71). APOBEC3G can be phosphorylated on tyrosine in the presence of Hck, and this tyrosine kinase can inhibit the packaging of APOBEC3G into HIV-1 particles, independently of Vif. Thus, the functional interaction between APOBEC3G and the HIV-1 assembly complex is modified by the activation of Src kinases, resulting in an enrichment of the phosphorylated form of APOBEC3G at the viral budding site (21). These diverse effects of Hck on viral replication suggest that the activity of this kinase must be finely tuned within the HIV-1 life cycle, an observation that justifies the presence of two viral proteins acting on this kinase with opposite effects (inhibition by Vif / activation by Nef). However, the molecular details of this mechanism are currently unknown.

Fgr- and Yes-related protein kinase, Fyn

The Vif protein also interacts with another SFK member: Fyn. This interaction is mediated by Fyn SH3 domain and reduces the catalytic activity of the kinase (21). Autophosphorylation of Fyn is reduced by Vif and the increased expression of Vif causes the decrease of active Fyn. Vif is not itself a substrate of either Fyn or Hck, however Fyn has been shown to phosphorylate APOBEC3G reducing its packaging into HIV-1 particles.

Lymphoid T-cell protein kinase, Lck

Various studies have suggested that Lck is involved in HIV-1 transcription, replication and pathogenesis (101). Strasner et al. (101) have demonstrated that Lck promotes efficient HIV-1 replication in T-cells. They showed that Lck regulates Gag trafficking from the intracellular compartments to the plasma membrane during HIV-1 assembly in T-cells. Moreover, the unique domain (UD) of Lck binds HIV-1 Gag during virus assembly facilitating efficient virus release. So Lck has a role during viral packaging (101). The palmitoylation and plasma membrane localization of Lck UD are critical for the ability of Lck to favor HIV-1 assembly (101). The palmitoylation of Lck is catalyzed in the early exocytic pathway and it allows for subsequent transport of the protein to the plasma membrane. Thus, this HIV-1 Gag can take advantage of this property of Lck for its targeting to the plasma membrane (101).

The physiologically exogenous TCR activation occurs through formation of the immunological synapse (IS) between an antigen presenting cell (APC) and a T-cell. The transduction of the signals occurs through Lck (63). Several reports indicate that, during exogenous TCR activation, Nef expression can reduce signal transmission, preventing cell activation and prolonging the lifespan of infected cells (37, 92, 108). It has been suggested that Nef interferes with the intracellular sorting of Lck, the IS proximal kinase, in HIV-1 infected primary human T lymphocytes (108) determining a significant change in the normal subcellular localization of this kinase in T lymphocytes. In addition, Thoulouze et al. also reported that Nef impairs the recruitment of Lck to the IS following TCR engagement (108).

Abelson leukemia kinase, Abl

c-Abl is a non-receptor tyrosine kinase which is localized both in the nucleus and the cytoplasm, and is implicated in the morphogenesis, survival of the cell and in cell growth (95). The organization of Abl proteins is similar to the one of Src, comprising a unique N-terminus followed by a SH3 domain, a SH2 domain and the catalytic core. The difference with Src is in the C-terminus tail, where there is a large and unique sequence, encoded by the last exon, comprising F-(filamentous) and G-(globular) actin-binding domains, NESs (nuclear export sequences) and proline-rich sequences. There is also NLSs (nuclear localization signal) and a DNA-binding sequence that are important for nuclear functions (82). c-Abl alternates between nuclear and cytoplasmic compartments. The function of nuclear c-Abl has been well documented (111); it is implicated in promotion of apoptosis, cell growth inhibition and modulation of the cellular response induced by DNA damage. The cytoplasmatic form of c-Abl has a central role in morphogenesis and F-actin dynamics, as revealed by genetic and biochemical analysis (115) and c-Abl has some role even in receptor endocytosis (95). Several reports underline that c-Abl is involved in different cytoplasmic signaling cascades induced by various extracellular stimuli (18, 81, 89, 110, 115, 124). Similar to SFKs, c-Abl alternates between two forms: active and inactive. The inactive form is characterized by a closed conformation of the kinase domain due to intramolecular interactions involving the SH3 domain and the proline-rich sequence in SH2-kinase linker domain (3). The catalytic activation is induced by the opening of the closed conformation. When a mutation induces the disruption of these interactions the activity is transformed, as observed in oncogenic Abl alleles such as the fusion BCR-Abl kinase (40). Activity of c-Abl is regulated by its phoshorylation status. The phosphorylation on Tyr 245 and Tyr 412 (functionally analogous to YA and YT of SFKs) is required for c-Abl activation; moreover c-Abl is phopspohrylated also on serine and threonine residues which are involved in the catalytic regulation (39).

Abl and HIV

HIV infects the cells by fusion at the plasma membrane, in a pH-independent manner (27, 35, 75). The entry of HIV-1 involves critical conformational changes in the HIV-1 glycoprotein, as well as rearrangements of the actin cytoskeleton at the entry site (20, 29, 41, 49, 50, 84, 85). These events are triggered when the Env subunit gp120 binds the primary receptor CD4 and the CCR5 or CXCR4 chemokine coreceptors (35, 85). This interaction determines the activation of many signaling events in the cell, such as Ca^{2+} mobilization, activation of RhoGTPases and phosphorylation of several tyrosine kinases, such as Pyk2, Zap70 and Lck (41, 85, 99). In particular, the signaling from the membrane receptors to the actin cytoskeleton is mediated by the Rho family GTPases, which include the Cdc42, Rac and Rho subfamilies (42).

It has been shown that when HIV-1 Env binds target cells, it induces activation of Rac. Conversely, overxepression of a dominant negative mutant of Rac, inhibits HIV fusion (84, 85). Among the fusion specific effectors of Rac, essential for the actin cytoskeleton rearrangements that mediate membrane fusion, there is the Arp2/3 complex that induces actin polymerization (42). Arp2/3 is activated by the Wave2 complex through the IRSp53 adaptor protein that binds Rac and Wave2 (11). The Wave2 complex, in turn, is associated with Abl, and phosphorylation mediated by Abl promotes Wave2 activation (29, 97). This modification is essential for the subsequent activation of Arp2/3–mediated

actin rearrangements which facilitate pore formation, pore enlargement, and entry of HIV-1. Recent studies demonstrated that the Env-mediated membrane fusion process is arrested by Abl kinase inhibitors (like imatinib, nilotinib and dasatinib) (42). Abl actin remodeling can act both upstream and downstream of Rac (120, 121). Harmon et al. (42) used siRNA and specific inhibitors to show that the activity of Abl kinase is required both upstream and downstream of Rac for the Env-induced membrane fusion.

Tyrosine kinase expressed in hepatocellular carcinoma, Tec and its family

The Tec family of tyrosine kinases (TEK) are important mediators of antigen receptor signaling in lymphocytes. TEKs are a group of five non-receptor tyrosine kinases: Tec, Btk, Itk, Rlk and Bmx, and they are primarily expressed in hematopoietic cells. These kinases are involved in different roles: TCR- mediated activation of phospholipase C-γ, regulation of actin cytoskeletal reorganization and cellular adhesion. Moreover they play parallel roles in the regulation of Rho GTPases, cell polarization, adhesion, and migration after their activation of phospholipase C-γ mediated by TCR (4).

The five members of Tec family kinases share a similar domain organization that recalls the organization of the Src family tyrosine kinases (96). In the C-terminus there is the kinase domain which is followed by a single SH2 and a single SH3 domain. However, there are also significant differences with the Src family kinases. Particularly, in the N-terminal side of the SH3 domain, all Tec kinases apart Bmx, have a proline-rich region (PRR). In Btk and Tec there is a second tandem PRR, near to a Zn^{2+}-binding region, called Btk homology (BH) motif. This BH motif is also found in Itk, adjacent to its single PRR.

The four members Itk, Btk, Tec and Bmx at the very N-terminus of the protein share a PH (pleckstrin homology) domain, whereas Rlk contains a cysteine-string motif. This PH domain binds to the products of phosphoinositide 3-kinase (PI3K), a property unique to TEKs. All the domains mentioned above (SH2, SH3, PRR, BH) mediate protein-protein interactions which regulate the binding partners of the TEKs determining their proximity to signaling complexes and potential substrates. Itk, Rlk and Tec are the three major TEKs that are expressed in T lymphocytes and they phosphorylated on specific tyrosines upon T cell receptor (TCR) stimulation (19, 32, 46, 117). These three TEKs have distinct patterns and levels of expression in response to their functions in different T cell subsets and stages of development. The predominant Tec kinase in T cell is Itk, which is expressed in thymocytes and mature T cells, mast cells, natural killer cells (31, 45, 94, 106, 116). Rlk is expressed like Itk in thymocytes, mature resting T cells, and mast cells (47, 98). The pattern of expression of Tec is broader and this kinase is present both in hematopoietic and other cell types (4).

Itk and HIV

Itk plays a critical role in HIV replication. As mentioned above the expression of Itk is important for TCR-mediated activation of T-cells, where it has a role in the regulation of PLCγ-1, Ca^{2+} mobilization and downstream activation of transcription factors (4). Thanks to its ability to coordinate cytoskeleton reorganization, signaling downstream the TCR and chemokine receptors, Itk could be viewed as a critical factor in regulating HIV infection and replication in T cells (88). For example, in response to stimulation of CXCR4 by SDF1α, ITK is activated and its tyrosine kinase activity is required for actin polarization and activation of Rac in response to SDF1α (26, 105). Readinger et al. (88) demonstrated that Itk is required for gp120-induced actin rearrangement, a process that is fundamental for efficient HIV entry into host cells, while viral reverse transcription or proviral DNA integration are not altered by the expression and/or function of Itk. Moreover, Itk stimulates virion assembly and release and it has been found that the suppression of HIV replication can be reached with inhibition of Itk either before or post-infection (88). Other cellular processes that modulate HIV infection in T cells may be influenced by Itk, like the interaction of Gag with the cyclophilin (28), a protein that also interacts with Itk (8), or increased intracellular Ca^{2+}, a process that has been linked to the production of viral particles and it is influenced by Itk in T cells (83).

Focal adhesion kinase, FAK

The focal adhesion kinase (FAK) is important for the assembly, signaling and disassembly of focal adhesions (FAs) and its activity influences key cellular processes, including proliferation, migration, attachment and survival (30). The kinase activity of FAK is activated upon phosphorylation by the non-receptor tyrosine kinase Src, which binds to an autophosphorylated tyrosine of FAK through its SH2 domain. Upon activation, FAK interacts with a number of downstream signaling proteins (paxillin, Grb2 and p85 subunit of phosphatidylinositol 3 kinase). FAK is a protein of 125kDa composed of a N-terminal 4.1-ezrin-radixin-moesin domain (also called FERM domain, that allow the ezrin, radixin and moesin proteins to interact with proteins of the plasma membrane) and a C-terminal FA targeting (FAT) domain, which is linked via a 220-amino-acid proline-enriched region to a central tyrosine kinase domain near to the N-terminal domain. FAK is recruited, through an interaction between its FAT domain and LD motifs of paxillin (the amino-terminal domain of paxillin that contains five leucine-rich sequences, called LD motifs), to integrin clusters at the site of cellular attachment. FAK is also implicated in T-cell signaling events, together with its close homolog (45% identical) proline-rich tyrosine kinase 2 (PYK2).

FAK and HIV

Both FAK and PYK2 are linked to immune system dysfunctions caused by HIV infection. When the HIV-1 envelope glycoprotein gp120 interacts with the extracellular domains of CD4 and CCR5, FAK colocalizes with these receptors on the inner face of the plasma membrane (15). After its recruitment, FAK becomes phosphorylated and then it is cleaved by the cellular proteases caspase-3 and caspase-6, this causes the inactivation of FAK and promotes apoptosis (15-16).

FAK has also been linked to T-cell receptor (TCR) signaling. When the TCR complex is stimulated, FAK becomes phosphorylated and associates with the SH2 domain of Lck (a tyrosine kinase of Src family that is most commonly found in T cells) causing CD4 dissociation from Lck and FAK association whit CD4. This interaction occurs through the FAT domain of FAK and is specific and almost identical to the FAT-LD interaction (30). Further-

more, the interaction surface of FAT-CD4 shows striking similarities with the binding surface of CD4-Nef (a HIV infection protein), in fact FAK and Nef bind the same region of CD4 with the same affinity (86). This interaction causes, however, different results. The FAK-CD4 gp120 mediated interaction determines the facilitation of viral post-entry stages and triggers apoptosis in uninfected T cell, through FAK inactivation by caspases, whereas Nef action on CD4 causes the block of the super infection and the proapoptotic signaling (67, 114).

All together these observations imply that gp120 signaling might be counteracted by Nef through displacing of FAK from CD4 and Lck (because they compete for binding); so, the ability of Nef to compete, in infected cell, with FAK avoiding apoptosis and super infection would be really important for virus replication (30).

Receptorial tyrosine kinases

Recepteur d'origine nantais" tyrosine kinase, RON

RON is a receptor tyrosine kinase that has been shown to be a regulator of macrophage function and inflammation (17). This protein is a member of the MET family of receptor tyrosine kinases, and regulates a variety of cellular responses, including proliferation, differentiation, apoptosis and cell movement (17). RON binds the macrophage-stimulating protein (MSP), a serum protein that shares high homology with the MET ligand, the hepatocyte growth factor (61). The production of proinflammatory mediators such as IL-2, TNF-α, and NO is inhibited by activation of RON by MPS, which also induces the expression of genes associated with inhibition of inflammation, including scavenger receptor A, IL-1Ra, and arginase (14, 65, 76, 77). Phagocytosis and adhesion of macrophages are also promoted by RON activation (68).

On chromosome 3p21 is located the RON gene that contains 20 exons and 19 introns, and this region has been observed to be frequently altered in cancer. RON is first synthesized as a single chain called pro-RON. The mature RON is generated as a result of a proteolytic conversion in a specific site and results in a 180kDa heterodimer protein composed of a 40kDa α-chain (284 amino acids) that is completely extracellular and a 150kDa transmembrane β-chain (which comprises an extracellular domain, a short transmembrane segment and a large cytoplasmic portion) linked by a disulfide bond. In the cytoplasmic portion of the β-chain is located the tyrosine kinase activity. When MSP binds to RON, it causes the phosphorylation of two tyrosine residues (Y1238 and Y1239) that reside in the catalytic domain and lead to an increase of kinase activity (112).

RON and HIV

RON has been shown to negatively regulate inflammation and macrophage function (17). In addition, Lee et al. (61) demonstrated that RON inhibits HIV-1 infection through the inhibition of virus transcription. In fact, RON activation inhibits NF-kB activity (65) which, besides being involved in the pro-inflammatory response, is a critical factor for efficient HIV-1 transcription in monocyte/macrophages, since it binds the LTR enhancer element of the HIV-1 proviral promoter. Thus, inhibition of NF-kB can compromise HIV-1 LTR activity and proviral transcription.

Klatt et al. (54) demonstrated that RON doesn't interfere with the formation of the pre-initiation complex, but it represses HIV-1 transcription by inhibiting elongation through the suppression of RNA pol II processivity. The HIV transcription in unstimulated cells is inhibited by RON signalling by promoting the association to RNA pol II with negative elongation factors NELF, DRB sensitivity-inducing factor (DSIF), and Pcf11 a transcription termination factor.

Another function of RON is its ability of altering the nucleosome organization. In fact, RON negatively regulates histone acetylation, inducing a transcriptionally repressed chromatin organization that correlates with pausing of RNA pol II and reduced HIV-1 provirus transcription in monocytic cells (54). Recently, it has been shown that Tat specifically induces downregulation of RON by targeting this receptor tyrosine kinase for ubiquitin-mediated proteosome degradation (53). Since RON has an important role in regulating tissue resident macrophage activity and the inflammation response, these findings can explain an additional mechanism by which HIV creates a microenvironment that favors virus replication (53).

VEGFR

The family of vascular endothelial growth factor (VEGF) is composed of five members: VEGFA, VEGFB, VEGFC, VEGFD and PIGF (placental growth factor), which are homodimeric polypeptides (although natural occurring heterodimers of VEGFA and PIGF have been described). Alternative splicing of VEGFA, VEGFB and PIGF and processing of VEGFC and VEGFD, make this family even more complex (25). This splicing and processing regulates the ability of the ligand to bind to VEGF receptors (VEGFR).

In humans, three structurally related VEGF receptor tyrosine kinases (VEGFR) have been identified: VEGFR1, VEGFR2, VEGFR3. These receptors show a similar organization; they have a C-terminal tail, a split tyrosine kinase domain, a juxtamembrane domain, a transmembrane domain and an extracellular, ligand-binding, domain composed of immunoglobulin-like loops. VEGFR1 is expressed in monocytes and macrophages, VEGFR2 in vascular endothelial cells and VEGFR3 in lymphatic endothelial cells.

The binding of VEGF to its receptor can occur in *cis* or in *trans*, on the N-terminal extracellular domain. This binding causes both the receptor dimerization and changes in the intracellular domain conformation. This changes lead to the exposure, in the intracellular kinase domain, of the ATP-binding site followed by binding of ATP and auto- or trans- phosphorylation of tyrosine residues on the receptor (55).

VEGFR and HIV

The HIV-1 infected cells can release soluble Tat protein in the extracellular medium that can activate mesenchymal cells. For example, it has been shown that in response to Tat release, monocytes migrate into tissues and release inflammatory mediators. Tat signaling inside the cells is mediated by the receptor for vascular endothelial growth factor, a tyrosine kinase (VEGFR-1/Flt-1) (74). Previously it was also shown that Tat binding to another related receptor, VEGFR-2/KDR, expressed on endothelial cells, activated its tyrosine kinase activity(2). Thus, the activation

of monocyte VEGFR-1/Flt-1 by Tat present in serum or tissue (74) could play an active role in the movement of monocyte out of the circulatory system and subsequent tissue damage in AIDS patients.

The Janus Kinase/Signal Transducer and Activator of Transcription, JAK/STAT pathway

In mammals there are four JAK kinases and seven STAT proteins. The pathway is initiated when a peptide ligand binds the transmembrane receptors. The receptor dimerizes and this causes the cross-activation of receptor-associated JAK kinases, which in turn phosphorylate tyrosine residues in the cytoplasmic tail of the receptor. JAK, then phosphorylates STAT proteins on a crucial C-terminus residue. This phosphorylation of STAT is possible because they are recruited from the cytoplasm after the phosphorylation of tyrosine residue of receptor that functions as doking site for STAT (64).

Now, via Src-homology 2-domain-phospho-tyrosine interaction, the phosphorylated STAT proteins dimerize and traslocate to the nucleus where induce the expression of target genes, working as transcriptional activators (1, 62). The JAK/STAT pathway regulates many cellular events and accumulating evidence indicates that its dysregulation causes human diseases and cancer (9, 119).

JAK/STAT and HIV

Infection by HIV-1 can up- or down-regulate the expression of several interferons and cytokines, whose signals are transduced by the JAK/STAT pathway (6). Several cytokines may have a direct or indirect effect on HIV-infected cells by inducing different response on virus replication. Bovolenta et al. (6) had found evidence indicating a clear role of the IFNγ and IFNα mediated JAK/STAT pathways in inhibiting HIV replication in human monocytes. In fact, it has been shown that stimulation of glial cells by HIV gp120 envelope glycoprotein induces STAT1 and JAK2 activation. Furthermore, it has been reported that inhibition of interleukin-2 receptor (IL-2R) expression in T lymphocytes is due to the binding of gp120 Env with CD4, and this effect has been correlated with the inhibition of both expression and activation of JAK3. Bovolenta et al. (6) demonstrated that a constitutive activation of STAT proteins occurs in the majority of HIV-infected individuals. JAK-dependent phosphorylation of one or more tyrosine residues is required for STAT binding to DNA, thus deregulated expression of specific cytokines or other factors, resulting in a constitutive JAK activation, could be the key event underlying STAT activation in HIV-infected individuals (6). During HIV infection the levels of phosphorylated STAT proteins is increased. According to Miller et al. (73) this is due to the inability of the SOCS-1 and SOCS-3 proteins to control the JAK/STAT pathway in infected cells. SOCS proteins are key feedback inhibitors of the JAK/STAT pathway. SOCS-1 deficient-mice show a constitutive and sustained activation of the JAK/STAT pathway, and these mice have a clinical phenotype reminiscent of advanced HIV disease. Accordingly, it was shown that T cells from patients had increased phosphor-STAT-1,-3 and -5 levels and reduced SOCS-1 and SOCS-3 protein levels.

It is known that the activation of the JAK/STAT signaling pathway plays a critical role in IL-2 induced T- lymphocyte proliferation and that activation of STAT5 is important in cell cycle progression and protection from apoptosis. Lack of IL-2 dependent STAT activation, could have a negative impact on the maintenance of a CD8 T cell population responsive to HIV infection. It has been observed that CD8 T cells from HIV infected patients are inactive and more prone to spontaneous apoptosis than those isolated from healthy individuals. This effect correlates with an impaired activation, in CD8T lymphocytes of HIV-infected individuals, of the upstream kinase JAK-3, which blocks the pathway of STAT5. Highly active antiretroviral therapy (HAART) has been observed to restore JAK/STAT and IL-2 responses (58).

Another important interleukin involved in maturation of lymphocytes is IL-7 that plays a central role in controlling CD4 T-cell homeostasis and T-cell proliferation. In HIV infection, the IL-7/CD4 regulatory loop is activated by increased plasma IL-7 levels that correlate with the decline CD4+ T-cell counts of patients. Juffroy et al. (51) provided evidence that HIV infection perturbs IL-7 response by decreasing the IL-7 binding capacity of memory CD4T cells and by inducing abnormal activation of the JAK/STAT5 signaling pathway (51).

Tyrosine kinases inhibitors

The efficacy of tyrosine kinase inhibitors in treating HIV-1 infection has been demonstrated in some works. Stantchev et al. (100) analyzed the role of the broad spectrum tyrosine kinase inhibitor Genestein in HIV infection, demonstrating that Genestein was able to affect both entry and early post-entry steps of the virus life cycle. Unfortunately the use of a broad spectrum inhibitor does not allow to identify the specific tyrosine kinases required for HIV-1 entry/infection. Nowadays there are few studies that focus on the efficacy of tyrosine kinase inhibitors on HIV-1 infection. However, compounds that interact with Nef specifically impeding Hck activation, showed to be strong inhibitors of HIV-1 replication (23), posing Hck as an attractive pharmacological target. Moreover, the efficacy of specific tyrosine kinase inhibitors was proved in other viral diseases. In fact a recent work (59) demonstrated that selective inhibitors of the platelet-derived growth factor receptor (PDGFR), as well as inhibitors of nerve growth factor receptor (TrkA) and heregulin receptor erbB-2 (HER-2), are effective against a variety of RNA and DNA viruses, including Influenza A virus, Sendai virus, herpes simplex virus, mouse hepatitis virus and rhesus rotavirus.

Taken together these data underline the emerging knowledge on the role of tyrosine kinases in HIV-1 life cycle and the growing interest on these enzymes as potential targets for innovative anti-HIV-1 treatments. The availability of inhibitors of several tyrosine kinases already approved for cancer therapy could represent an opportunity for the rapid discovery of new effective pharmacological HIV-1 therapies.

ACKNOWLEDGEMENTS

The work in authors' laboratory has been partially supported by the AIDS National Research Program Grant 40H26.

Other articles in this theme issue include references (125-152).

REFERENCES

1. Aaronson, D.S. and Horvath, C.M., A road map for those who don't

know JAK-STAT. *Science* 2002, **296**:1653-1655.
2. Albini, A., Soldi, R., Giunciuglio, D., Giraudo, E., Benelli, R., Primo, L., Noonan, D., Salio, M., Camussi, G., Rockl, W., and Bussolino, F., The angiogenesis induced by HIV-1 tat protein is mediated by the Flk-1/KDR receptor on vascular endothelial cells. *Nat. Med*. 1996, **2**:1371-1375.
3. Barila, D. and Superti-Furga, G., An intramolecular SH3-domain interaction regulates c-Abl activity. *Nat. Genet.* 1998, **18**: 280-282.
4. Berg, L.J., Finkelstein, L.D., Lucas, J.A., and Schwartzberg, P.L., Tec family kinases in T lymphocyte development and function. *Annu. Rev. Immunol*. 2005, **23**: 549-600.
5. Borner, K., Hermle, J., Sommer, C., Brown, N.P., Knapp, B., Glass, B., Kunkel, J., Torralba, G., Reymann, J., Beil, N., Beneke, J., Pepperkok, R., Schneider, R., Ludwig, T., Hausmann, M., Hamprecht, F., Erfle, H., Kaderali, L., Krausslich, H.G., and Lehmann, M.J., From experimental setup to bioinformatics: an RNAi screening platform to identify host factors involved in HIV-1 replication. *Biotechnol. J*. 2010, **5**:39-49.
6. Bovolenta, C., Camorali, L., Lorini, A.L., Ghezzi, S., Vicenzi, E., Lazzarin, A., and Poli, G., Constitutive activation of STATs upon in vivo human immunodeficiency virus infection. *Blood* 1999, **94**:4202-4209.
7. Brass, A.L., Dykxhoorn, D.M., Benita, Y., Yan, N., Engelman, A., Xavier, R.J., Lieberman, J., and Elledge, S.J., Identification of host proteins required for HIV infection through a functional genomic screen. *Science* 2008, **319**:921-926.
8. Brazin, K.N., Mallis, R.J., Fulton, D.B., and Andreotti, A.H., Regulation of the tyrosine kinase Itk by the peptidyl-prolyl isomerase cyclophilin A. *Proc. Natl. Acad. Sci. U S A* 2002, **99**:1899-1904.
9. Bromberg, J., Stat proteins and oncogenesis. *J. Clin. Invest.* 2002, **109**: 1139-1142.
10. Bukrinsky, M.I., Sharova, N., Dempsey, M.P., Stanwick, T.L., Bukrinskaya, A.G., Haggerty, S., and Stevenson, M., Active nuclear import of human immunodeficiency virus type 1 preintegration complexes. *Proc. Natl. Acad. Sci. U S A* 1992, **89**:6580-6584.
11. Burridge, K. and Wennerberg, K., Rho and Rac take center stage. *Cell* 2004, **116**:167-179.
12. Bushman, F.D., Malani, N., Fernandes, J., D'Orso, I., Cagney, G., Diamond, T.L., Zhou, H., Hazuda, D.J., Espeseth, A.S., Konig, R., Bandyopadhyay, S., Ideker, T., Goff, S.P., Krogan, N.J., Frankel, A.D., Young, J.A., and Chanda, S.K., Host cell factors in HIV replication: meta-analysis of genome-wide studies. *PLoS Pathog*. 2009, **5**:e1000437.
13. Checkley, M.A., Luttge, B.G., and Freed, E.O., HIV-1 envelope glycoprotein biosynthesis, trafficking, and incorporation. *J. Mol. Biol*. 2011, **410**:582-608.
14. Chen, Y.Q., Fisher, J.H., and Wang, M.H., Activation of the RON receptor tyrosine kinase inhibits inducible nitric oxide synthase (iNOS) expression by murine peritoneal exudate macrophages: phosphatidylinositol-3 kinase is required for RON-mediated inhibition of iNOS expression. *J. Immunol*. 1998, **161**: 4950-4959.
15. Cicala, C., Arthos, J., Ruiz, M., Vaccarezza, M., Rubbert, A., Riva, A., Wildt, K., Cohen, O., and Fauci, A.S., Induction of phosphorylation and intracellular association of CC chemokine receptor 5 and focal adhesion kinase in primary human CD4+ T cells by macrophage-tropic HIV envelope. *J. Immunol*. 1999, **163**: 420-426.
16. Cicala, C., Arthos, J., Rubbert, A., Selig, S., Wildt, K., Cohen, O.J., and Fauci, A.S., HIV-1 envelope induces activation of caspase-3 and cleavage of focal adhesion kinase in primary human CD4(+) T cells. *Proc Natl. Acad. Sci. U S A* 2000, **97**:1178-1183.
17. Correll, P.H., Morrison, A.C., and Lutz, M.A., Receptor tyrosine kinases and the regulation of macrophage activation. *J. Leukoc. Biol*. 2004, **75**:731-737.
18. Daniels, C.E., Wilkes, M.C., Edens, M., Kottom, T.J., Murphy, S.J., Limper, A.H., and Leof, E.B., Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. *J. Clin. Invest*. 2004, **114**:1308-1316.
19. Debnath, J., Chamorro, M., Czar, M.J., Schaeffer, E.M., Lenardo, M.J., Varmus, H.E., and Schwartzberg, P.L., rlk/TXK encodes two forms of a novel cysteine string tyrosine kinase activated by Src family kinases. *Mol. Cell. Biol*. 1999, **19**:1498-1507.
20. del Real, G., Jimenez-Baranda, S., Mira, E., Lacalle, R.A., Lucas, P., Gomez-Mouton, C., Alegret, M., Pena, J.M., Rodriguez-Zapata, M., Alvarez-Mon, M., Martinez, A.C., and Manes, S., Statins inhibit HIV-1 infection by down-regulating Rho activity. *J Exp Med*, 2004, **200**:541-547.
21. Douaisi, M., Dussart, S., Courcoul, M., Bessou, G., Lerner, E.C., Decroly, E., and Vigne, R., The tyrosine kinases Fyn and Hck favor the recruitment of tyrosine-phosphorylated APOBEC3G into vif-defective HIV-1 particles. *Biochem. Biophys. Res. Commun*. 2005, **329**: 917-924.
22. Durden, D.L., Kim, H.M., Calore, B., and Liu, Y., The Fc gamma RI receptor signals through the activation of hck and MAP kinase. *J. Immunol*. 1995, **154**: 4039-4047.
23. Emert-Sedlak, L., Kodama, T., Lerner, E.C., Dai, W., Foster, C., Day, B.W., Lazo, J.S., and Smithgall, T.E., Chemical library screens targeting an HIV-1 accessory factor/host cell kinase complex identify novel antiretroviral compounds. *ACS Chem. Biol*. 2009, **4**:939-947.
24. Fassati, A. and Goff, S.P., Characterization of intracellular reverse transcription complexes of human immunodeficiency virus type 1. *J. Virol*. 2001, **75**: 3626-3635.
25. Ferrara, N., Binding to the extracellular matrix and proteolytic processing: two key mechanisms regulating vascular endothelial growth factor action. *Mol. Biol. Cell*. 2010, **21**: 687-690.
26. Fischer, A.M., Mercer, J.C., Iyer, A., Ragin, M.J., and August, A., Regulation of CXC chemokine receptor 4-mediated migration by the Tec family tyrosine kinase ITK. *J. Biol. Chem*. 2004, **279**: 29816-29820.
27. Gallo, S.A., Finnegan, C.M., Viard, M., Raviv, Y., Dimitrov, A., Rawat, S.S., Puri, A., Durell, S., and Blumenthal, R., The HIV Env-mediated fusion reaction. *Biochim. Biophys. Acta* 2003, **1614**: 36-50.
28. Gamble, T.R., Vajdos, F.F., Yoo, S., Worthylake, D.K., Houseweart, M., Sundquist, W.I., and Hill, C.P., Crystal structure of human cyclophilin A bound to the amino-terminal domain of HIV-1 capsid. *Cell* 1996, **87**:1285-1294.
29. Gao, Y., Dickerson, J.B., Guo, F., Zheng, J., and Zheng, Y., Rational design and characterization of a Rac GTPase-specific small molecule inhibitor. *Proc. Natl. Acad. Sci. U S A*, 2004, **101**: 7618-7623.
30. Garron, M.L., Arthos, J., Guichou, J.F., McNally, J., Cicala, C., and Arold, S.T., Structural basis for the interaction between focal adhesion kinase and CD4. *J. Mol. Biol*. 2008, **375**: 1320-1328.
31. Gibson, S., Leung, B., Squire, J.A., Hill, M., Arima, N., Goss, P., Hogg, D., and Mills, G.B., Identification, cloning, and characterization of a novel human T-cell-specific tyrosine kinase located at the hematopoietin complex on chromosome 5q. *Blood* 1993, **82**:1561-1572.
32. Gibson, S., August, A., Kawakami, Y., Kawakami, T., Dupont, B., and Mills, G.B., The EMT/ITK/TSK (EMT) tyrosine kinase is activated during TCR signaling: LCK is required for optimal activation of EMT. *J. Immunol*. 1996, **156**: 2716-2722.
33. Girard, M.P., Osmanov, S., Assossou, O.M., and Kieny, M.P., Human immunodeficiency virus (HIV) immunopathogenesis and vaccine development: a review. *Vaccine* 2011, **29**:6191-6218.
34. Goff, S.P., Intracellular trafficking of retroviral genomes during the early phase of infection: viral exploitation of cellular pathways. *J, Gene Med*. 2001, **3**:517-528.
35. Greene, W.C. and Peterlin, B.M., Charting HIV's remarkable voyage through the cell: Basic science as a passport to future therapy. *Nat. Med*. 2002, **8**:673-680.
36. Guiet, R., Poincloux, R., Castandet, J., Marois, L., Labrousse, A., Le Cabec, V., and Maridonneau-Parini, I., Hematopoietic cell kinase (Hck) isoforms and phagocyte duties - from signaling and actin reorganization to migration and phagocytosis. *Eur. J. Cell. Biol*. 2008, **87**:527-542.

37. Haller, C., Rauch, S., Michel, N., Hannemann, S., Lehmann, M.J., Keppler, O.T., and Fackler, O.T., The HIV-1 pathogenicity factor Nef interferes with maturation of stimulatory T-lymphocyte contacts by modulation of N-Wasp activity. *J. Biol. Chem*. 2006, **281**:19618-19630.
38. Haller, C., Rauch, S., and Fackler, O.T., HIV-1 Nef employs two distinct mechanisms to modulate Lck subcellular localization and TCR induced actin remodeling. *PLoS One* 2007, **2**:e1212.
39. Hantschel, O., Nagar, B., Guettler, S., Kretzschmar, J., Dorey, K., Kuriyan, J., and Superti-Furga, G., A myristoyl/phosphotyrosine switch regulates c-Abl. *Cell* 2003, **112**:845-857.
40. Hantschel, O. and Superti-Furga, G., Regulation of the c-Abl and Bcr-Abl tyrosine kinases. *Nat. Rev. Mol. Cell. Biol.* 2004, **5**:33-44.
41. Harmon, B. and Ratner, L., Induction of the Galpha(q) signaling cascade by the human immunodeficiency virus envelope is required for virus entry. *J. Virol*. 2008, **82**: 9191-9205.
42. Harmon, B., Campbell, N., and Ratner, L., Role of Abl kinase and the Wave2 signaling complex in HIV-1 entry at a post-hemifusion step. *PLoS Pathog*. 2010, **6**:e1000956.
43. Harris, R.S., Bishop, K.N., Sheehy, A.M., Craig, H.M., Petersen-Mahrt, S.K., Watt, I.N., Neuberger, M.S., and Malim, M.H., DNA deamination mediates innate immunity to retroviral infection. *Cell* 2003, **113**:803-809.
44. Hassaine, G., Courcoul, M., Bessou, G., Barthalay, Y., Picard, C., Olive, D., Collette, Y., Vigne, R., and Decroly, E., The tyrosine kinase Hck is an inhibitor of HIV-1 replication counteracted by the viral vif protein. *J. Biol. Chem*. 2001, **276**:16885-16893.
45. Heyeck, S.D. and Berg, L.J., Developmental regulation of a murine T-cell-specific tyrosine kinase gene, Tsk. *Proc. Natl. Acad. Sci. U S A* 1993, **90**:669-673.
46. Heyeck, S.D., Wilcox, H.M., Bunnell, S.C., and Berg, L.J., Lck phosphorylates the activation loop tyrosine of the Itk kinase domain and activates Itk kinase activity. *J. Biol. Chem*. 1997, **272**: 25401-25408.
47. Hu, Q., Davidson, D., Schwartzberg, P.L., Macchiarini, F., Lenardo, M.J., Bluestone, J.A., and Matis, L.A., Identification of Rlk, a novel protein tyrosine kinase with predominant expression in the T cell lineage. *J. Biol. Chem*. 1995, **270**: 1928-1934.
48. Hubbard, S.R. and Till, J.H., Protein tyrosine kinase structure and function. *Annu. Rev. Biochem*. 2000, **69**: 373-398.
49. Iyengar, S., Hildreth, J.E., and Schwartz, D.H., Actin-dependent receptor colocalization required for human immunodeficiency virus entry into host cells. *J. Virol*. 1998, **72**: 5251-5255.
50. Jimenez-Baranda, S., Gomez-Mouton, C., Rojas, A., Martinez-Prats, L., Mira, E., Ana Lacalle, R., Valencia, A., Dimitrov, D.S., Viola, A., Delgado, R., Martinez, A.C., and Manes, S., Filamin-A regulates actin-dependent clustering of HIV receptors. *Nat. Cell. Biol*. 2007, **9**:838-846.
51. Juffroy, O., Bugault, F., Lambotte, O., Landires, I., Viard, J.P., Niel, L., Fontanet, A., Delfraissy, J.F., Theze, J., and Chakrabarti, L.A., Dual mechanism of impairment of interleukin-7 (IL-7) responses in human immunodeficiency virus infection: decreased IL-7 binding and abnormal activation of the JAK/STAT5 pathway. *J. Virol*. 2010, **84**: 96-108.
52. Jung, J., Byeon, I.J., Ahn, J., and Gronenborn, A.M., Structure, dynamics, and Hck interaction of full-length HIV-1 Nef. *Proteins* 2011, **79**:1609-1622.
53. Kalantari, P., Harandi, O.F., Hankey, P.A., and Henderson, A.J., HIV-1 Tat mediates degradation of RON receptor tyrosine kinase, a regulator of inflammation. *J. Immunol*. 2008, **181**: 1548-1555.
54. Klatt, A., Zhang, Z., Kalantari, P., Hankey, P.A., Gilmour, D.S., and Henderson, A.J., The receptor tyrosine kinase RON represses HIV-1 transcription by targeting RNA polymerase II processivity. *J. Immunol*. 2008, **180**: 1670-1677.
55. Koch, S., Tugues, S., Li, X., Gualandi, L., and Claesson-Welsh, L., Signal transduction by vascular endothelial growth factor receptors. *Biochem. J*. 2011, **437**:169-183.
56. Kok, K.H., Lei, T., and Jin, D.Y., siRNA and shRNA screens advance key understanding of host factors required for HIV-1 replication. *Retrovirology* 2009, **6**: 78.
57. Konig, R., Zhou, Y., Elleder, D., Diamond, T.L., Bonamy, G.M., Irelan, J.T., Chiang, C.Y., Tu, B.P., De Jesus, P.D., Lilley, C.E., Seidel, S., Opaluch, A.M., Caldwell, J.S., Weitzman, M.D., Kuhen, K.L., Bandyopadhyay, S., Ideker, T., Orth, A.P., Miraglia, L.J., Bushman, F.D., Young, J.A., and Chanda, S.K., Global analysis of host-pathogen interactions that regulate early-stage HIV-1 replication. *Cell* 2008, **135**: 49-60.
58. Kryworuchko, M., Pasquier, V., Keller, H., David, D., Goujard, C., Gilquin, J., Viard, J.P., Joussemet, M., Delfraissy, J.F., and Theze, J., Defective interleukin-2-dependent STAT5 signalling in CD8 T lymphocytes from HIV-positive patients: restoration by antiretroviral therapy. *Aids* 2004, **18**: 421-426.
59. Kumar, N., Sharma, N.R., Ly, H., Parslow, T.G., and Liang, Y.Y., Receptor Tyrosine Kinase Inhibitors That Block Replication of Influenza A and Other Viruses. *Antimicrobial Agents and Chemotherapy* 2011, **55**: 5553-5559.
60. Lecossier, D., Bouchonnet, F., Clavel, F., and Hance, A.J., Hypermutation of HIV-1 DNA in the absence of the Vif protein. *Science* 2003, **300**:1112.
61. Lee, E.S., Kalantari, P., Tsutsui Section, S., Klatt, A., Holden, J., Correll, P.H., Power Section, C., and Henderson, A.J., RON receptor tyrosine kinase, a negative regulator of inflammation, inhibits HIV-1 transcription in monocytes/macrophages and is decreased in brain tissue from patients with AIDS. *J. Immunol*. 2004, **173**: 6864-6872.
62. Levy, D.E. and Darnell, J.E., Jr., Stats: transcriptional control and biological impact. *Nat. Rev. Mol. Cell. Biol*. 2002, **3**:651-662.
63. Li, Q.J., Dinner, A.R., Qi, S., Irvine, D.J., Huppa, J.B., Davis, M.M., and Chakraborty, A.K., CD4 enhances T cell sensitivity to antigen by coordinating Lck accumulation at the immunological synapse. *Nat. Immunol*. 2004, **5**: 791-799.
64. Li, W.X., Canonical and non-canonical JAK-STAT signaling. *Trends Cell. Biol*. 2008, **18**:545-451.
65. Liu, Q.P., Fruit, K., Ward, J., and Correll, P.H., Negative regulation of macrophage activation in response to IFN-gamma and lipopolysaccharide by the STK/RON receptor tyrosine kinase. *J. Immunol*. 1999, **163**: 6606-6613.
66. Lowell, C.A., Fumagalli, L., and Berton, G., Deficiency of Src family kinases p59/61hck and p58c-fgr results in defective adhesion-dependent neutrophil functions. *J. Cell. Biol*. 1996, **133**: 895-910.
67. Lusso, P., HIV and the chemokine system: 10 years later. *Embo J*. 2006, **25**: 447-456.
68. Lutz, M.A. and Correll, P.H., Activation of CR3-mediated phagocytosis by MSP requires the RON receptor, tyrosine kinase activity, phosphatidylinositol 3-kinase, and protein kinase C zeta. *J. Leukoc. Biol*. 2003, **73**: 802-814.
69. Manavi, K., A review on infection with human immunodeficiency virus. *Best Pract Res. Clin. Obstet. Gynaecol*. 2006, **20**: 923-940.
70. Mangeat, B., Turelli, P., Caron, G., Friedli, M., Perrin, L., and Trono, D., Broad antiretroviral defence by human APOBEC3G through lethal editing of nascent reverse transcripts. *Nature* 2003, **424**: 99-103.
71. Mariani, R., Chen, D., Schrofelbauer, B., Navarro, F., Konig, R., Bollman, B., Munk, C., Nymark-McMahon, H., and Landau, N.R., Species-specific exclusion of APOBEC3G from HIV-1 virions by Vif. *Cell* 2003, **114**:21-31.
72. Meng, F. and Lowell, C.A., A beta 1 integrin signaling pathway involving Src-family kinases, Cbl and PI-3 kinase is required for macrophage spreading and migration. *Embo J*. 1998, **17**: 4391-4403.
73. Miller, R.C., Schlaepfer, E., Baenziger, S., Crameri, R., Zeller, S., Byland, R., Audige, A., Nadal, D., and Speck, R.F., HIV interferes with SOCS-1 and -3 expression levels driving immune activation. *Eur. J. Immunol*. 2011, **41**: 1058-1069.

74. Mitola, S., Sozzani, S., Luini, W., Primo, L., Borsatti, A., Weich, H., and Bussolino, F., Tat-human immunodeficiency virus-1 induces human monocyte chemotaxis by activation of vascular endothelial growth factor receptor-1. *Blood* 1997, **90**:1365-1372.
75. Miyauchi, K., Kim, Y., Latinovic, O., Morozov, V., and Melikyan, G.B., HIV enters cells via endocytosis and dynamin-dependent fusion with endosomes. *Cell* 2009, **137**:433-444.
76. Morrison, A.C. and Correll, P.H., Activation of the stem cell-derived tyrosine kinase/RON receptor tyrosine kinase by macrophage-stimulating protein results in the induction of arginase activity in murine peritoneal macrophages. *J. Immunol*. 2002, **168**: 853-860.
77. Morrison, A.C., Wilson, C.B., Ray, M., and Correll, P.H., Macrophage-stimulating protein, the ligand for the stem cell-derived tyrosine kinase/RON receptor tyrosine kinase, inhibits IL-12 production by primary peritoneal macrophages stimulated with IFN-gamma and lipopolysaccharide. *J. Immunol*. 2004, **172**: 1825-1832.
78. Nada, S., Okada, M., MacAuley, A., Cooper, J.A., and Nakagawa, H., Cloning of a complementary DNA for a protein-tyrosine kinase that specifically phosphorylates a negative regulatory site of p60c-src. *Nature* 1991, **351**: 69-72.
79. Neet, K. and Hunter, T., Vertebrate non-receptor protein-tyrosine kinase families. *Genes Cells* 1996, **1**:147-169.
80. Nguyen, D.G., Wolff, K.C., Yin, H., Caldwell, J.S., and Kuhen, K.L., "UnPAKing" human immunodeficiency virus (HIV) replication: using small interfering RNA screening to identify novel cofactors and elucidate the role of group I PAKs in HIV infection. *J. Virol*. 2006, **80**: 130-137.
81. Noren, N.K., Foos, G., Hauser, C.A., and Pasquale, E.B., The EphB4 receptor suppresses breast cancer cell tumorigenicity through an Abl-Crk pathway. *Nat. Cell. Biol*. 2006, **8**: 815-825.
82. Pendergast, A.M., The Abl family kinases: mechanisms of regulation and signaling. *Adv. Cancer Res*. 2002, **85**: 51-100.
83. Perlman, M. and Resh, M.D., Identification of an intracellular trafficking and assembly pathway for HIV-1 gag. *Traffic* 2006, **7**: 731-745.
84. Pontow, S., Harmon, B., Campbell, N., and Ratner, L., Antiviral activity of a Rac GEF inhibitor characterized with a sensitive HIV/SIV fusion assay. *Virology* 2007, **368**: 1-6.
85. Pontow, S.E., Heyden, N.V., Wei, S., and Ratner, L., Actin cytoskeletal reorganizations and coreceptor-mediated activation of rac during human immunodeficiency virus-induced cell fusion. *J. Virol* 2004, **78**: 7138-7147.
86. Preusser, A., Briese, L., and Willbold, D., Presence of a helix in human CD4cytoplasmic domain promotes binding to HIV-1 Nef protein. *Biochem. Biophys. Res. Commun*. 2002, **292**: 734-740.
87. Rato, S., Maia, S., Brito, P.M., Resende, L., Pereira, C.F., Moita, C., Freitas, R.P., Moniz-Pereira, J., Hacohen, N., Moita, L.F., and Goncalves, J., Novel HIV-1 knockdown targets identified by an enriched kinases/phosphatases shRNA library using a long-term iterative screen in Jurkat T-cells. *PLoS One* 2010, **5**:e9276.
88. Readinger, J.A., Schiralli, G.M., Jiang, J.K., Thomas, C.J., August, A., Henderson, A.J., and Schwartzberg, P.L., Selective targeting of ITK blocks multiple steps of HIV replication. *Proc. Natl. Acad. Sci. U S A* 2008, **105**:6684-9.
89. Rhee, J., Mahfooz, N.S., Arregui, C., Lilien, J., Balsamo, J., and VanBerkum, M.F., Activation of the repulsive receptor Roundabout inhibits N-cadherin-mediated cell adhesion. *Nat. Cell. Biol*. 2002, **4**:798-805.
90. Robertson, S.C., Tynan, J.A., and Donoghue, D.J., RTK mutations and human syndromeswhen good receptors turn bad. *Trends Genet*. 2000, **16**: 265-271.
91. Robinson, D.R., Wu, Y.M., and Lin, S.F., The protein tyrosine kinase family of the human genome. *Oncogene* 2000, **19**: 5548-5557.
92. Schindler, M., Munch, J., Kutsch, O., Li, H., Santiago, M.L., Bibollet-Ruche, F., Muller-Trutwin, M.C., Novembre, F.J., Peeters, M., Courgnaud, V., Bailes, E., Roques, P., Sodora, D.L., Silvestri, G., Sharp, P.M., Hahn, B.H., and Kirchhoff, F., Nef-mediated suppression of T cell activation was lost in a lentiviral lineage that gave rise to HIV-1. *Cell* 2006, **125**:1055-1067.
93. Sheehy, A.M., Gaddis, N.C., Choi, J.D., and Malim, M.H., Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. *Nature* 2002, **418**: 646-650.
94. Siliciano, J.D., Morrow, T.A., and Desiderio, S.V., itk, a T-cell-specific tyrosine kinase gene inducible by interleukin 2. *Proc. Natl. Acad. Sci. U S A* 1992, **89**:11194-11198.
95. Sirvent, A., Benistant, C., and Roche, S., Cytoplasmic signalling by the c-Abl tyrosine kinase in normal and cancer cells. *Biol. Cell*. 2008, **100**: 617-631.
96. Smith, C.I., Islam, T.C., Mattsson, P.T., Mohamed, A.J., Nore, B.F., and Vihinen, M., The Tec family of cytoplasmic tyrosine kinases: mammalian Btk, Bmx, Itk, Tec, Txk and homologs in other species. *Bioessays* 2001, **23**: 436-446.
97. Soderling, S.H. and Scott, J.D., WAVE signalling: from biochemistry to biology. *Biochem. Soc. Trans*. 2006, **34**: 73-76.
98. Sommers, C.L., Huang, K., Shores, E.W., Grinberg, A., Charlick, D.A., Kozak, C.A., and Love, P.E., Murine txk: a protein tyrosine kinase gene regulated by T cell activation. *Oncogene* 1995, **11**: 245-251.
99. Stantchev, T.S. and Broder, C.C., Human immunodeficiency virus type-1 and chemokines: beyond competition for common cellular receptors. *Cytokine Growth Factor Rev*. 2001, **12**: 219-243.
100. Stantchev, T.S., Markovic, I., Telford, W.G., Clouse, K.A., and Broder, C.C., The tyrosine kinase inhibitor genistein blocks HIV-1 infection in primary human macrophages. *Virus Research* 2007, **123**: 178-189.
101. Strasner, A.B., Natarajan, M., Doman, T., Key, D., August, A., and Henderson, A.J., The Src kinase Lck facilitates assembly of HIV-1 at the plasma membrane. *J. Immunol*. 2008, **181**: 3706-3713.
102. Superti-Furga, G., Fumagalli, S., Koegl, M., Courtneidge, S.A., and Draetta, G., Csk inhibition of c-Src activity requires both the SH2 and SH3 domains of Src. *Embo J*. 1993, **12**: 2625-2634.
103. Suzuki, Y. and Craigie, R., The road to chromatin - nuclear entry of retroviruses. *Nat. Rev. Microbiol*. 2007, **5**: 187-196.
104. Swanstrom, R. and Wills, J.W., Synthesis, Assembly, and Processing of Viral Proteins. 1997.
105. Takesono, A., Horai, R., Mandai, M., Dombroski, D., and Schwartzberg, P.L., Requirement for Tec kinases in chemokine-induced migration and activation of Cdc42 and Rac. *Curr. Biol*. 2004, **14** :917-922.
106. Tanaka, N., Asao, H., Ohtani, K., Nakamura, M., and Sugamura, K., A novel human tyrosine kinase gene inducible in T cells by interleukin 2. *FEBS Lett*. 1993, **324**: 1-5.
107. Thomas, S.M. and Brugge, J.S., Cellular functions regulated by Src family kinases. *Annu. Rev. Cell. Dev. Biol*. 1997, **13**: 513-609.
108. Thoulouze, M.I., Sol-Foulon, N., Blanchet, F., Dautry-Varsat, A., Schwartz, O., and Alcover, A., Human immunodeficiency virus type-1 infection impairs the formation of the immunological synapse. Immunity 2006, **24**:547-561.
109. Trible, R.P., Emert-Sedlak, L., and Smithgall, T.E., HIV-1 Nef selectively activates Src family kinases Hck, Lyn, and c-Src through direct SH3 domain interaction. *J. Biol. Chem*. 2006, **281**: 27029-27038.
110. Ushio-Fukai, M., Zuo, L., Ikeda, S., Tojo, T., Patrushev, N.A., and Alexander, R.W., cAbl tyrosine kinase mediates reactive oxygen species- and caveolin-dependent AT1 receptor signaling in vascular smooth muscle: role in vascular hypertrophy. *Circ. Res*. 2005, **97**: 829-836.
111. Van Etten, R.A., Cycling, stressed-out and nervous: cellular functions of c-Abl. *Trends Cell Biol*. 1999, **9**: 179-186.
112. Wang, M.H., Wang, D., and Chen, Y.Q., Oncogenic and invasive potentials of human macrophage-stimulating protein receptor, the RON receptor tyrosine kinase. *Carcinogenesis* 2003, **24**:1291-300.

113. Whittaker, G.R., Kann, M., and Helenius, A., Viral entry into the nucleus. *Annu. Rev. Cell. Dev. Biol*. 2000, **16**: 627-651.
114. Wildum, S., Schindler, M., Munch, J., and Kirchhoff, F., Contribution of Vpu, Env, and Nef to CD4 down-modulation and resistance of human immunodeficiency virus type 1-infected T cells to superinfection. *J. Virol*. 2006, **80**: 8047-8059.
115. Woodring, P.J., Hunter, T., and Wang, J.Y., Regulation of F-actin-dependent processes by the Abl family of tyrosine kinases. *J. Cell. Sci*. 2003, **116**: 2613-2626.
116. Yamada, N., Kawakami, Y., Kimura, H., Fukamachi, H., Baier, G., Altman, A., Kato, T., Inagaki, Y., and Kawakami, T., Structure and expression of novel protein-tyrosine kinases, Emb and Emt, in hematopoietic cells. *Biochem. Biophys. Res. Commun*. 1993, **192**: 231-240.
117. Yang, W.C., Ghiotto, M., Barbarat, B., and Olive, D., The role of Tec protein-tyrosine kinase in T cell signaling. *J. Biol. Chem*. 1999, **274**: 607-617.
118. Yeung, M.L., Houzet, L., Yedavalli, V.S., and Jeang, K.T., A genome-wide short hairpin RNA screening of jurkat T-cells for human proteins contributing to productive HIV-1 replication. *J. Biol. Chem*. 2009, **284**:19463-19473.
119. Yu, H. and Jove, R., The STATs of cancer--new molecular targets come of age. *Nat. Rev. Cancer* 2004, **4**:97-105.
120. Zandy, N.L., Playford, M., and Pendergast, A.M., Abl tyrosine kinases regulate cell-cell adhesion through Rho GTPases. *Proc. Natl. Acad. Sci. U S A*, 2007, **104**:17686-17691.
121. Zandy, N.L. and Pendergast, A.M., Abl tyrosine kinases modulate cadherin-dependent adhesion upstream and downstream of Rho family GTPases. *Cell Cycle* 2008, **7**: 444-448.
122. Zhang, H., Yang, B., Pomerantz, R.J., Zhang, C., Arunachalam, S.C., and Gao, L., The cytidine deaminase CEM15 induces hypermutation in newly synthesized HIV-1 DNA. *Nature* 2003, **424**: 94-98.
123. Zhou, H., Xu, M., Huang, Q., Gates, A.T., Zhang, X.D., Castle, J.C., Stec, E., Ferrer, M., Strulovici, B., Hazuda, D.J., and Espeseth, A.S., Genome-scale RNAi screen for host factors required for HIV replication. *Cell Host Microbe* 2008, **4**: 495-504.
124. Zipfel, P.A., Zhang, W., Quiroz, M., and Pendergast, A.M., Requirement for Abl kinases in T cell receptor signaling. *Curr. Biol*. 2004, **14**: 1222-1231.
125. Singh, M. P., and Kumar, V., Biodegradation of vegetable and agrowastes by *Pleurotus sapidus*: A noble strategy to produce mushroom with enhanced yield and nutrition. *Cell. Mol. Biol.* 2012, **58** (1): 1-7.
126. Pandey, V. K., Singh, M.P., Srivastava, A. K., Vishwakarma S. K., and Takshak, S., Biodegradation of sugarcane bagasse by white rot fungus *Pleurotus citrinopileatus. Cell. Mol. Biol.* 2012, **58** (1): 8-14.
127. Ruhal, A., Rana, J. S., Kumar S., and Kumar, A., Immobilization of malate dehydrogenase on carbon nanotubes for development of malate biosensor. *Cell. Mol. Biol.* 2012, **58** (1): 15-20.
128. Vishwakarma, S. K., Singh, M. P., Srivastava A.K. and Pandey, V. K., Azo dye (direct blue) decolorization by immobilized extracellular enzymes of *Pleurotus* species. *Cell. Mol. Biol.* 2012, **58** (1): 21-25.
129. Dash, S. K., Sharma, M., Khare, S. and Kumar, A., *rmpM* gene as a genetic marker for human bacterial meningitis. *Cell. Mol. Biol.* 2012, **58** (1): 26-30.
130. Sandalli, C., Singh, K., and Modak, M. J., Characterization of catalytic carboxylate triad in non-replicative DNA polymerase III (pol E) of *Geobacillus kaustophilus* HTA. *Cell. Mol. Biol.* 2012, **58** (1): 44-49.
131. Kaushal, A., Kumar, D., Khare, S. and Kumar, A., *speB* gene as a specific genetic marker for early detection of rheumatic heart disease in human. *Cell. Mol. Biol.* 2012, **58** (1): 50-54.
132. Datta, J. and Lal, N., Application of molecular markers for genetic discrimination of *fusarium* wilt pathogen races affecting chickpea and pigeonpea in major regions of India. *Cell. Mol. Biol.* 2012, **58** (1): 55-65.
133. Siddiqi, N. J., Alhomida, A. S., Khan, A. H. and Onga, W.Y., Study on the distribution of different carnitine fractions in various tissues of bovine eye. *Cell. Mol. Biol.* 2012, **58** (1): 66-70.
134. Ong, Y. T., Kirby, K. A., Hachiya, A., Chiang, L. A., Marchand, B., Yoshimura, K., Murakami, T., Singh, K., Matsushita, S. and Sarafianos, S. G., Preparation of biologically active single-chain variable antibody fragments that target the HIV-1 GP120 v3 loop. *Cell. Mol. Biol.* 2012, **58** (1): 71-79.
135. Singh, J., Gautam, S. and Bhushan Pant, A., Effect of UV-B radiation on UV absorbing compounds and pigments of moss and lichen of Schirmacher Oasis region, East Antarctica. *Cell. Mol. Biol.* 2012, **58** (1): 80-84.
136. Singh, V. P., Srivastava, P. K., and Prasad, S. M., Impact of low and high UV-B radiation on the rates of growth and nitrogen metabolism in two cyanobacterial strains under copper toxicity. *Cell. Mol. Biol.* 2012, **58** (1): 85-95.
137. Datta, J. and Lal, N., Temporal and spatial changes in phenolic compounds in response *Fusarium* wilt in chickpea and pigeonpea. *Cell. Mol. Biol.* 2012, **58** (1): 96-102.
138. Sharma, R. K., JAISWAL, S. K., Siddiqi, N. J., and Sharma, B., Effect of carbofuran on some biochemical indices of human erythrocytes *in vitro. Cell. Mol. Biol.* 2012, **58** (1): 103-109.
139. Singh, A. K., Singh, S. and Singh, M. P., Bioethics A new frontier of biological Science. *Cell. Mol. Biol.* 2012, **58** (1): 110-114.
140. Adedeji, A. O., Singh, K. and Sarafianos, S. G., Structural and biochemical basis for the difference in the helicase activity of two different constructs of SARS-CoV helicase. *Cell. Mol. Biol.* 2012, **58** (1): 115-121.
141. Singh, S., Choudhuri, G., Kumar, R. and Agarwal, S., Association of 5, 10-methylenetetrahydrofolate reductase C677T polymorphism in susceptibility to tropical chronic pancreatitis in North Indian population. *Cell. Mol. Biol.* 2012, **58** (1): 122-127.
142. Sharma, R. K., Rai, K. D. and Sharma, B., *In* vitro carbofuran induced micronucleus formation in human blood lymphocytes. *Cell. Mol. Biol.* 2012, **58** (1): 128-133.
143. Naraian, R., Ram, S., Kaistha S. D. and Srivastava J., Occurrence of plasmid linked multiple drug resistance in bacterial isolates of tannery effluent. *Cell. Mol. Biol.* 2012, **58** (1): 134-141.
144. Pandey, A. K., Mishra, A. K., And Mishra, A., Antifungal and antioxidative potential of oil and extracts, respectively derived from leaves of Indian spice plant *Cinnamomum tamala. Cell. Mol. Biol.* 2012, **58** (1): 142-147.
145. Mishra, N., and Rizvi, S. I., Quercetin modulates na/k atpase and sodium hydrogen exchanger in type 2 diabetic erythrocytes. *Cell. Mol. Biol.* 2012, **58** (1): 148-152.
146. Kumar, A., Sharma, B. and Pandey, R. S., Assessment of stress in effect to pyrethroid insecticides, λ-cyhalothrin and cypermethrin in a freshwater fish, *Channa punctatus* (Bloch). *Cell. Mol. Biol.* 2012, **58** (1): 153-159.
147. Srivastava N., Sharma, R. K., Singh, N. and Sharma, B., Acetylcholinesterase from human erythrocytes membrane: a screen for evaluating the activity of some traditional plant extracts. *Cell. Mol. Biol.* 2012, **58** (1): 160-169.
148. Singh, M.P., Pandey, A. K., Vishwakarma S. K., Srivastava, A. K. and Pandey, V. K., Extracellular Xylanase Production by *Pleurotus* species on Lignocellulosic Wastes under *in vivo* Condition using Novel Pretreatment. *Cell. Mol. Biol.* 2012, **58** (1): 170-173.
149. Kumar, S., Sharma, U. K., Sharma, A. K., Pandey, A. K., Protective efficacy of *Solanum xanthocarpum* root extracts against free radical damage: phytochemical analysis and antioxidant effect. *Cell. Mol. Biol.* 2012, **58** (1): 174-181.
150. Shukla, A., Singh, A., Singh, A., Pathak, L.P., Shrivastava, N., Tripathi, P. K., Singh, K. and Singh, M.P., Inhibition of *P. falciparum* pfATP6 by curcumin and its derivatives: A bioinformatic Study. *Cell.*

Mol. Biol. 2012, **58** (1): 182-186.
151. Michailidis, E., Singh, K., Ryan, E. M., Hachiya, A., Ong, Y. T., Kirby, K. A., Marchand, B., Kodama, E. N., Mitsuya, H., Parniak, M.A. and Sarafianos, S.G., Effect of translocation defective reverse transcriptase inhibitors on the activity of n348i, a connection subdomain drug resistant HIV-1 reverse transcriptase mutant. *Cell. Mol. Biol.* 2012, **58** (1): 187-195.
152. Parveen, A., Rizvi, S. H. M., Gupta, A., Singh, R., Ahmad, I., Mahdi, F., and Mahdi, A. A., NMR-based metabonomics study of sub-acute hepatotoxicity induced by silica nanoparticles in rats after intra-nasal exposure. *Cell. Mol. Biol.* 2012, **58** (1): 196-203.