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HIV persistence: Chemokines and their signalling pathways

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Abstract

Latently infected resting CD4+ T cells are the major barrier to curing HIV. We have recently demonstrated that chemokines, which bind to the chemokine receptors CCR7, CXCR3 and CCR6, facilitate efficient HIV nuclear localisation and integration in resting CD4+ T cells, leading to latency. As latently infected cells are enriched in lymphoid tissues, where chemokines are highly concentrated, this may provide a mechanism for the generation of latently infected cells in vivo. Here we review the role of chemokines in HIV persistence; the main signalling pathways that are involved; and how these pathways may be exploited to develop novel strategies to reduce or eliminate latently infected cells.

Keywords

Human immunodeficiency virus (HIV); Chemokine; Signalling; Latency; Persistence

1. Introduction

Combination antiretroviral therapy (cART) for the treatment of human immunodeficiency virus (HIV) has resulted in a significant reduction in morbidity and mortality [1,2]. However, cART is currently unable to cure HIV, which means treatment needs to be life-long [3]. The major reason why HIV persists on treatment is the ability of HIV to establish a latent infection in long-lived CD4+ T cells [4–7]. Latently infected cells are enriched in lymphoid tissues, in particular the lymph nodes, spleen and gastrointestinal tract [8–11]. These tissue sites are rich in small chemotactic cytokines known as chemokines that, together with chemokine receptors, coordinate the highly regulated process of lymphocyte migration [12–14]. Here we review the role of chemokines in the establishment of HIV latency and how these pathways may be exploited to develop novel strategies to reduce or eliminate latently infected cells.

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2. HIV latency

The first step of the HIV life cycle is binding of the viral glycoprotein 120 (gp120) to both the CD4 receptor and a chemokine co-receptor (CCR5 or CXCR4) expressed on the surface of the host cell [15]. This is followed by uncoating and reverse transcription to form double-stranded cDNA [16,17], which then enters the nucleus, accompanied by integrase, in the form of pre-integration complexes (PICs). Inside the nucleus, the viral cDNA will either integrate into the host genome or form 1-long terminal repeat (LTR) or 2-LTR circles that are made following “self-ligation” of the HIV LTR at each end of the cDNA [18]. In activated CD4+ T cells, the integrated HIV provirus undergoes transcription to form unspliced (US) and multiply-spliced (MS) RNA in the nucleus. These transcripts are then translated in the cytoplasm to produce viral proteins leading to the production of new viral particles. Latency occurs when the virus life cycle is arrested following integration.

2.1. Pre- and post-integration latency

HIV latency can occur either as pre-integration or post-integration latency. Pre-integration latency refers to unintegrated HIV DNA that is unstable and will either degrade or will integrate into the host cell genome, usually following cell activation [19]. Post-integration latency is defined by the presence of stable integrated HIV DNA in the absence of virus production [6]. In vivo, the major reservoir of cells that harbour post-integration latency consists of resting central (CD45RA−CCR7+CD27+) and transitional (CD45RA −CCR7−CD27+) memory CD4+ T cells [20,21], and to a lesser extent, naïve CD4+ T cells [22].

In activated CD4+ T cells the virus life cycle is efficient with rapid integration, virion production and death of infected cells (Fig. 1A). In contrast, direct infection of resting CD4+ T cells is difficult to establish in vitro due to multiple blocks in the viral life cycle. These blocks include low or absent expression of the HIV co-receptor CCR5, which limits the ability for CCR5-using virus to enter resting CD4+ T cells, inefficient reverse transcription [19,23] and limited nuclear import of the reverse transcription complex (RTC)/PIC [24]. However, resting CD4+ T cells are clearly infected in vivo [25,26], as well as ex vivo in tissue blocks [27,28], and contain stable integrated forms of HIV. Once integration occurs in resting CD4+ T cells, the virus remains silent due to multiple molecular mechanisms. These include transcriptional interference [29–31]; a lack of transcription factors such as nuclear factor-kappa B (NF-κB), nuclear factor of activated T cells (NFAT) and transcriptional elongation factor (pTEFb; [32]); impaired export of MS RNA from the nucleus to the cytoplasm [33,34]; and microRNAs that inhibit translation [35,36].

2.2. Establishment of post-integration latency in resting CD4+ T cells

There are two theories on how post-integration latency is established in resting $CD4^+$ T cells. One suggests that latency arises from HIV-infected activated $CD4^+$ T cells that survive and revert to a resting memory CD4+ T cell carrying integrated virus. We refer to this as post-activation latency (Fig. 1B). In vitro models that support this pathway demonstrate that latency can be established after prolonged culture of activated infected cells [30,37,38];

together with IL-7 [39]; or by inhibiting cell death of infected activated cells via over-expression of the anti-apoptotic gene, *bcl-2* [40].

The alternative pathway is that HIV can directly infect a subset of resting CD4+ T cells. We refer to this as pre-activation latency (Fig. 1C). This has been demonstrated in vitro using CD4+ thymocytes [41,42] and circulating resting CD4+ T cells by some but not all groups [43–45]. We have recently demonstrated that latent infection can be established in resting memory CD4+ T cells following incubation with multiple chemokines [43].

2.3. Chemokines and HIV latency

Our initial experiments focused on the chemokines CCL19 and CCL21. These chemokines bind to the chemokine receptor CCR7 that is highly expressed on both central memory and naïve CD4+ T cells [46]. We demonstrated that incubation of resting CD4+ T cells with either CCL19 or CCL21, allowed for high levels of HIV integration with only low levels of productive infection [43]. This was observed with both CXCR4-using and CCR5-using viruses and in memory but not naïve CD4+ T cells [43]. Chemokine exposure did not result in cell activation (as measured by expression of CD69, CD25 and HLA-DR) [43,47] or significant changes in gene expression [47]. This was the first evidence to support a role for chemokines both in mediating infection of resting CD4+ T cells and in the establishment of HIV latency.

We subsequently demonstrated that multiple chemokines, in addition to CCL19 and CCL21, are able to induce latency in resting CD4+ T cells [47]. These included CXCL9 and CXCL10, which bind to CXCR3, and CCL20, which binds to CCR6 [48–50]. By quantifying various viral intermediates in the virus life cycle, we showed that the major effect of these chemokines was to facilitate efficient nuclear localisation and integration. Following HIV infection of unactivated or CCL19-treated resting CD4+ T cells, as well as PHA/IL-2-activated CD4+ T cells, we found no difference in early and late reverse transcripts. However, when we compared the CCL19-treated cells to unactivated cells we observed a more rapid and significant increase in the production of 2-LTR circles and integrated HIV DNA [47]. These results demonstrated that in the presence of CCL19, HIV can efficiently enter the nucleus and integrate in resting memory CD4+ T cells.

The lack of progression to productive infection in CCL19-treated cells suggested that there were factors that blocked the virus life cycle following integration. We therefore analysed viral transcripts in the nucleus and cytoplasm, including US RNA and MS RNA. In latently infected CCL19-treated CD4+ T cells we detected expression of MS RNA in the nucleus, but not in the cytoplasm [51]. Additionally, we did not detect any US RNA in the CCL19-treated latently infected cells. As MS RNA encodes for the positive regulators Rev and Tat that are crucial for the efficient expression of US RNA [52,53], the absence of MS RNA in the cytoplasm could explain the lack of US RNA expression and viral production observed in infected CCL19-treated CD4+ T cells. These data demonstrate that in latently infected CCL19-treated CD4+ T cells, production of MS RNA occurs, but that there is a block in the transport of MS RNA from the nucleus to the cytoplasm, similar to descriptions of resting CD4+ T cells from HIV-infected patients on cART [34]. Taken together, our data support the hypothesis that latency can result from direct infection of resting memory CD4+ T cells,

possibly as a result of exposure to chemokines found in lymphoid tissues, which could explain the efficient infection of resting cells observed in vivo [54] and in lymphoid tissue explants [28].

3. Chemokine signalling: a role in HIV nuclear localisation and integration

Chemokine ligation of G-coupled chemokine receptors leads to the activation of three main pathways, which include the Rho/GTPase pathway [55], the phosphoinositide-3 kinase (PI3K) pathway [56] and the phospholipase (PLC) pathway [57,58]. Activation of the Rho/GTPase pathway activates RhoA leading to cofilin dephosphorylation and changes in actin polymerisation [59]. This pathway also mediates endocytosis via cdc42 and RAC1 [60]. The PI3K pathway mediates chemotaxis via activation of the extracellular signal-regulated kinases 1 and 2 (Erk1/2) and c-Jun N-terminal kinases (JNK), as well as cell survival via activation of NF-κB (reviewed in [61,62]) (Fig. 2).

3.1. Rho/GTPase pathway

The Rho family of GTPases, including RAC1, RhoA and Cdc42, directly modulate the cytoskeleton through effects on actin/myosin and microtubules [63,64]. Actin/myosin and microtubules are important for cell migration [63], as well as migration of HIV to the nucleus in T cell lines [65] and activated CD4+ T cells [66]. In HIV infection, the viral PIC binds to actin via the matrix protein [67].

Infection of resting CD4+ T cells with a CXCR4-using virus, results in HIV gp120-induced chemokine signalling, through the HIV entry co-receptor CXCR4, and activation of the RhoA/GTPase pathway. This pathway activates Lim kinase, the actin-binding protein cofilin and changes in cortical F-actin, which allow for nuclear localisation of HIV [45,68]. We found that a similar pathway was critical for CCL19-induced latency and showed that the addition of jasplakolinolide, which blocks F-actin polymerisation, inhibited the detection of integrated HIV DNA and 2-LTR circles [47].

It has been proposed that in unactivated resting CD4+ T cells the PIC is carried to the nucleus by a process of actin cycling that does not require microtubule involvement [69]. This is supported by recent data showing that microtubule inhibitors do not inhibit direct infection of resting T cells [70]. However, it is not yet clear if microtubule involvement will be critical for infection of resting T cells that have undergone cytoskeletal changes following exposure to exogenous chemokine [47].

These findings shed new light on how HIV can exploit cellular machinery, including the cytoskeleton in resting CD4+ T cells. However, unlike our model of chemokine-induced latency, binding of gp120 to CXCR4 in unactivated cells did not result in viral integration and post-integration latency [71,72]. Furthermore, it is unclear if a similar process occurs following infection of resting CD4+ T cells with CCR5-using virus. In unactivated cells, accumulation of pre-integrated virus occurs [19,23], which may persist for many days [73] and can induce apoptosis [74]. We therefore propose that additional signalling is required for efficient integration in resting CD4+ T cells to generate stable post-integration latency.

There may be mechanisms other than direct chemokine receptor signalling, that could contribute to changes in the cell cytoskeleton allowing for efficient nuclear localisation. Cell migration alone may also lead to cytoskeletal changes that will favour transport of virus to the nucleus. Support for this theory can be derived from infection of resting CD4+ T cells via spinoculation, which involves infection of cells in the presence of high centrifugal force. Spinoculation was initially conceived as a method for increasing virus exposure during infection [44], however, it has since been shown to be effective in inducing efficient integration and establishment of latency in resting memory and, to some extent, naïve T cells [75–77]. Recent work has now demonstrated that spinoculation is associated with cytoskeletal changes, in addition to the activation of the cofilin/Lim kinase pathway [78]. These changes resemble the changes observed in the cytoskeleton following both direct gp120-co-receptor signalling and exogenous chemokine signalling [45,47]. Further studies on the relationship between cytoskeletal changes and the signalling pathways downstream of the chemokine receptors will help clarify the mechanisms controlling nuclear localisation and integration in resting CD4+ T cells.

3.2. PI3K pathway

The PI3K signalling pathway and its downstream transcription factors have been intensively studied for their role in lymphocyte proliferation, survival and cycle control in cancer [79,80]. PI3K is also upstream of the critical nuclear transcription activator NF-κB, which regulates gene expression in response to inflammation and activates transcription of the HIV provirus [81]. A recent report has suggested that the generation of either latent or productive infection in T cell lines is determined by the relative amount of NF-κB [38], and that basal levels of NF-κB are required for HIV integration, even in the absence of productive infection [31,38]. Therefore, NF-κB may indeed play a role in both facilitating integration as well as viral transcription.

The PI3K pathway also activates JNK and ERK1/2, which are important in cell survival and proliferation. The Raf/Mek/ERK pathway has previously been associated with the nuclear import of the HIV reverse transcriptase complex [69]. PI3K signalling, via the transcription factor JNK and the protein PIN-1, has been shown to result in the phosphorylation of HIV integrase, leading to increased stability of integrase and enhanced HIV integration in activated CD4+ T cells [82]. Whether similar pathways are required for efficient integration in resting CD4+ T cells remains unknown.

3.3. PLC signalling

The PLC pathway is also activated by chemokine receptor ligation and participates in the regulation of NFAT through Ca^{2+} and the Ca^{2+}/calmodulin-dependent serine phosphatase calcineurin. NFAT consists of a family of transcription factors that play important roles in the transcription of many cytokine genes. Reactivation of HIV from latency in some but not all models of latently infected memory CD4+ T cells has been shown to be mediated via NFAT, rather than NF-κB [38]. Furthermore, the inhibition of NFAT is associated with the inhibition of HIV gene expression [83]. The potential role of NFAT in HIV integration in resting CD4+ T cells is still unknown. However, the potency of NFAT activation of virus

expression [84,85] would suggest that latency occurs in the presence of low levels of NFAT activation.

Multiple chemokine signalling pathways seem to play a role either directly or indirectly in HIV infection. It is clear from our work and others that in resting CD4+ T cells, exogenous chemokines do increase the rate of nuclear localisation and dramatically increase the efficiency of viral integration compared to gp120-mediated chemokine signalling. It is currently unknown which of the signalling pathways is critical for HIV integration and latency in resting CD4+ T cells and whether these pathways differ from activated CD4+ T cells. It is most likely that separate downstream chemokine signalling pathways are critical for establishing latent infection in resting CD4+ T cells.

4. Chemokine receptors and productive HIV infection

Specific chemokine receptors (other than the HIV co-receptors CXCR4 and CCR5) have also recently been shown to be important in productive HIV infection. Activated memory CD4+ T cells are heterogeneous in their susceptibility to infection. In particular, Th17 cells, which express the chemokine receptor CCR6 [86], have been shown to be highly permissive to HIV infection [87]. Integrated HIV was found to be significantly enriched in CCR6+ cells when compared with other memory T cell subsets in treatment naïve HIV-infected patients [50]. Furthermore, the frequency of CCR6 expressing cells was diminished in blood from HIV-infected patients [50,88], even when HIV was controlled following cART [50]. Although Th17 cells also express the $\alpha 4\beta 7$ receptor, which has recently been shown to bind HIV gp120 [89], CCR6 and not $\alpha 4\beta 7$ expression has been shown to account for the increased permissiveness to HIV infection. CCR6+ T cells have the ability to be recruited to both gut and lymph node tissues [87] via the CCR6 ligand, CCL20 [90,91]. Therefore, HIV infection of CCR6+ CD4+ memory T cells may provide a pathway for HIV dissemination to the T cell rich compartments of lymphoid tissues.

5. Effects of HIV infection on chemokine expression in vivo

Elevated levels of numerous chemokines have been detected in the plasma of HIV-infected patients, including CCL2, CCL19, CCL21, CCL20 [92–95], CXCL9, CXCL10 [96], CXCL16 [97] and CXCL13 [98,99], and expression of these chemokines increases with disease progression. Additionally, many of these chemokines remain elevated on cART [95,96,100] or, if reduced, fail to return to the levels observed in uninfected individuals [95,98,99]. The addition of CCL19, CCL21 or CXCL16 to PBMC isolated from HIV-infected individuals, resulted in a significant increase in pro-inflammatory cytokines, such as TNF-alpha and IFN-gamma [93,100]. Furthermore, elevated plasma CXCL10 and CXCL9 have recently been associated with elevated markers of immune activation (including IL-12 and soluble IL-2 receptor) in HIV-infected patients on cART [96]. Therefore, it is possible that elevated chemokines may potentially drive immune activation in the setting of HIV infection. Persistent immune activation may also facilitate ongoing virus replication in tissue sites where penetration of cART may be suboptimal [101]. Further studies, however, are required to establish if there is any relationship between elevated chemokine levels and the localisation of latently infected cells and/or residual virus replication on cART.

6. Blocking chemokine function – implications for clinical strategies aimed at eradicating latency

Currently, there is intense interest in finding novel strategies to eliminate latency as a potential path towards finding a cure for HIV. How might we then translate some of our findings on the role of chemokines and latent infection into novel therapeutics?

The lack of decay of long-lived latently infected resting memory CD4+ T cells may be explained by the long half-life of memory CD4+ T cells [102,103]. Alternatively, there could be proliferation or replenishment of this reservoir. There is some evidence to suggest that IL-7 may drive homeostatic proliferation of latently infected cells [20]. Ongoing infection of resting CD4+ T cells in sites, such as the gastrointestinal tract or lymphoid tissue, may be another way the pool of latently infected CD4+ T cells is replenished. The source of this virus could be intermittent release of virus from long-lived latently infected cells and/or long-lived productively infected cells, such as infected myeloid cells and dendritic cells, or their progenitors [104]. Reduced efficacy of cART in these tissues may also arise from suboptimal penetration of cART [101] and/or limited efficacy of cART in blocking cell–cell transfer of virus [105,106]. Therefore, cART alone may never be able to sufficiently limit infection of resting CD4+ T cells in these tissue sites. Strategies other than cART that specifically block infection of resting memory CD4+ T cells and, therefore, the establishment of latent infection, may be an important intervention to limit replenishment and accelerate the decay of latently infected cells.

Our data raise the possibility of an entirely new approach to eliminating latent infection – via inhibition of specific chemokine receptors, including CCR7, CXCR3 and CCR6 [47]. Chemokine receptor antagonists, which are active against CXCR3, have undergone phase II trials for efficacy in psoriasis (T-487; Tularik and AMG-487, Amgen; reviewed in [107,108]). Additionally, the CCR5 antagonist, TAK-779, has activity as both a CCR5 and CXCR3 antagonist [109]. There are currently no available antagonists that block CCR7 and CCR6.

In addition to chemokine receptor antagonists, chemokine function can also be inhibited using synthetic chemokine antagonists [110–112]. Studies in murine models have demonstrated that truncation of the N-terminus of some chemokines, including CCL19, CXCL11 and CCL20 can antagonise specific functions of the corresponding wild-type chemokine [110–114]. Therefore, inhibition of chemokines that are important for the establishment of latency via either chemokine antagonists or chemokine receptor antagonists may be a novel strategy to be tested in the future that could potentially block ongoing infection of resting CD4+ T cells.

7. Conclusion

Chemokines and their receptors clearly play an important role in HIV infection. In addition to their role in productive infection, numerous chemokines have now been shown to induce post-integration latency in resting memory CD4+ T cells. Chemokine signalling can induce changes in the actin cytoskeleton of resting CD4+ T cells that facilitate efficient nuclear

localisation. Other signalling pathways such as PI3K may also be important for efficient integration. Increases in the concentration of specific chemokines in either tissue or blood in the setting of HIV infection may potentially provide a unique environment for ongoing infection of resting CD4+ T cells in tissue sites. Blocking ongoing infection of resting CD4+ T cells by inhibiting host targets may present a novel strategy to inhibit the establishment of latent HIV infection and accelerate the decay of latently infected cells in patients on cART.

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Biographies

Vanessa Evans obtained her Bachelor's degree in Science and her PhD in Immunology from Monash University, Australia. Her PhD explored the role of dendritic cells in the spread and persistence of HIV. In 2011, Dr. Evans began her post-doctoral training with Professor Sharon Lewin within the Department of Infectious Diseases at Monash University. Her research focus is on dendritic cells and the development of physiologically relevant in vitro models for the study of HIV latency.

Gabriela Khoury is currently completing her PhD at the Department of Medicine, Monash University, Australia. She is a successful recipient of a competitive post-graduate scholarship from the Australian National Health and Medical Research Council. Prior to starting her PhD, Gabriela had 5 years of HIV basic science research experience including the development of a new class of antiretroviral compounds. Ms. Khoury's PhD focuses on the role of naïve T cells in HIV pathogenesis, in particular how these cells remain persistently infected during long-term antiretroviral therapy.

Suha Saleh obtained her Bachelor's degree in Veterinary Science from Baghdad University, Iraq, and her PhD in Molecular Virology from The University of Queensland, Australia. She then joined the Department of Microbiology at Monash University, Australia, where she conducted her post-doctoral training as part of the malaria vaccine initiative team project. Dr. Saleh continued her vaccine work with Viral Holding Limited, an Australian biotech company, where she was involved in the development of new recombinant vaccine vectors for HIV, prostate cancer, Hepatitis B and other infectious and autoimmune diseases. In 2005, she joined the research team of Professor Sharon Lewin within the Department of Medicine at Monash University. Dr. Saleh is an amFAR fellow and her major research interests include chemokines and their role in the establishment of HIV latency.

Paul Cameron trained as a clinician in clinical immunology and immunopathology at the Royal Perth Hospital and University of Western Australia. After completing a PhD in immunogenetics he spent a post-doc with Ralph Steinman at Rockefeller University where

he defined the ability of dendritic cells (DC) to efficiently infect CD4+ T cells during DC-T cells interactions. He has subsequently had research positions at the Burnet Institute and the University of Melbourne, Australia where he defined the infection of DC and T cells in ex vivo models of HIV infection. More recently, he has joined the Alfred Hospital as a Clinical Immunologist and immunopathologist and co-heads a research laboratory with Prof Sharon Lewin in the Departments of Medicine and Immunology of Monash University. Dr. Cameron is continuing his research in HIV immunopathology with a particular interest in the mechanisms of latency in T cells and during DC-T cell interactions.

Sharon Lewin is an infectious diseases physician and basic scientist. She is Director of the Department of Infectious Diseases The Alfred Hospital and Monash University; co-head of the Centre for Virology, Burnet Institute, Melbourne, Australia and a practitioner fellow of the National Health and Medical Research Council of Australia. Professor Lewin completed her specialist and PhD training in Melbourne and her post-doctoral fellowship at the Aaron Diamond AIDS Research Centre, The Rockefeller University. She is a past president of the Australasian Society for HIV Medicine. Her laboratory focuses on understanding how HIV persists in patients on antiviral therapy, strategies to cure HIV infection and biological determinants of immune recovery following antiviral therapy.

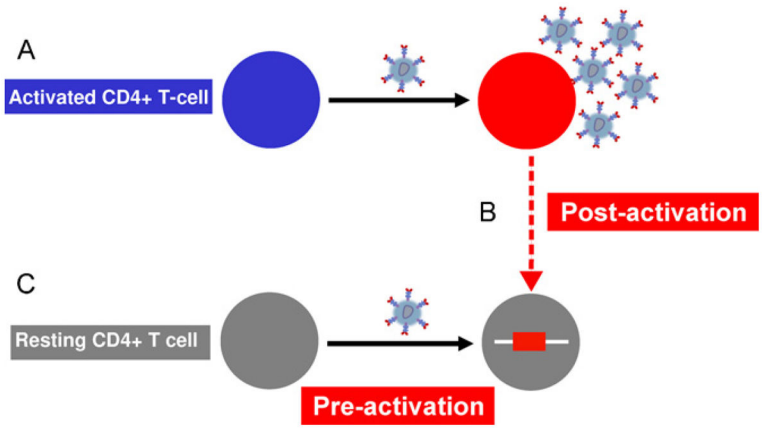

Fig. 1.

Pathways for the establishment of latent infection in resting CD4+ T cells. (A) In activated CD4+ T cells (blue) the virus life cycle is efficient, multiple virions are produced and the infected cell dies. In latently infected cells, virus enters and integrates but there is limited or no virus production. There are two potential pathways for the establishment of latent infection in resting CD4+ T cells. (B) Some activated infected cells (red) may survive and revert to become central memory T cells with an associated integrated provirus (post-activation latency). (C) The alternate pathway is the direct infection of resting CD4+ T cells (grey) in the presence of factors that modify the actin cytoskeleton, such as chemokines (pre-activation latency).

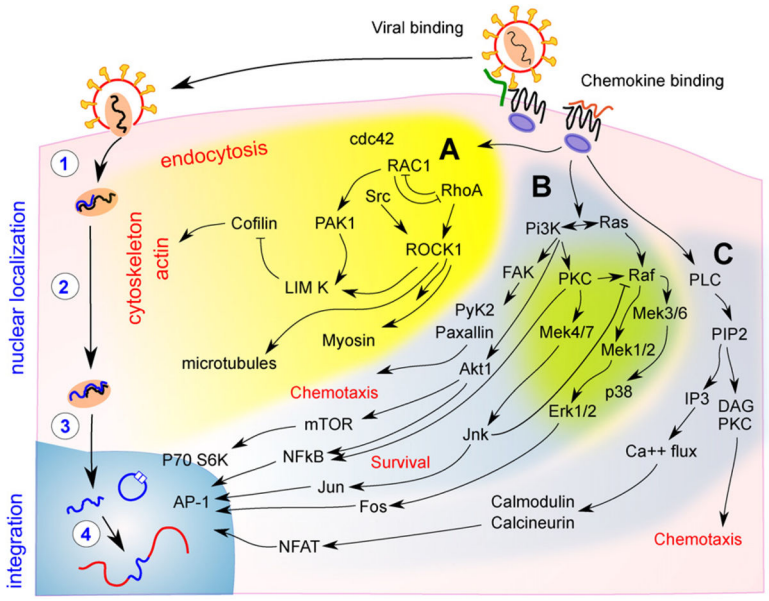

Fig. 2.

Signalling pathways activated by chemokine receptors. The binding of both gp120 to CXCR4 and exogenous chemokines to their respective chemokine receptors is associated with signalling by (A) cdc42/RAC1/RhoA (yellow); (B) phosphoinositide-3 kinase (PI3K; blue/green); and (C) phospholipase (PLC; blue). These pathways can mediate HIV replication via modification of post entry events such as (1) reverse transcription; (2) migration of the reverse transcriptase and pre-integration complex to the perinuclear region; and (3) nuclear entry. After nuclear entry, (4) the full length linear DNA may be integrated or form 2-long terminal repeat circles, a virologically dead end product. The RhoA pathway has been shown to modify cofilin activation and actin depolymerisation, which enhances nuclear localisation in chemokine treated cells. The PI3K and PLC pathways, via nuclear factors such as nuclear factor-kappa B (NF-κB) and nuclear factor of activated T cells (NFAT), mediate cellular functions, such as cell survival and chemotaxis, and can also activate viral transcription. These pathways may potentially have a role in enhancing the efficiency of HIV integration in resting CD4+ T cells.