UJEMI PEARLS

Solving the Paradox: Deciphering HIV-I Persistence in Hematopoietic Stem

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SUMMARY Opposing the common interferon-stimulated antiviral mechanisms employed by terminally differentiated cells, a recent study revealed that stem cells constitutively express critical subsets of interferon stimulated genes (ISGs) that confer effective protection against viral infection. Three members of the Interferon-induced Transmembrane (IFITM) protein family, IFITM 1, 2, and 3 have known anti-HIV-1 activities, and were found intrinsically expressed in various stem cell types including the hematopoietic stem cells. Interestingly, strong evidence reported recently indicates that the multipotent hematopoietic stem and progenitor cells (HSPCs) could serve as an HIV-1 reservoir which harbours latent, clonal and functional HIV-1 proviral genomes in anti-retroviral therapy-treated patients. This observation then prompts the apparent paradox: how does HIV-1 establish functional proviral reservoirs in HSPCs in the presence of a potent and constitutive expression of the antiviral IFITM proteins? Based on available literature, this study attempts to elucidate the paradox by summarizing reported anti-HIV-1 ISGs expressed intrinsically in hematopoetic stem cells (HSCs), outlining a model for HIV-1 reservoir establishment in HSCs in the context of IFITMs, and finally proposing an IFITM-based therapeutic strategy against HIV-1 transmission.

INTRODUCTION

During viral infection, the incoming viral genome is sensed by pattern recognition receptors, which initiate signaling cascades that activate transcription factors and induce production of interferons (IFNs). Type I (IFNα/β), type II (IFNγ), and type III (IFNλ) interferons are secreted cytokines with well-established antiviral effects that act in an auto- and/or paracrine manner to induce the expression of interferon-stimulated genes (ISGs) - many of which play a central role in antiviral defense. Recently, it was found that selected groups of ISGs are being constitutively expressed to protect stem cells from viral infection. The intrinsic expression of ISGs is restricted to stem cells and not differentiated cells [1]. Various types of stem cells are able to resist viral infection, yet the degree of resistance depends largely on viral species and host cell characteristics, and the causes behind such differential resistance are not well-understood. The human embryonic stem cell (hESC)-derived HSCs, like other stem cell lineages, express a distinct set of ISGs [1]. Members of a classic family of ISGs, known as the interferon-induced transmembrane (IFITM) protein family, are robustly expressed in various types of stem cells including HSCs and are known to exert antiviral effects targeting early steps of the enveloped virus life cycle [2]. Despite various studies reporting the broad-spectrum antiviral activities of IFITMs, their mechanism of action remains incompletely understood. The human immunodeficiency virus (HIV) is one of the many viral targets of IFITMs, and numerous attempts have been made to interpret the molecular mechanism of IFITMs in blocking HIV type 1 (HIV-1) infection in the past decade [3-5].

Two of the major unsolved questions in the field of HIV research which have been hindering the development of an effective cure revolve around the cellular identity of HIV latent proviral reservoirs and the reactivation stimuli acting on the latent viruses. By late last year, important progress had been made on the former by identifying the ability of hematopoietic stem and progenitor cells (HSPCs) to serve as long-term HIV reservoirs [17].

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Despite various studies focusing on the anti-HIV mechanism of IFITM proteins, none of these studies elucidated their findings in the context of HSCs.

Considering the observed antiviral effect of IFITMs against HIV-1, the potent expression of IFITM proteins in HSCs, and the proposed role of HSCs in serving as an HIV-1 reservoir, an apparent paradox then emerges: how can HIV-1 bypass the antiviral functions of IFITM and establish functional proviral reservoirs in HSCs? This review attempts to address this paradox by summarizing the identified anti-HIV-1 ISGs expressed distinctively in HSCs, sketching a model for HIV-1 reservoir establishment in HSCs based on available literature evidence, and concluding with the proposal of a possible therapeutic avenue against the establishment HIV-1 reservoirs in association with IFITMs.

RESEARCH QUESTIONS

1. What anti-HIV-1 ISGs are reported to be expressed intrinsically by hematopoietic stem cells and how do they limit viral infection?
2. How can HIV-1 infect and persist in hematopoietic stem cells despite potent and constitutive expression of HIV-restricting IFITMs?
3. What might serve as potential IFITM-based therapeutics to restrict HIV-1 invasion of HSCs?

PROJECT NARRATIVE

IFITM Family Proteins, Along with Others, are Anti-HIV-1 ISGs Expressed Intrinsically by Hematopoietic Stem Cells. Based on transcriptome analyses performed by Wu *et al*., a large variety of ISGs are being intrinsically expressed in HSCs, a number of which have been identified to restrict HIV-1 [1]. Table 1 summarizes the key anti-HIV-1 genes identified in various literature sources [1, 6, 7] and their expression status in HSCs. As shown in Table 1, consensus on basic antiviral mechanisms has been established for various HSC-associated anti-HIV-1 proteins. For instance, tetherin traps budding virions to the plasma membrane upon viral release, thereby blocking viral egress [8], and SAMHD1's dNTPase function blocks HIV reverse transcription by depleting the cellular nucleotide triphosphate pool. However, a unified view on the specific mechanism of action of IFITMs is still lacking.

IFITM is a family of small transmembrane proteins expressed basally in several cell types that are strongly induced by IFNs. The antiviral properties of the three members of this family, IFITM1, 2, and 3, were first reported in 2009 against influenza A virus [9]. In 2011, an shRNA knock-down screen reported potent HIV-1 limiting activity of IFITM-1, and inducing the expression of IFITM1, 2, and 3 in various cell lines further confirmed their anti-HIV-1 effect. More importantly, the authors showed that although all three IFITM proteins suppress HIV Gag protein production, IFITM 2 and 3 also associate with endocytosed cargos and impede viral entry [10]. Two years later, IFITM proteins' function were further demonstrated to be blocking viral entry by preventing hemifusion of the viral and host cell membrane [11]. An excellent review by Smith *et al.* from 2014 summarizes the history and recent advances on the study of IFITMs and their broad-spectrum antiviral functions [12].

Wu *et al.* have reported particularly high expression levels of IFITM 1, 2, and 3 in HSCs via RNA-seq, Western blotting, and qRT-PCR. Interestingly, such expression was not observed in various HSC derivatives, namely proerythroblasts, early basophilic erythroblasts, and late basophilic erythroblasts [1]. The complex and versatile antiviral functions of IFITMs and their distinct expression in stem cells make this family of proteins exceptionally enigmatic and attractive for further investigation.

HIV-1 Infects and Persists in Hematopoietic Stem Cells Despite Robust and Constitutive Expression of HIV-Restricting IFITMs. It has been established that resting CD4+ T cells serve as HIV-1 reservoirs in patients treated with combination anti-retroviral therapy (cART) and contribute to lifelong persistence of plasma viral load [13]. However, frequent observation of incomplete viral genome matches between HIV-1 infected CD4+ T cells and a patient's residual viremia suggests that additional unidentified reservoirs likely exist and contribute to HIV-1 persistence [14, 15, 16]. Zaikos *et al.* recently showed that hematopoietic stem and progenitor cells (HSPCs) serve as an HIV reservoir by identifying

full sequence matches between genomes of patient plasma residual virus and clonal HSPC-associated HIV-1 provirus [17]. Together with the observation that HSCs intrinsically express IFITMs at high levels, this raises the question of how HIV is able to establish a reservoir in these cells in the face of IFITM-mediated antiviral function.

To resolve this apparent paradox, a thorough understanding of the antiviral mechanism of IFITMs in the context of HIV will be needed. A likely possibility is that IFITM proteins may be expressed intrinsically at a level insufficient to completely block HIV-1 invasion. However, immunoblotting indicated that IFITM3 is constitutively expressed at a significantly higher amount in HSCs than their derivatives (proerythroblasts, early, and late basophilic erythroblasts) after IFN-β stimulation [1]. Two transmission modes are known to be associated with *in vivo* HIV-1: the cell-to-cell (cell-associated) transmission mediated by the formation of a virological synapse between the donor and the target cell, and cell-free transmission [18, 19, 20]. Although the extent of the two modes of transmission occurring *in vivo* remains unclear, it has been demonstrated that cell-to-cell transmission allows the transfer of virions with high local multiplicity of infection (MOI) [20]. In 2014, Compton *et al.* demonstrated that IFITM3 is incorporated into nascent HIV-1 virions to impair cell-to-cell transmission and fusion of the virion with the target cell. Interestingly, the authors showed that unlike the donor, virus-producing cells, target-cell IFITM3 expression alone is insufficient to mediate anti-HIV-1 protection [3]. This observation lends support to their virion-membrane incorporation model of IFITMs and provides a possible explanation for the paradox - when an HIV-1 infected CD4+ T cell transmits its virions to an HSC, the T cell serves much as an IFITM(-) viral donor cell. Despite a robust expression of IFITM in the target HSC, the donor T cell-originated virions lack virion-membrane IFITM incorporation,

Table. 1 Summary of reported anti-HIV-1 genes, their response to interferon induction, mechanisms of inhibition, and intrinsic expression in HSCs.

	Interferon inducible (ISG)?	Life cycle	Mechanism of inhibition	Intrinsically expressed in HSCs?	Ref.
BST2/Tetherin	Yes	Egress/budding	Traps virions to plasma membrane	Yes	[8]
IFITM1/2/3	Yes	Entry	Unclear	Yes	[2,3,5]
CD74	Yes	Replication	Unclear; chaperones MHCII for antigen presentation?	Yes	[6]
ISG15	Yes	Various	Modulate protein function by ISGylation	Yes	[6]
APOBEC3	Yes	Replication	Hypermutate viral genome	Not observed	[25]
IDO1	Yes	Replication	L-Trp depletion	Not detected	[7]
ZAP	Yes	Replication	Promote degradation of viral mRNAs	Not detected	[6]
TRIM56	Yes	Replication	Unknown	Not detected	[7]
MOV10	Yes	Post-entry	Unknown	Not detected	[6]
Mx2/MxB	Yes	Post-entry, prior to integration	Unknown	Not detected	[6]
TRIM5α	Yes	Before RT	Target viral capsid uncoating, promote innate signaling	Not detected	[6]
SUN2/UNC848B	Yes	Unknown	Unknown	Not detected	[6]
SAMHD1	Yes (non-classical)	RT	dNTPase activity depletes nucleotide triphosphate pool	Yes	[7]
SERINC 3/5	No	Entry	Unknown		[32]

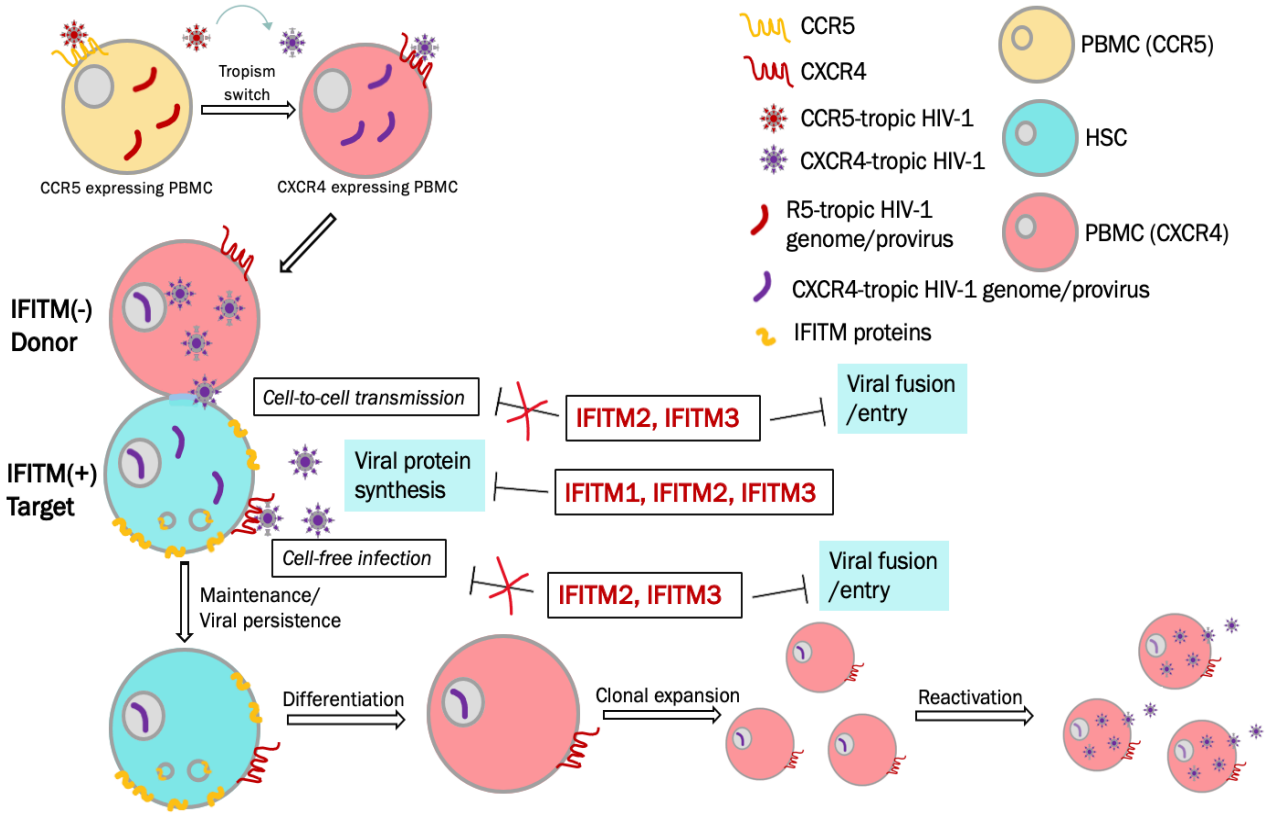
and these virions can still gain efficient entry into the HSC (Figure 1B). Ten months later, Yu *et al.* revealed that IFITM proteins, especially IFITM2 and 3, directly target the HIV-1 Env glycoprotein and impair gp160 processing into gp120 and gp141, thereby impacting Env-mediated cell fusion and HIV transmission [4]. In support of this finding, another study showing that combined amino acid mutations in the HIV Vpu and Env proteins together are necessary for the evasion of IFITM1-mediated restriction of viral entry [21].

As HIV-1 provirus-carrying HSCs go through cycles of maintenance, the viral genome persists in the infected individual. HSCs then differentiate and clonally expand in the peripheral blood and bone marrow, contributing to residual plasma virus (Figure 1C) [17, 22]. This process is accompanied by a gradual loss of intrinsic IFITM expression, which allows the production of infectious viral particles upon proviral reactivation [1].

To take a few steps back, the same group that discovered HSPCs acting as an HIV-1 latent reservoir also demonstrated that the virus uses the CXCR4 chemokine receptor to infect HSPCs [17]. Since CCR5-utilizing (R5-tropic) HIV-1 are often detected in early infection whereas CXCR4-utilizing (X4-tropic) HIV-1 appear at later stages, it is possible that a tropism switch, likely mediated by mutations in the viral Env V3 loop regions, could initiate the virus' invasion of HSCs (Figure 1A) [22]**.** Further supporting this hypothesis, one study showed that the Env V3 critically determines the IFITM susceptibility of the virus [23].

As a summary, the model proposes that HIV-1 begins its infection cycle in HSCs with a viral tropism switch (from CCR5- to CXCR4-tropic). The infected CXCR4-displaying peripheral blood mononuclear cells (PBMCs), which do not yet express IFITMs, now become

FIG. 1 Model illustrating HIV invasion and propagation in HSPCs leading to established HIV reservoirs. (A) HIV-1 begins its infection cycle in HSCs with a viral tropism switch (from CCR5- to CXCR4-tropic) (B) CXCR4 expressing peripheral blood mononuclear cells (PBMCs), which do not yet express IFITMs, serve as HIV-1 donors and contact an HSC target thereby transmitting the virions. HIV provirus integrates into the host HSC genome, establishing latent proviral reservoirs. (C) Proviral reservoirs persist after multiple cycles of cellular maintenance. As HSCs differentiate, the proviruses then can be reactivated to produce infectious HIV-1 particles. (D) Although the IFITM proteins expressed by the target HSC insufficiently block HIV-1 invasion, viral protein synthesis may still be restricted at a reduced scale.

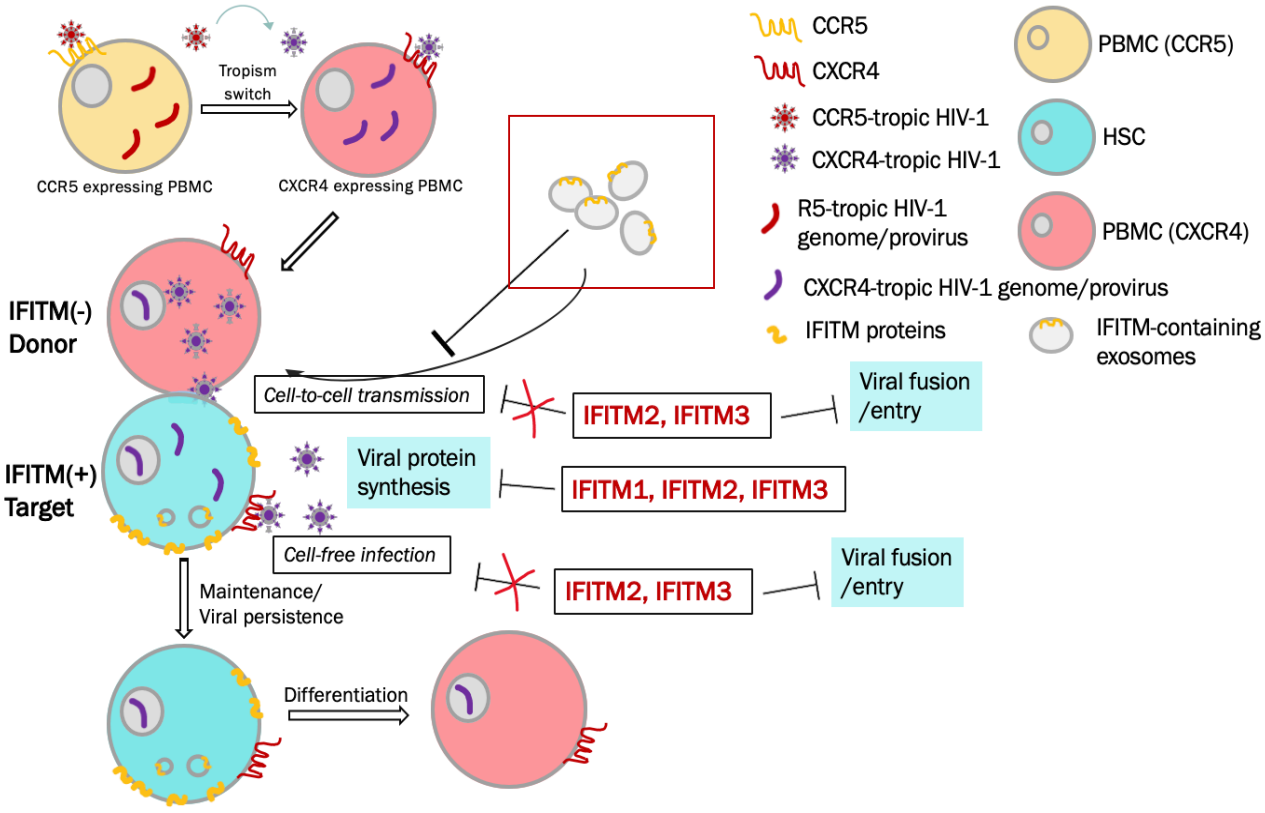


HIV-1 donors that can interact with another HSC target to transmit the virions. Intrinsic IFITM expression in the target cell is insufficient to block viral entry, and after reverse transcription, the HIV provirus integrates into the host HSC genome, thereby establishing latent proviral reservoirs that persist after multiple cycles of cellular maintenance. Eventually, as the HSCs differentiate into other cell types (e.g. CD4+ T cells), the provirus then becomes reactivated to produce infectious HIV-1 virions (Figure 1).

Exosome-mediated delivery of IFITM proteins could serve as therapeutic strategy to limit HIV-1 transmission. Exosomes represent one of the three major classes of endosome-derived vesicles that are released from cells into the extracellular environment, and their distinct size (30 - 100nm in diameter), density and molecular markers allow their differentiation from microvesicles and apoptotic bodies. The biogenesis of exosomes involves the inward budding of late endosomal vesicles, forming multivesicular bodies; subsequent fusion with the cytoplasmic membrane leads to their release [24]. The immunomodulatory and antiviral activities of exosomes have been explored by numerous studies. There has been a growing interest in exosomes in the context of HIV infection: human semen derived exosomes exhibit a potent block of post-entry HIV-1 replication; the anti-HIV APOBEC3G was shown to be transported to recipient cells via exosomes; and exosomes mediate the transmission of anti-HIV factors from the blood brain barrier to macrophages [25, 26, 27].

It has recently been shown that IFITM-containing extracellular vesicles are being produced and can be detected even in the absence of HIV-1 infection [4]. The cellular origin and fate of these cargo-containing extracellular vesicles (EVs) are unknown and their cell or tissue targets have not been investigated. Nonetheless, this observation raises the possibility of exploiting IFITM-containing vesicles as vehicles for IFITM delivery to HIV-1-susceptible T cells and macrophages. Figure 2 illustrates how IFITM-associated exosomes may block

FIG. 2 Exosome mediated delivery of IFITM proteins targeting PBMC HIV donor cells that non-intrinsically express IFITM proteins. IFITM-containing exosomes are emphasized in the red square, which perform targeted delivery of the IFITM proteins to the IFITM(-) donor cells (arrow goes to the donor cell), confers these cells IFITM-mediated antiviral activity by blocking cell-to-cell transmission via virion incorporation of IFITMs.



HIV-1 transmission based on the proposed infection model. For instance, the exosomes may be engineered to be specifically targeting CXCR4+ IFITM(-) T cells ("donor T cells") that will be infected first by the incoming virus, and the exosome-mediated delivery of IFITM proteins will turn these T cells into IFITM(+) T cells which generate virions with defective entry. In order to exploit exosomes as an IFITM transporter, strategies need to be developed to efficiently isolate these vesicles. Zhu *et al.* recently described the dengue virus serotype 2 (DENV-2)-restricting effect of IFITM-3-containing exosomes exported from HUVEC cells, which intrinsically express high basal levels of IFITM3 [28]. The study employed filtration, differential ultracentrifugation, and sucrose gradient centrifugation to isolate exosomes from other extracellular components based on exosome-specific densities and diameters, and confirmed IFITM3 enrichment in the isolated exosomes using Western blotting analysis and mass spectrometry. These exosomes were shown to be readily taken up by recipient HeLa cells, which exhibited significantly reduced DENV entry [28].

In addition to purifying IFITM-associated exosomes from *in vitro* cultures, the abovementioned method for exosome purification and concentration could also be applied for *in vivo* isolation of plasma exosomes. Alternatively, due to the membrane-associated nature of IFITMs, magnetic bead-conjugated IFITM antibodies could be utilized to pull down IFITM-carrying exosomes. Since the biological properties and functions of exosomes largely depend on their cellular origin, IFITM-carrying exosomes obtained from plasma exhibit primary host-intrinsic molecular patterns, which may suggest improved uptake efficiency by specific target cells expressing similar molecular patterns [24, 27].

The cellular origin of IFITM-associated exosomes makes them great candidates for anti-viral therapy with low expected toxicity. However, since different studies showed that HIV-1 particles could form aggregates with viral protein-laden exosomes as an immune-evasion strategy, and that exosomes derived from HIV-infected cells have a greater tendency to enhance infection, care must be taken to prevent inter-exosomal communication and cargo exchange between infused IFITM-containing exosomes and virulent exosomes carrying HIV proteins [29, 30, 31]. Thus, primary cell HIV-1 transmission modeling and *in vivo* studies will be important to ensure that IFITM-containing exosomes does not further promote HIV-1 infection in relevant physiological conditions.

CONCLUSIONS

HSCs intrinsically express high levels of anti-viral IFITM family proteins, yet HIV-1 is able to evade IFITM-mediated restriction, persist in the HSCs of treated patients, and produce functional provirus. This study proposes a model as a first attempt to resolve this apparent contradiction, followed by the introduction of an exosome-based therapeutic strategy targeting against HIV-1 propagation in HSCs. For better articulation of the model, a thorough mechanistic understanding of the anti-HIV-1 function of IFITM proteins remains crucial. By summarizing, linking, and extending beyond present knowledge, this article aims to offer new insights into HIV-1 bone marrow pathology and persistent infection mechanisms, and to reveal potential future directions in the study of virus–host immune interaction.

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