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The dual function of the MHC class II transactivator CIITA against HTLV retroviruses

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1. ABSTRACT

The *AIR-1* gene product CIITA is the master regulator of MHC class II gene expression. This makes CIITA a crucial element for triggering antigen presentation to CD4+ T cells and thus the cascade of events leading to an efficient adaptive immune response. Recently we discovered that CIITA is also endowed with the capacity to directly inhibit both HIV-1 and HTLV retroviruses in infected cells by blocking the function of the viral transactivators Tat and Tax. Thus CIITA exerts a dual role against human retroviruses. The first, classical role is the upregulation of MHC class II expression and thus the capacity to present viral antigens to CD4+ T cells. The other, evolutionary new and fundamental role is to inhibit directly viral replication and spreading. We will discuss the molecular mechanisms by which CIITA counteracts specifically viral transactivators. These distinct properties of CIITA will shed new light on the molecular mechanisms of adaptive coevolution of hosts and pathogens and may be exploited to envisage novel therapeutic strategies aimed at counteracting retroviral infections and thus their oncogenic potential.

2. INTRODUCTION

The human T-cell leukemia virus type 1 (HTLV-1) and type 2 (HTLV-2) are related retroviruses with similar genomic organization, common modes of transmission but different disease manifestations (1, 2). HTLV-1 is the etiologic agent of adult T-cell leukemia/lymphoma (ATLL) and of the tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM) (3-6). Conversely, HTLV-2 has not been epidemiologically linked to lymphoproliferative disorders. HTLV-1 and HTLV-2 show a preferential tropism for CD4+ and CD8+ T cells, respectively, but they can also infect other populations including monocytes and B cells (7-11). These different tropisms may reflect the preferential usage of distinct cell surface receptors (12). Both viruses encode homologous transcription activators, Tax-1 and Tax-2, respectively, that are important mediators of viral pathogenesis and essential for immortalization of T lymphocytes (13, 14). Tax-1 activates transcription of the HTLV-1 viral genome by interacting with the CREB/ATF family of transcription factors, which bind to the viral long terminal repeat (LTR) (15). This interaction facilitates the

recruitment of general transcription factors and coactivators, such as CBP, p300 and PCAF, resulting in the enhancement of transcription (16-18). Tax-1 also deregulates the expression of a variety of cellular genes and signaling pathways, involved in cell cycle, cell growth, DNA repair and apoptosis, favouring the initiation of leukemogenesis and maintenance of the malignant phenotype in ATLL (19).

In contrast to Tax-1, very little is known on the cellular factors interacting with and/or utilized by Tax-2 to mediate its biological functions and although its mechanism of action is assumed to be similar to that of Tax-1, several reports have shown distinct biological properties (20-24).

As HTLV viral products affect the function of several cellular factors modifying the homeostatic behaviour of infected cells, similarly host cell may have developed during evolution molecular mechanisms to counteract retrovirus actions. Recently, several mechanisms of innate resistance to retrovirus infection and spreading have been described, particularly for the lentivirus HIV infection (25-30). In particular, we found that the main transcriptional activator of HLA-II genes, CIITA, whose encoding locus *AIR-1* and specific function were discovered in our laboratory (31) could strongly inhibit HIV replication in infected cells by inhibiting the viral transcriptional activator Tat (26). These findings prompted our group to investigate whether similar mechanisms are put in place by the host cells during HTLV infection.

3. THE INVOLVEMENT OF THE HLA CLASS II MOLECULES AND OF THEIR TRANSCRIPTIONAL REGULATOR CIITA IN HUMAN RETROVIRUS – HOST CELL INTERACTION

The response of the immune system against virus-infected cells is mainly controlled by cytolytic T lymphocytes (CTL) that require for their optimal function the help of CD4+ T helper cells (TH). TH cells recognize foreign antigens presented by MHC class II (HLA class II or HLA-II in human) molecules expressed on antigen presenting cells (APC), particularly dendritic cells (DC) and macrophages, as well as B cells (32). Thus HLA-II molecules are fundamental to trigger the immune effector mechanisms that will counteract viral infections, including retroviral infections.

Moreover, HLA-II molecules may influence the biologic behaviour of the cells with which the HTLV retrovirus interacts. We originally observed that HTLV-2 virus stemming from infected T cells is highly mitogenic for CD34+ hematopoietic precursors. In contrast, virus particles budding from B cells are not mitogenic. The envelope of HTLV-2 virus derived from infected B cells is highly enriched in HLA-II molecules, and pre-treatment of the virus with antibodies against HLA-II molecules restores the mitogenic potential of the virus for the hematopoietic precursors. This indicated that host-derived HLA-II molecules present in the viral envelope could block an important biological effect of the retrovirus, potentially involved in the extrinsic control of cell proliferation (33).

In an attempt to get further knowledge of the relationship between HLA-II molecules and retrovirus infection we investigated the role of HLA-II expression in infected cells.

The expression of HLA-II genes is regulated primarily at the level of transcription (34). The elucidation of the molecular defects at the basis of HLA-II deficiency in mutant somatic cells generated *in vitro* and in patients affected by the Bare Lymphocytes Syndrome (BLS), an inherited severe form of combined immunodeficiency (35), allowed the identification of four transacting factors, namely, RFX5, RFXAP, RFXB/RFXANK, and CIITA controlling the transcription of HLA-II genes. Thus, BLS is a prototypical disease of gene regulation with four complementation groups defined by defects in either one of these factors (36). Among them, CIITA (31, 37) plays a prominent role as the master regulator of the expression of HLA-II genes (38). In this respect, CIITA is therefore a crucial factor for the regulation of antigen presentation and of the activation of the adaptive immune response.

CIITA is a non DNA-binding transcriptional co-activator recruited to HLA-II promoters via multiple interactions with DNA-bound transcription factors, including the RFX and the NF-Y complexes (39-42). CIITA contains 1130 aminoacids and its N-terminal acidic region forms the transcriptional activation domain which binds components of the general transcriptional machinery and other co-factors with HAT activity (CBP, p300, PCAF, SRC-1) to promote HLA-II genes transcription (43-46). Moreover CIITA interacts with CARM1, a histone metyltransferase (47), and with BRG1, an ATP-dependent chromatin remodelling factor (48), favouring the accessibility of HLA-II promoter to transcription factors. CIITA controls the transition from transcription initiation to elongation by recruiting to HLA-II promoter the kinase CDK7, involved in promoter clearance (49) and, then, the kinase CDK9 of the positive transcription elongation factor-b (P-TEFb), that enhances transcriptional processivity of RNAPolII. The recruitment of CDK9 is mediated by the direct interaction of CIITA with CyclinT1, the other subunit of P-TEFb complex (50). P-TEFb is also used by Tat to promote the elongation of HIV-1 viral transcripts (51) and we have shown that sequestration of Cyclin T1 is the major mechanism by which CIITA blocks the transactivating function of Tat (25, 26).

HLA-II molecules are expressed constitutively on B cells and, after activation with a variety of stimuli, in other cell types including monocytes and T cells. All the above cell types may be targets of HTLV-2 infection. Thus, it seemed reasonable to investigate in more detail the role of both the HLA-II molecules and of their transcriptional regulator CIITA during the life cycle of the retrovirus. An experimental system was set up in which the initial reservoir for virus production was an isogenic cell system composed of the B-cell Raji, expressing large amounts of HLA-II molecules, and its HLA-II–negative derivative

RJ2.2.5, which has lost the expression of the entire repertoire of HLA-II genes because of a defect in the *AIR-1* locus (31, 52). We found that HTLV-2 productive infection was dramatically different in the two isogenic cells because Raji cells sustained very poorly viral replication, whereas RJ2.2.5 cells allowed a massive replication of the virus that resulted in extensive cell lysis (53), an event particularly rare in *in vitro* infection by HTLV-2. The cellular and molecular basis of this event was investigated by extending the HTLV-2 infection to other HLA-II-negative and HLA-II–positive cells both of the B- and T-cell type. Among the HLA-II-negative cells we included the crucial BLS-1 B cell line (54), which has a defect in the RFXANK expression and a normal CIITA expression (55). The results showed that all HLA-II-negative cell lines, with the exception of BLS-1, supported efficient viral replication, strongly indicating that the inhibition of HTLV-2 replication in HLA-II-positive lymphoid cell lines correlated with the presence of CIITA and not of HLA-II molecules (53).

Because CIITA targets the viral transactivator Tat to inhibit HIV-1 replication (26), we hypothesized that CIITA-mediated inhibition of HTLV-2 replication could be similarly due to the functional suppression of HTLV-2 Tax-2.

Indeed this was the case as CIITA strongly inhibits the Tax-2-mediated transactivation of the HTLV-2 LTR promoter, suggesting that this is the major, if not the exclusive, mechanism involved in the reduction of HTLV-2 productive infection in HLA-II-positive cells (53, 56).

As previously mentioned, CIITA inhibits Tat function through the squelching of Cyclin T1 of P-TEFb complex (26). This prompted us to determine if a similar sequestration of a critical cellular factor could account for the observed inhibition of Tax-2 by CIITA.

Several lines of evidence suggested that the histone acetyltransferases CBP, p300 and PCAF could be attractive candidates. First, they are used by both CIITA and Tax-1, the Tax-2 homologue of the HTLV-1 retrovirus, to activate the corresponding target promoters; second, their squelching seems to be a common mechanism by which CIITA mediates gene suppression (57-60). Our studies have shown for the first time that CBP and p300, but not PCAF, enhance Tax-2-directed LTR transactivation (56) and that direct sequestration of these HATs is not the primary mechanism by which CIITA causes suppression of Tax-2 function. The fact that PCAF, p300 and CBP are all essential for optimal LTR transactivation by Tax-1 (17, 18), substantiates the existence of important differences between HTLV-2 Tax-2 and HTLV-1 Tax-1. The different requirement for PCAF between the two viral transactivators also implies that Tax-1, but not Tax-2, might influence nuclear PCAF-containing complexes, potentially contributing to the pleiotropic deregulated expression of cellular genes during leukemogenesis. Relevant to this aspect it should be noted that Tax-1 mutants interacting poorly with PCAF exibit an impaired transactivation capacity and are defective for transformation (18, 61). The differential usage of co-activators with HAT activity between Tax-2 and Tax-1 is not unprecedented. Recently, it has been shown that while Tax-1 can use CBP or p300 for inhibiting p53, Tax-2 utilizes only CBP (62). In addition, it has been shown that Tax-1 transforms rat fibroblasts and inhibit p53 function more efficiently than Tax-2 (20, 21). These observations suggest that a selective usage of HATs in different transcriptional pathways could be responsible, at least in part, for the higher oncogenic potential of Tax-1 with respect to Tax-2.

Among the other cellular factors that are known to interact with both Tax-1 and CIITA, we focussed on the heterotrimeric NF-Y complex, whose B subunit has been shown to bind directly to Tax-1 both *in vivo* and *in vitro (*63). Our results demonstrated that over-expression of NF-Y inhibited Tax-2-dependent HTLV-2 LTR transactivation, in a way similar to the inhibition induced by physiological levels of CIITA. Since physiologic levels of NF-Y did not prevent either Tax-2-mediated LTR-driven gene expression or the replication of HTLV-2 virus it was suggested that NF-Y complex requires CIITA to contribute its inhibitory activity on Tax-2 (56).

This inhibitory action by CIITA and /or NF-Y could inhibit the recruitment of Tax-2 to the viral LTR promoter, or alternatively could still permit its recruitment to the LTR, but not its transcriptional activity, for example by masking the interacting surface for a transcription co-activator. Both hypotheses are presently under scrutiny.

Are the findings obtained in the HTLV-2 system applicable to HTLV-1 infection and, in particular, does CIITA inhibit Tax-1 function and HTLV-1 replication?

Preliminary results of our group (Tosi *et al.*, manuscript in preparation) indicate that CIITA inhibits Tax-1-mediated HTLV-1 LTR transactivation as well. Interestingly, the sequence of CIITA involved in the inhibition maps to the N-terminal region of the molecule and overlaps completely with the region responsible for the Tax-2 inhibition (56). A CIITA fragment encompassing the Tax-2 and Tax-1 inhibitory region is almost exclusively localized in the nucleus, suggesting a strict correlation between nuclear localization of CIITA and its capacity to inhibit Tax-1 and Tax-2 function.

Nevertheless, it will be interesting to assess whether CIITA deletion mutants containing the region inhibiting Tax, but having cytoplasmic localization, still interfere with Tax activity. This will be particularly relevant for Tax-2 that, in contrast with Tax-1, shows a predominant cytoplasmic accumulation (64). In this regard, our previous results have shown that BLS2 cell line expressing a cytoplasmic mutant form of CIITA that contains the minimal region inhibiting Tax-2, is less permissive to HTLV-2 productive infection than CIITA-negative RJ.2.2.5 (53).

It is important to underline that the specific sequence involved in the inhibition of Tax-1 and Tax-2 is different from the sequence involved in the inhibition of HIV-1 Tat function (Tosi *et al.*, unpublished data), further

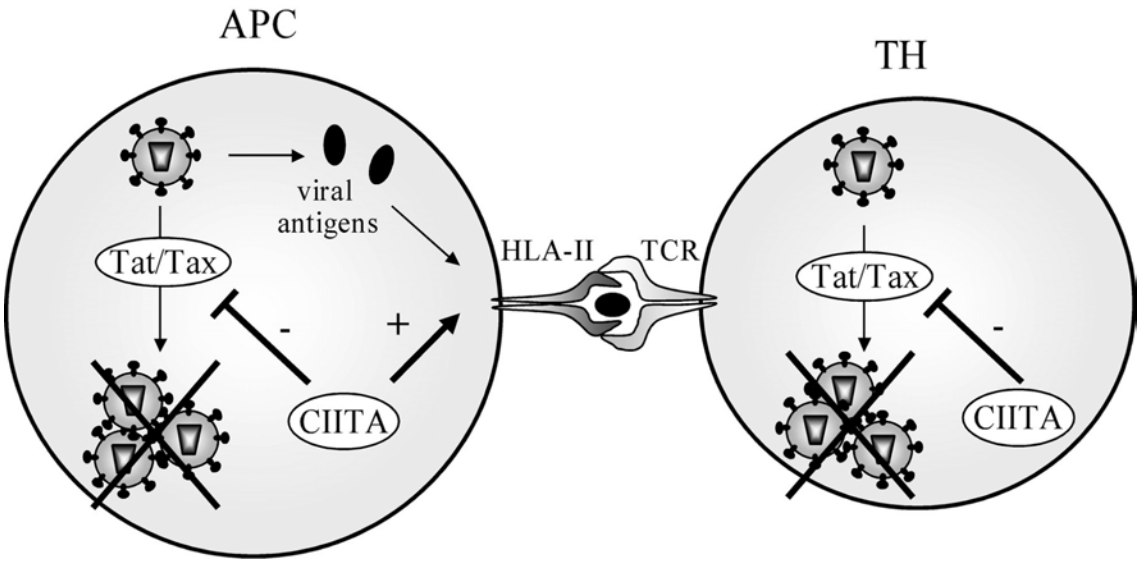

Figure 1. Schematic representation of the dual function exerted by CIITA to counteract HIV-1/HTLV retroviral infections and spreading. From one side, CIITA induces (+) the expression of HLA-II molecules and, thus, increases the antigen presenting function of APC cells for viral antigens. From the other side, it suppresses (-) the viral replication by inhibiting the transcriptional activity of the viral activators Tat and Tax both in APC and TH cells.

emphasizing that CIITA inhibits oncogenic retroviral Tax transactivators and HIV-1 Tat transactivator trough distinct molecular mechanisms. Moreover, distinct post-translational modification of CIITA, such as dimerization, phosphorylation and acetylation (49, 65), could potentially affect its capacity to inhibit Tax and Tat transactivators. Experiments are now in progress to assess whether the CIITA-dependent Tax-1 inhibition may affect the HTLV-1 viral replication as well. Additional preliminary experiments suggest that excess of NF-Y complex may also inhibit Tax-1-mediated HTLV-1 LTR transactivation, thus closely mimicking the situation observed in the control of HTLV-2 LTR transactivation.

It has been shown that NF-Y-Tax-1 interaction activates transcription from HLA-II DQB promoter in gene reporter assays performed in Jurkat T cells (63). It must be stressed that NF-Y complex is necessary but not sufficient for HLA-II gene expression, which absolutely requires the presence of CIITA. The reasons for this Tax-1-mediated transcriptional activation of HLA-II genes in Jurkat T cells, which do not express constitutive CIITA (26), are presently unknown and require further investigations.

Recently the Brady's group reported the interesting finding that HTLV-1 Tax-1 interacts with the P-TEFb complex via Cyclin T1, and recruits CDK9 to the viral LTR stimulating HTLV-1 transcription (66, 67). This finding suggests that the use of P-TEFb complex may be a common theme to facilitate processivity and elongation of viral genomes for both oncogenic retroviruses and lentiviruses. CIITA inhibits HIV-1 replication by competing with Tat for Cyclin T1 of P-TEFb complex (26), although it inhibits HTLV-2 Tax-2 and HTLV-1 Tax-1 by an apparently distinct mechanism. It will be interesting to assess whether part of CIITA inhibitory action on Tax transactivators may also be ascribed to its competitive recruitment of Cyclin T1.

4. PERSPECTIVE

The expression of HLA-II genes which is fundamental to trigger the adaptive immune effector mechanisms counteracting retroviral infections is under the control of the transcriptional activator, CIITA.

Besides its classical role, we have shown that CIITA plays also an important role against human retroviruses. It inhibits viral replication by blocking specifically the function of the viral transactivators, HIV-1 Tat and HTLV-2 Tax-2 (Figure 1). Since CIITA blocks also HTLV-1 Tax-1 activity, it is possible that it may interfere also with HTLV-1 replication. In this newly discovered and unexpected role, CIITA might represent an innate immunity mechanism of the host cells to counteract viral spreading.

We do not know whether this innate role of CIITA is a more recent acquisition with respect to its transcriptional function, but it is suggestive that CIITA has been included as a member in the NOD-LRR/CATERPILLAR family of proteins that are involved in inflammation and innate immunity against bacteria, viruses and fungi (68, 69).

Further investigation on the dual function of CIITA in retrovirus infection will shed new light on the molecular mechanisms of adaptive co-evolution of hosts and pathogens and will help substantially in tailoring new therapeutic strategies aimed at inhibiting retroviral replication. Within this frame, the importance of obtaining

a sustained and persistent expression of CIITA in retrovirus infected cells should stimulate the search for potential synthetic and natural mediators, drugs and bio-molecules that can act on CIITA expression.

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Abbreviations: HTLV-1 and HTLV-2, human T cell leukemia virus type 1 and type 2; CIITA, class II transactivator; HLA, human leukocyte antigens; RFX, regulatory factor X; NF-Y, nuclear factor Y; BLS, bare lymphocyte syndrome; HAT, histone acetyltransferase; CREB, cAMP response element binding protein; CBP, CREB-binding protein; PCAF, p300-CBP-associated factor; BRG1, brahama-related gene 1; SRC1, steroid receptor co-activator 1; CARM1, co-activator associated arginine methyltransferase 1

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