Biochimica et Biophysica Acta 1799 (2010) 266–274

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagrm

Review

The HTLV-1 Tax protein: Revealing mechanisms of transcriptional activation through histone acetylation and nucleosome disassembly

Jennifer K. Nyborg *, Dinaida Egan, Neelam Sharma

Department of Biochemistry and Molecular Biology, Campus Box 1870, Colorado State University, Fort Collins, CO 80523-1870, USA

ARTICLE INFO

Article history:
Received 24 April 2009
Received in revised form 11 September 2009
Accepted 12 September 2009
Available online 25 September 2009

Keywords:
HTLV
Tax
Nucleosome eviction
Histone acetylation
Chromatin
CBP
p300
CREB

ABSTRACT

The human T-cell leukemia virus, type-1 (HTLV-1)-encoded Tax protein is required for high-level transcription of the virus. Tax function is strictly dependent upon the phosphorylated form of the cellular transcription factor CREB (pCREB), and together they bind novel cAMP response elements located within the viral promoter. The DNA-bound Tax/pCREB complex recruits the cellular coactivators CBP/p300, which are essential for viral gene expression. The coactivators, via their histone acetyltransferase activity, function to promote changes in chromatin architecture that are permissive to transcriptional activation. Tax expression in vivo recruits p300 to the HTLV-1 promoter and correlates with depletion of nucleosomes from the integrated provirus. We recently developed a novel in vitro, chromatin-based experimental system that recapitulates the eviction of nucleosomes from the HTLV-1 promoter observed in vivo. These assays establish the essential function of Tax/pCREB recruitment of CBP/p300, and concomitant histone acetylation, in the nucleosome disassembly process. These observations are of particular significance, as Tax mediates disassembly of the full nucleosome octamer independent of transcriptional activity and ATP utilization. Instead, nucleosome eviction is absolutely dependent upon acetyl CoA and the histone chaperone Nap1. In this review, we will discuss HTLV-1, Tax transactivation, and our recent findings that uncover the critical role of Tax in promoting chromatin transitions that accompany activation of viral transcription. We will describe the phenomenon of acetylation-dependent promoter nucleosome disassembly and the emerging view that the formation of nucleosome-free promoter regions may represent a general prerequisite for transcriptional activation in eukaryotes.

1. Introduction

In the nucleus of a eukaryotic cell, DNA is organized into a highly compacted structure called chromatin. Chromosomal DNA wraps around a protein octamer composed of the histone H2A/H2B dimer and the histone H3/H4 tetramer to form a nucleosome, the basic unit of chromatin [1,2]. Arrays of nucleosomes and other chromatin-associated proteins cooperate to compact and organize chromosomal DNA to fit into the nucleus, profoundly impacting genome accessibility and resulting in strong repression of gene expression. For example, the presence of a nucleosome near the start site of a gene physically hinders the binding of the large RNA polymerase-containing pre-initiation complex, resulting in transcriptional repression. To achieve highly regulated gene expression, the transcription machinery must utilize strategies that enable access to genes packaged into this dense chromatin environment. These molecular mechanisms are highly complex and poorly understood.

Retroviruses serve as outstanding model systems for the study of gene regulation in a chromatin context in higher eukaryotes. Following infection, the retroviral DNA genome stably and permanently integrates into a host-cell chromosome to form the provirus (Fig. 1). During this process, the proviral DNA is assembled into nucleosomal arrays that package and compact the viral genome such that the provirus is indistinguishable from a cellular gene and is regulated in an analogous manner. Because chromosomal integration is an obligatory event in the retroviral life cycle, these viruses have evolved highly efficient mechanisms to potently activate transcription (and thus viral replication) from compacted chromatin.

The human T-cell leukemia virus, type 1 (HTLV-1) is a clinically relevant retroviral model for both in vivo and in vitro studies on eukaryotic transcriptional activation in a chromatin context. Expression of the HTLV-1-encoded Tax protein is required for high-level transcription of the provirus [3–6]. As such, the Tax protein must have evolved a highly efficient mechanism to convert the provirus from a chromatin-dense, transcriptionally repressed state into an open, transcriptionally competent state. Recent studies have utilized in vivo and chromatin-based in vitro binding and transcription assays to significantly advance our understanding of Tax function in the

* Corresponding author. Tel.: +1 970 491 0420; fax: +1 970 491 0494.
E-mail address: Jennifer.Nyborg@ColoState.Edu (J.K. Nyborg).

1874-9399/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbagrm.2009.09.002

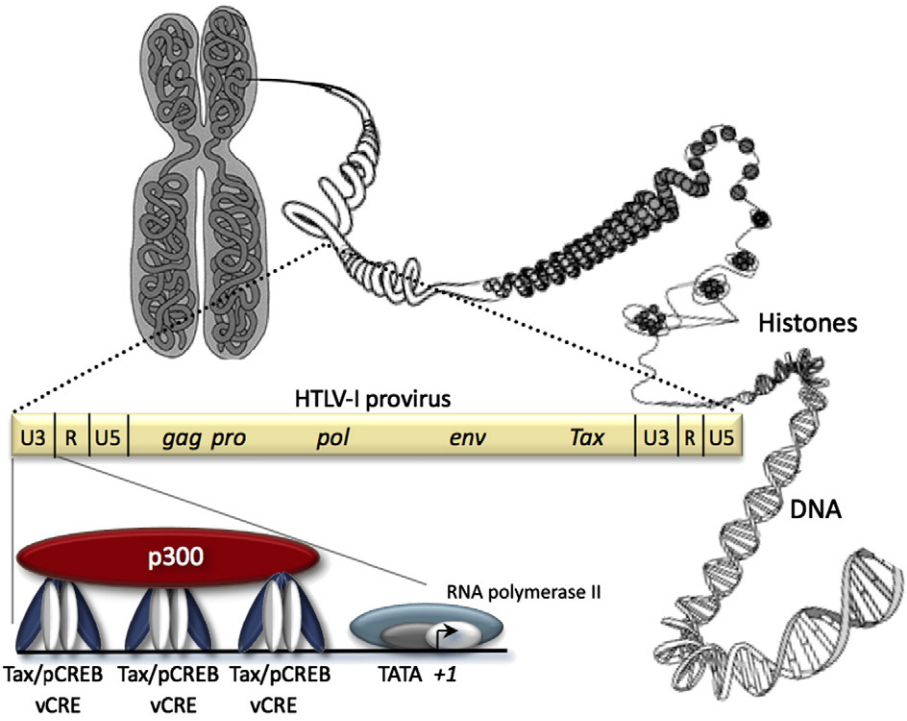

Fig. 1. Schematic of the chromosomally integrated HTLV-1 provirus. The viral promoter (U3 region) is expanded to show Tax/pCREB binding the vCREs and recruitment of the coactivator p300. However, the chromasomally-integrated provirus is assembled into nucleosomes and highly compacted into dense, higher-order chromatin structure.

transition of the proviral promoter into a transcriptionally-competent state [7–16].

To achieve this transition, which is associated with subsequent high-level expression of the virus, Tax works in concert with the phosphorylated form of the cellular transcription factor CREB and the cellular histone acetyltransferases CBP/p300 (Fig. 1). Notably, we recently found that Tax recruitment of CBP/p300 promotes histone acetylation concomitant with reduced nucleosome density at the HTLV-1 promoter in vivo and in vitro [14,16]. These observations indicate that Tax is required for promoting histone acetylation and nucleosome eviction, supporting the emerging hypothesis that acetylation-dependent promoter nucleosome disassembly is a pre-requisite for strong transcriptional activation.

In this review, we will discuss Tax activation of transcription from chromatin-assembled templates carrying the HTLV-1 promoter. This experimental system continues to serve as an outstanding tool for dissecting the molecular mechanisms of acetylation-dependent chromatin dynamics and the formation of transcriptionally-competent nucleosome-free regions. We will begin with a brief overview of HTLV-1-associated disease, viral replication, and viral infectivity. We will then describe the function of Tax as potent activator of HTLV-1 transcription, with specific emphasis on the role played by Tax in the orchestration of CBP/p300-mediated histone acetylation and the attendant chromatin dynamics that lead to nucleosome disassembly and transcriptional activation.

2. Clinical and molecular features of HTLV-1

HTLV-1 is a complex retrovirus that is the causative agent of multiple disparate diseases including a malignancy of T-lymphocytes called adult T-cell leukemia/lymphoma (ATLL) and a chronic inflammatory disease that is referred to as both tropical spastic paraparesis (TSP) and HTLV-1 associated myelopathy (HAM), commonly called TSP/HAM (for review, see [17]). The majority of infected individuals remain lifelong asymptomatic carriers, despite the fact that up to 70% of CD4+ T-cells carry integrated provirus [18,19]. ATLL is a highly aggressive malignancy that has a rapid clinical course, is refractory to chemotherapy and radiation treatment, and is invariably fatal [17,20]. The disease presents clinically with skin lesions (due to infiltrating leukemic cells), lytic bone lesions, and greater than 5% abnormal T-cells with large, multi-segmented nuclei. At the molecular level, ATLL is characterized by the presence of a chromosomally integrated HTLV-1 provirus present in aneuploid T-cells [21–24]. Expression of the HTLV-1 encoded Tax protein plays an essential role in the etiology of TSP/HAM, and is directly linked to malignant transformation [24].

The initial transmission of HTLV-1 to an uninfected individual occurs via cell–cell contact vertically, sexually, or through exposure to contaminated blood products. However, following infection, numerous lines of evidence implicate mitotic replication as the major route of viral expansion within the infected individual. Support for mitotic replication of the retrovirus includes (i) the near absence of extracellular virions, (ii) a high proportion of CD4+ T-cells carrying integrated provirus, (iii) low sequence variation of the provirus (e.g., viral replication via host cell DNA polymerase), and (iv) the ineffectiveness of reverse transcriptase inhibitors on reduction of proviral loads [25,26]. Together, these data support a dominant mechanism of proviral transmission in an infected individual via clonal expansion of T-cells carrying the provirus.

T-cell proliferation positively correlates with Tax expression, and individuals with the highest proviral load also express the highest levels of Tax [18,19,27]. As such, it is not surprising that in a small percentage of infected individuals, persistent proliferation of infected T-cells leads to the emergence of a dominant T-cell clone carrying the malignant phenotype [28]. Once transformed, however, the malignant ATLL cells acquire the ability to aggressively proliferate, often in the absence of Tax expression [29] (Fig. 2). Consistent with these observations, several studies have shown that in primary ATL leukemic cells and ATL cell lines the DNA within the 5′ LTR is hypermethylated, resulting in transcriptional silencing of the HTLV-1 provirus, and consequently the expression of Tax [30–32]. These studies support the hypothesis that Tax is required for the acquisition of genetic and epigenetic changes that occur during progression of the infected T-cell to the leukemic state. However, once transformation is