BIOCHEMICAL PHARMACOLOGY 72 (2006) 1570–1576

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# Epigenetic silencing of *MHC2TA* transcription in cancer

*Tjadine M. Holling* [a], *Marja C.J.A. van Eggermond* [a], *Martine J. Jager* [b], *Peter J. van den Elsen* [a,c,*]

[a] *Division of Molecular Biology, Depart of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands*
[b] *Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands*
[c] *Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands*

ARTICLE INFO

*Article history:*
Received 15 May 2006
Accepted 23 June 2006

*Keywords:*
Major histocompatibility complex class II
Class II transactivator
Cancer
Gene regulation
DNA methylation
Histone modification

ABSTRACT

Lack of expression of major histocompatibility complex (MHC) molecules of both classes is frequently noted on tumour cells [1]. It is thought that in this way tumour cells escape immunosurveillance. The genes encoding both classes of MHC molecules are localized on the distal part of chromosome 6 (6p21.3). The class II transactivator (CIITA), encoded by the *MHC2TA* gene, is essential for transcriptional activation of all *MHC-II* genes, while it has a helper function in the transcriptional regulation of *MHC-I* genes (with the exception of human leukocyte antigen (*HLA*)-*G*) and of the gene encoding β2-microglobulin (β2*m*) [2]. Here we discuss our current knowledge on the expression characteristics of *MHC2TA* and argue for an important role of epigenetic factors and mechanisms in the transcriptional silencing of *MHC2TA* in cancer cells.



## 1. MHC-II function and regulation

*MHC-II* genes encode the polymorphic human leukocyte antigen (HLA)-DR, -DQ and -DP glycoprotein's, which are expressed as αβ heterodimers on the cell surface. MHC-II molecules play an essential role in the initiation of antigen-specific immune responses by virtue of their ability to present antigenic peptides to the T-cell receptor (TCR) of $CD4^+$ T lymphocytes [3,4]. Constitutive expression of MHC-II molecules therefore is normally restricted to specialized antigen-presenting cells (APCs) of the immune system, while on other cell types their expression can be induced by various inflammatory cytokines [5,6]. Inactivation of *MHC-II* genes therefore may be one of the mechanisms through which cells create an immune privilege and through which tumours may escape recognition by the host immune system.

Studies with cell lines established from patients with an MHC-II deficiency, also referred to as bare lymphocyte syndrome (BLS), have revealed that the absence of MHC-II molecule expression in these patients is not due to mutations in the genes encoding MHC-II molecules but due to mutations in transcription factors that regulate MHC-II expression [7]. A schematic overview of the elements and factors critical for activation of MHC-II promoters is presented in Fig. 1. Mutations have been described in individual components of the RFX complex (consisting of RFX5, RFXB/ANK and RFXAP) or CIITA, which account for the observed deficiency in MHC-II molecule expression [8]. Several studies have demonstrated that the RFX complex binds in a mutual cooperative fashion with the transcription factors CREB/ATF, and NFY to the SXY-module found in all *MHC-II* and accessory genes (i.e. *invariant chain*, *HLA-DM* and *HLA-DO*) [9]. This multiprotein complex bound to

* *Corresponding author*. Tel.: +31 71 5263831; fax: +31 71 5216751.
E-mail address: pjvdelsen@lumc.nl (P.J. van den Elsen).
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doi:10.1016/j.bcp.2006.06.034

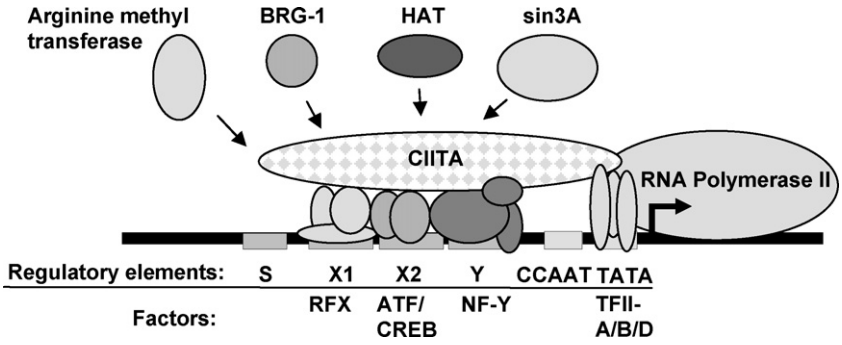


**Fig. 1 – Elements and factors governing *MHC-II* gene transcription. Shown is the conserved SXY-module, which is bound by the multiprotein complex comprised of RFX, CREB/ATF and NF-Y. CIITA binds to this multiprotein complex bound to the SXY-module through interactions with RFX5, RFXB/ANK, CREB, NF-YB and NF-YC and acts as a platform for recruitment of various chromatin remodelling activities.**

the SXY-module acts as an enhanceosome in the transcriptional activation of *MHC-II* genes. The SXY-module is also present in the promoters of *MHC-I* (with the exception of *HLA-G*) and *β2m* genes [10]. However, binding of this multiprotein complex to the SXY-module is not sufficient for MHC-II expression. Transcriptional activation of *MHC-II* genes requires the recruitment of CIITA to the MHC-enhanceosome [11–13]. On one hand, CIITA interacts with most of the components of the MHC-enhanceosome, and on the other hand also interacts with components of the basal transcription initiation complex. In this way CIITA connects the enhanceosome with the gene transcription initiation machinery [14–16]. Of the four transcription factors essential for *MHC-II* transcriptional activation, which were identified through the analysis of BLS-derived cell lines, only CIITA has the same restricted expression pattern as MHC-II and therefore is considered to be the master-regulator for *MHC-II* gene expression [17].

The transcriptional regulation of *MHC2TA* is controlled by a 14 kb multi-promoter region that harbours four-independent promoter units (Fig. 2A) [18]. Of these promoters, CIITA-PIV has been shown to be the promoter predominantly involved in IFNγ-inducible *MHC2TA* expression in human non-haematopoietic cells, such as fibroblasts and epithelial cells [18,19]. Promoter PI (CIITA-PI) is solely utilized for the expression in dendritic cells (DCs), whereas PIII (CIITA-PIII) is active in B-cells, DCs, monocytes and in activated human T-cells [18–22]. In addition to CIITA-PIV, IFNγ can also activate the CIITA-PIII

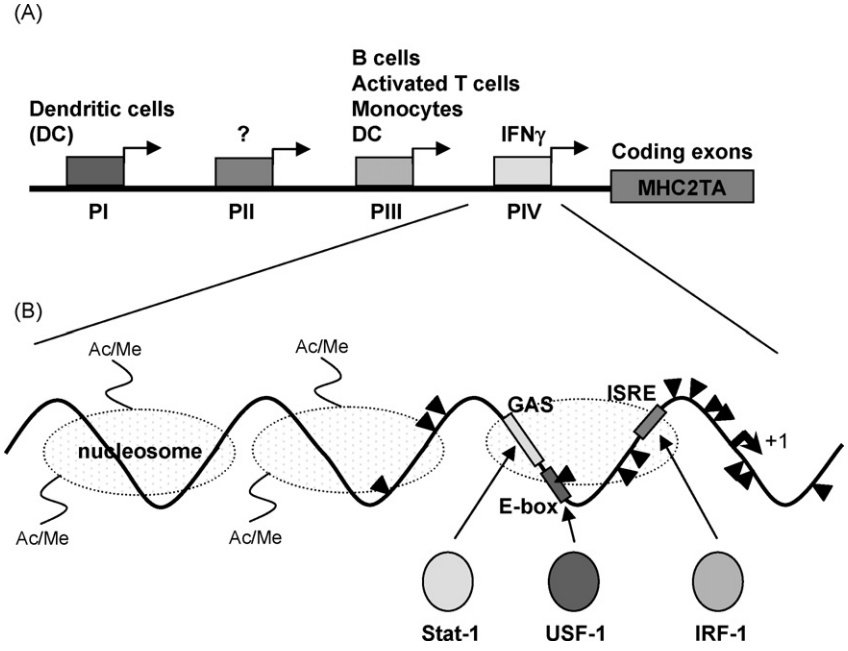


**Fig. 2 – (A) Genomic organisation of the 14 kb *MHC2TA* multi-promoter region, encompassing CIITA-PI, -PII, -PIII and -PIV. (B) Factors and elements critical for IFNγ-mediated activation of CIITA-PIV. Stat-1 and USF-1 bind in a cooperate fashion to the GAS and adjacent E-box, while IRF-1 interacts with the ISRE. The positions of the various CpG dinucleotides analyzed in our studies are indicated by arrow heads. Ac/Me represent histone tail modifications evaluated by ChIP and include histone H3-triple methylated lysine 27 and acetylated histones H3 and H4.**