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Review

The MHC class II transactivator CIITA induction as a potential new tool to develop anti-tumor vaccines and predict the efficacy of immunotherapy

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ABSTRACT

The MHC class II transactivator (CIITA) is the master regulator of MHC class II (MHC-II) genes expression. In fact, it promotes both constitutive and interferon gamma-inducible expression of all MHC-II genes and thus regulates the optimal activation of adaptive immunity, which depends on the proper activation of $CD4^+$ T helper cells. In this review we will briefly discuss the role and regulation of CIITA and the downstream expression of MHC-II in adaptive immunity, followed by a discussion of how the induction of CIITA and MHC-II expression in tumor cells of different histological origins can make them surrogate antigen presenting cells for their own tumor antigens, thereby enabling them to elicit a protective adaptive anti-tumor immune response. Based on this concept, we will discuss possible strategies to use CIITA-driven MHC-II-positive tumor cells to unveil tumor antigens and develop different types of anti-tumor vaccines, including CIITA-based vaccination strategies. We will also address the

Abbreviations: AAD, Acidic activation domain; AAV, Adeno-associated virus; ACSL4, Acyl-CoA synthetase long chain family member 4; Ad5, Adenoviral serotype 5; AIR-1, Activator of immune response genes-1; AML, Acute myeloid leukemia; APC, Antigen presenting cells; ARE-1/2, Activation responsive element 1/2; ATF1, Activating transcription factor 1; BAP1, BRCA1 associated protein 1; BLIMP-1, Transcription factor B lymphocyte-induced maturation protein-1; BLS-II, Bare lymphocyte syndrome type II; CBP, CREB-binding protein; CDK7, Cyclin-dependent kinase 7; ChIP, Chromatin immunoprecipitation; CIITA, MHC class II transactivator; CNS, Central nervous system; COVID-19, Coronavirus disease 2019; CpG, Cytosine-phosphate-guanine; CREB, cAMP response element-binding protein; CTA, Cancer testis antigens; CTL, T cytotoxic cells; CTLA4, Cytotoxic T-lymphocyte antigen 4; DC, Dendritic cells; DHA, DNA hypomethylating agents; DNMT, DNA methyltransferases; DNMTi, DNMT inhibitors; E-box, Enhancer box; EBV, Epstein-Barr virus; EHMT2, Euchromatic histone-lysine *N*-methyltransferase 2; EZH2, Enhancer of zeste homolog 2; FBXO11, F-box protein 11; FCRL6, Fc receptor-like 6; FDA, Food and Drug Administration; GAS, IFN-γ-activated; GBM, Glioblastoma; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GNLY, Granulysin GZMA/B/H/K, Granzymes A/B/H/K; H2K119Ub, Ubiquitination of histone H2 lysine 119; H3K4me3, Trimethylation of histone H3 lysine 4; H3K27ac, Acetylation of histone H3 lysine 27; H3K27me3, Trimethylation of histone H3 lysine 27; HAT, Histone acetyltransferases; HBV, Hepatitis B virus; HDAC, Histone deacetylases; HDAC1/2, Histone deacetylase 1/2; HDACi, HDAC inhibitors; HERV, Human endogenous retroviruses; HIV-1, Human immunodeficiency virus 1; HMGB1, High mobility group box 1; HMT, Histone methyltransferases; HMTi, HMT inhibitors; HTLV-1/2, Human T cell leukemia virus 1/2; ICI, Immune checkpoint inhibitors; IFN-γ, Interferon gamma; IFN-I, Type-I interferons Ii; Invariant chain, IL-4/10/13/15, Interleukins-4/10/13/15; IRF-1, IFN-regulatory factor 1; IRF-E, IRF-element; KDM1A, Lysine-specific histone demethylase 1A; KMT, Lysine methyltransferases; KMT2A, Lysine methyltransferase 2A; LAG-3, Lymphocyte-activation gene 3; lncRNA, Long non-coding RNA; LNP, Lipid nanoparticles; LRR, Leucine-rich repeat domain; LV, Lentiviral vectors; MAP1LC3C, Microtubule associated protein 1 light chain 3 gamma; MDM2, Mouse double minute 2 homolog; MEN1, Menin; MHC, Major histocompatibility complex; MHC-I/II, MHC class I/II; miRNA, MicroRNA; MS, Mass spectrometry; NACHT, Nucleotide-binding domain; NFAT5, Nuclear factor of activated T-cells 5; NF-YA/B/C, Nuclear transcription factor YA/B/C; NK, Natural killer; NKG7, Natural killer cell granule protein 7; NLRC5, NOD-like receptor family CARD domain containing 5; NLRC5-SA, NLRC5-superactivator; NPM1, Nucleophosmin; NSG, NOD scid gamma mice; P/S/T, Proline-, serine-, and threonine-rich domain; P-TEFb, Positive transcription elongation factor-b complex; P27KIP1, Cyclin dependent kinase inhibitor 1B; PBMC, Peripheral blood mononuclear cells; PCAF, P300/CBP-associated factor; PD-1, Programmed cell death protein 1; PD-L1, Programmed cell death ligand 1; pI/II/III/IV, Promoters I/II/III/IV; PRC1/2, Polycomb repressive complex 1/2; PRF1, Perforin-1; PRMT, Protein arginine *N*-methyltransferases; PRMT4, Protein arginine *N*-methyltransferase 4; RCOR2, REST corepressor 2; RFX-5/ANK/AP, Regulatory factor X-5/ANK/AP; RNF2, Ring finger protein 2; SARSr-CoV, Severe acute respiratory syndrome-related Coronaviruses; SE, Super-enhancers; SLAMF7, Signaling lymphocyte activation molecule family 7; SMARCA4, SWI/SNF related BAF chromatin remodeling complex subunit ATPase; SRC-1, Steroid receptor coactivator-1; STAT1, Signal transducer and activator of transcription 1; TAA, Tumor-associated antigens; TAF1, Transcription initiation factor TFIID subunit 1; TBP, TATA-binding protein; TCR, T-cell receptors; TEC, Thymic epithelial cells; TEX, Tumor-derived exosomes; TF, Transcription factors; TFIID/B, Transcription factor II D/B; TGF-β, Transforming growth factor beta; Th, T helper cells; TIL, Tumor-infiltrating lymphocytes; TMB, Tumor mutational burden; TME, Tumor microenvironment; TNF-α, Tumor necrosis factor-α; TP53, Tumor protein P53; Treg, Regulatory T cells; TSA, Tumor-specific antigens; USF-1, Upstream transcription factor 1; XL, X-like; ZBTB48, Zinc finger and BTB domain containing 48..

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major challenges associated with *in vivo* CIITA delivery and critically discuss the apparently conflicting preclinical evidence obtained in glioblastoma models. Finally, we will highlight the potential of epigenetic drugs to directly induce CIITA-driven MHC-II-positive tumor cells capable of stimulating the immune system and discuss the potential of CIITA and MHC-II expression as predictive markers of response to immunotherapy, thereby providing a rationale for combining CIITA-inducing strategies with immune checkpoint inhibitors for future human clinical setting.

1. Introduction

1.1. CIITA and the adaptive immune response

The MHC class II transactivator (CIITA) is the major transcriptional coordinator of the major histocompatibility complex (MHC) class II (MHC-II) genes. CIITA was discovered in 1980s on the locus designed as activator of immune response genes-1 (AIR-1), mapped on the chromosome 16 both in mouse and in human (Accolla, 1983; Accolla et al., 1986). CIITA promotes both constitutive and interferon gamma (IFN-γ)-inducible expression of all MHC-II genes (Steimle et al., 1994) and regulates the expression of other important genes necessary for MHC-II transport to endosomal compartments and loading of peptides, including the invariant chain (Ii), MHC-DM and MHC-DO, in addition to enhance the constitutive expression of MHC class I (MHC-I) genes (Devaiah and Singer, 2013). MHC-II molecules are constitutively expressed only in a few cell types such as thymic epithelial cells (TEC), activated T cells and professional antigen presenting cells (APC), including B cells, macrophages, and dendritic cells (DC), in comparison to MHC-I molecules, which are expressed in almost all nucleated cells, including many types of tumor cells (LeibundGut-Landmann et al., 2004). However, tumor cells can also constitutively express MHC-II molecules depending by their histological origin and due to genetic dysregulations (Zeng et al., 2022). MHC-II molecules can be also induced after stimulation with IFN-γ both in tumor cells and in non-haemopoietic cells. Normally, professional APC present antigens to $CD4^+$ T helper cells (Th), which recognize them *via* their T-cell receptors (TCR), only if the antigens are presented within the context of MHC-II molecules expressed on the surface of APC, loaded in endosomal compartments (Rock et al., 2016). Different from MHC-I molecules that

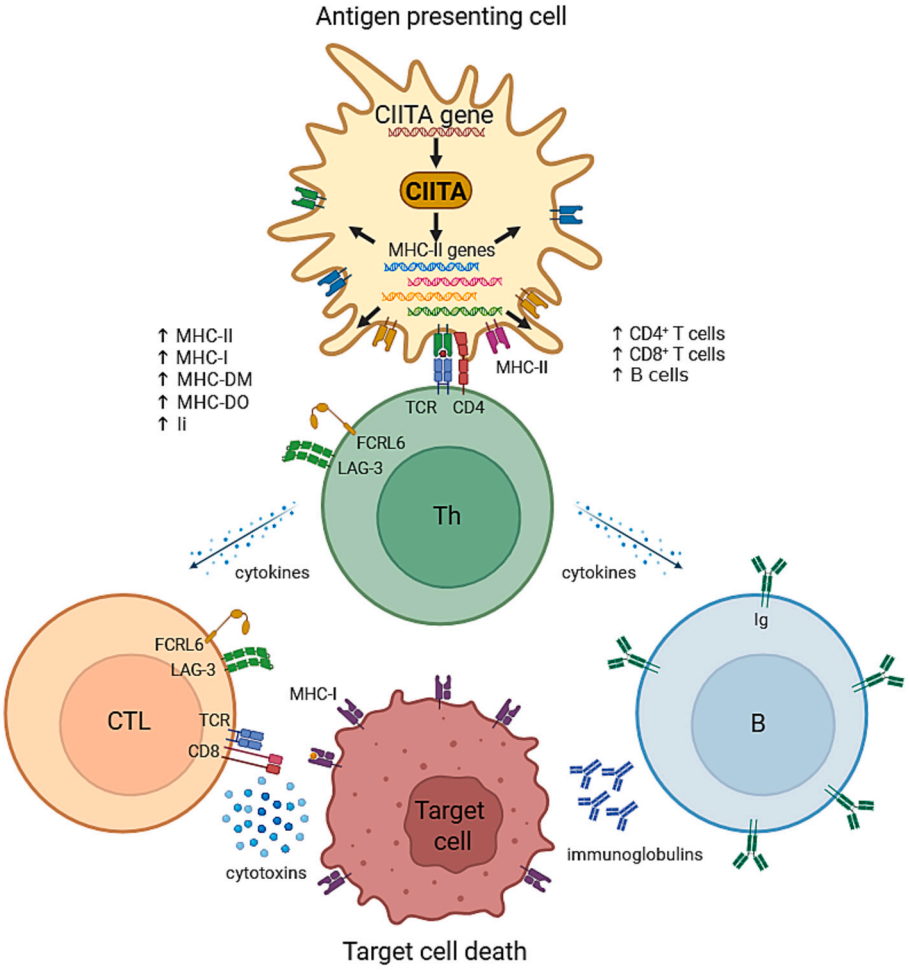


Fig. 1. CIITA-dependent regulation of antigen presentation and adaptive immunity. In professional APC, CIITA coordinates the expression of MHC-II and associated components of the antigen-processing and presentation machinery, including MHC-DM, MHC-DO, and Ii, while also contributing to MHC-I expression. MHC-II-mediated antigen presentation promotes $CD4^+$ Th cell activation, which supports both $CD8^+$ CTL responses and B cell activation through cytokine-mediated signals. CTL recognize MHC-I-presented antigens on target cells and mediate cytotoxic killing, whereas activated B cells contribute to humoral immunity through immunoglobulin production. Inhibitory receptors such as LAG-3 and FCRL6 expressed on T cells, may interact with MHC-II molecules, thereby potentially delivering inhibitory signals and modulating the adaptive immune response. Created in BioRender.com.

present peptides derived from the processing of endogenously synthesized proteins, MHC-II molecules usually present peptides derived from the digestion of exogenous proteins and, to a lesser extent, those deriving from endogenous proteins (Rudensky et al., 1991; Chicz et al., 1993). Anyway, after antigen presentation, activated Th stimulate the clonal expansion and activation of B cells and $CD8^+$ T cytotoxic cells (CTL), which are the major effectors of adaptive immune responses. Thus, CIITA regulates the optimal activation of adaptive immunity (Fig. 1). Because of this, MHC-II-restricted peptides tend to be less expressed by tumors under pressure of immune surveillance (Marty Pyke et al., 2018). Recently, it was shown that CIITA is also involved in the intrinsic immunity (Bieniasz, 2004), playing a crucial role as restriction factor for human retroviruses such as human immunodeficiency virus 1 (HIV-1) (Forlani et al., 2016), human T cell leukemia virus 1 and 2 (HTLV-1/2) (Forlani et al., 2013) and other viruses such as Ebola, severe acute respiratory syndrome-related Coronaviruses (SARSr-CoV) and hepatitis B virus (HBV) (Bruchez et al., 2020; Dezhbord et al., 2024; Park and Miyano, 2025), demonstrating its pivotal role in the immune system.

1.2. Regulation and expression of CIITA

The genetic and epigenetic regulation of CIITA expression, as well as the expression of MHC-II molecules, has been widely studied in the past. The constitutive and the inducible expression of MHC-II molecules depends by the constitutive and inducible expression of CIITA. This gene is regulated by four different promoters known as I,II,III, and IV (pI/II/III/IV), which do not share sequence homology (Muhlethaler-Mottet, 1997). pII is found only in human gene and presents low transcriptional activity, even if recently it is demonstrated its enhanced activation by the aryl hydrocarbon receptor (Jin et al., 2026), whereas pI, pIII and pIV are conserved between mouse and human gene and have the main transcriptional activity. These promoters control the transcription of different mRNA coding isoforms characterized by a common general structure comprising: an acidic activation domain (AAD), a proline-, serine-, and threonine-rich domain (P/S/T), a nucleotide-binding domain (NACHT), and a leucine-rich repeat domain (LRR). These isoforms differ only in the N-terminal region: a) isoform of 132KDa induced by pI; b) isoform of 124 KDa induced by pIII; c) isoform of 121 KDa, starting from a common second exon shared by the other isoforms, induced by pIV. pI and pIII are constitutive active in APC, promoting the constant expression of CIITA and consequently that of MHC-II molecules. However, both promoters can be partially induced by IFN-γ. pI is active in cells of myeloid origin such as conventional DC and macrophages (Nickerson et al., 2001). pIII is active in B cells, plasmacytoid DC and human activated T cells (Lennon et al., 1997). pIV is the inducible promoter of CIITA, which promotes its expression in non-professional APC after IFN-γ stimulation. The signal transducer and activator of transcription 1 (STAT1), upstream transcription factor 1 (USF-1) and IFN-regulatory factor 1 (IRF-1) are the three transcription factors (TF) recruited on pIV, which bind to the IFN-γ-activated site (GAS), the enhancer box (*E*-box) and the IRF-element (IRF-E), respectively. STAT1 binds the promoter within 5–30 min, followed by IRF-1 which depends on STAT1, whereas USF-1 binds the promoter independently by IFN-γ (Morris et al., 2002). Distal regulatory elements are also involved in CIITA expression, inducing chromatin loops which promote protein interactions. At the same time, pIV can be repressed by several cytokines such as transforming growth factor beta (TGF-β) and interleukins 4,10, and 13 (IL-4/10/13) (O'Keefe et al., 1999). Related to its kinetics, mRNA of CIITA appears in 90–120 min after stimulation, increasing in 3–4 h and reaching the peak at 24 h. However, the protein has a short half-life of about 30–45 min (Schnappauf et al., 2003). This is due to the N-terminal region, in which the AAD is responsible for CIITA rapid degradation but at the same time important for its transactivation (Schnappauf et al., 2003; Beaulieu et al., 2016), as well as the ubiquitation of P/S/T mediated by the ubiquitin ligase F-box protein 11 (FBXO11), belonging to F-box family, causing CIITA proteasome-dependent degradation (Chan et al., 2022; Kasuga et al., 2023).

CIITA is finely regulated epigenetically, since its expression is cell-specific and plays a crucial role in coordinating the adaptive immune response (Wright and Ting, 2006). Little is known about the regulation of pI. Immature DC express CIITA and synthetize MHC-II, but during maturation, pI is silenced due to loss of histone acetylation and the involvement of chromatin remodeling complexes, even if accompanied by an increase in antigen-presenting capacities (Landmann et al., 2001). The nuclear factor of activated T-cells 5 (NFAT5) is involved in the activation of pI in macrophages after binding a distal element (Buxadé et al., 2018). Chromatin remodeling is also involved in pIII regulation. It is known that B cells, after activation and differentiation in plasma cells, do not express CIITA due to the involvement of the transcription factor B lymphocyte-induced maturation protein-1 (BLIMP-1), which in turn recruits histone deacetylases (HDAC) such as HDAC1/2 and the histone methyltransferases (HMT) such as euchromatic histone-lysine *N*-methyltransferase 2 (EHMT2) on the promoter (Piskurich et al., 2000). The opposite mechanism was found in human T cells, in which CIITA is expressed only after their activation (Van Eggermond et al., 2011). Recently it was shown that the zinc finger and BTB domain containing 48 (ZBTB48) is involved in activation of pIII in B cells, by binding the activation responsive element 1 and 2 (AR*E*-1/2), causing chromatin opening and gene expression (Rane et al., 2024). Moreover, C—C motif chemokine ligand 21 seems involved in activation of pIII in pDC through β-arrestin pathway (Zhao et al., 2024). The regulation of pIV is more studied. After IFN-γ stimulation, histone acetylation is induced on histone H3 and H4 of pIV by the histone acetyltransferases (HAT) p300 and cAMP response element-binding protein (CREB)-binding protein (CBP) within 15 min, before IRF-1 binding and thus CIITA transcription. Moreover, the SWI/SNF related BAF chromatin remodeling complex subunit ATPase (SMARCA4), a member of the SWI/SNF family, is required for the activation of pIV. SMARCA4 is present on pIV before STAT1 and IRF-1 binding and seems required to modify chromatin to favor their binding (Ni et al., 2005). Likewise, pIV can be silenced by HDAC, HMT and DNA methyltransferases (DNMT) which hypermethylate DNA at cytosine-phosphate-guanine (CpG) sites. However, no CpG sites are found on GAS and IRF-E, and only one CpG site is present on E-box, whose methylation is not sufficient to induce CIITA silencing. Thus, it is more likely that a more extensive CpG methylation of pIV, reduced acetylation and increased deacetylation and methylation of histones are responsible for CIITA silencing (O'Keefe et al., 1999; Van Den Elsen et al., 2001; Holtz et al., 2003). In addition to conventional promoters, a new regulatory gene sequence was recently discovered downstream of pIV, named SEa, characterized by super-enhancers (SE) formation in response to high mobility group box 1 (HMGB1) protein. In fact, HMGB1 is able to induce CIITA expression and thus MHC-II after interaction with its receptors, toll-like receptor 4 and receptor for advanced glycation end-products, which induce SE formation on SEa by recruiting the TF IRF-4, as seen in a murine model of allograft rejection (Sun et al., 2025).

1.3. Regulation and expression of MHC-II

Once expressed, CIITA does not bind directly to DNA promoter of MHC-II genes but interacts with specific and general TF, coactivators and chromatin remodelers in order to form the MHC-II enhanceosome, which will promote the MHC-II expression (Jabrane-Ferrat et al., 2002; Zika and Ting, 2005; Wright and Ting, 2006). For this reason, CIITA is defined as the major transcriptional coordinator and coactivator of MHC-II genes (Harton and Ting, 2000; Masternak et al., 2000). The MHC-II promoter contains a conserved DNA sequence known as W/SXY, which is bound by the regulatory factor X complex including RFX-5, RFX-ANK, and RFX-AP, CREB, activating transcription factor 1 (ATF1), and nuclear transcription factor Y complex including NF-YA, NF-YB, and NF-YC. All these proteins are recruited by CIITA, together

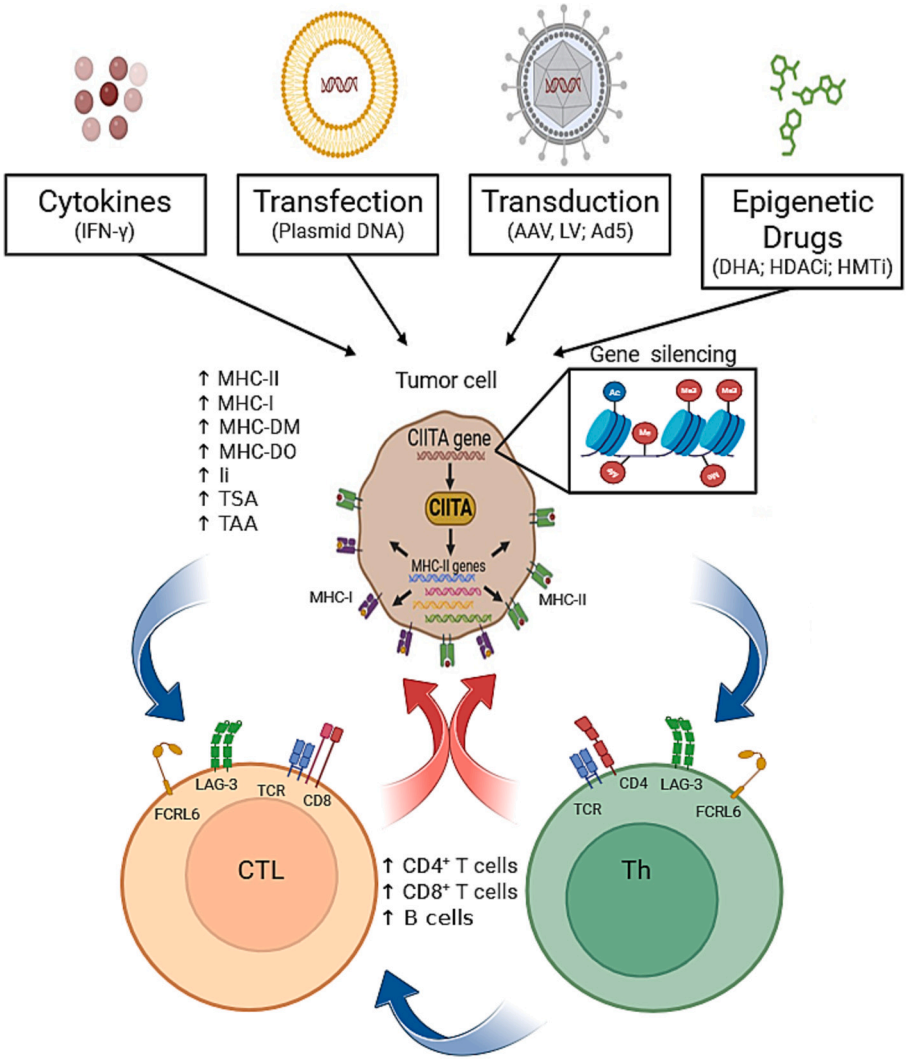


Fig. 2. Strategies to induce CIITA expression in tumor cells and promote surrogate APC function. CIITA expression in tumor cells, including in the context of epigenetic silencing, can be induced through different approaches, including cytokine treatment, transfection, transduction, and epigenetic drugs. Restoration of CIITA expression promotes the induction of MHC-II and associated components of the antigen-processing and presentation machinery, including MHC-DM, MHC-DO, and Ii, and may also enhance MHC-I expression, as well as the expression of TSA and TAA. By acquiring APC-like functions, CIITA-positive tumor cells may function as surrogate APC and promote adaptive anti-tumor immune responses, primarily through $CD4^+$ Th activation and the subsequent support of $CD8^+$ CTL responses, with an associated increase in $CD4^+$ T cells, $CD8^+$ T cells, and B cells. Inhibitory receptors such as LAG-3 and FCRL6 expressed on tumor-infiltrating T cells, may modulate these responses. Created in BioRender.com.

with HAT such as p300, CBP, and p300/CBP-associated factor (PCAF), HMT such as the protein arginine *N*-methyltransferases (PRMT) family, including PRMT4, chromatin remodelers such as SMARCA4, and steroid receptor coactivator-1 (SRC-1) (León Machado and Steimle, 2021). CIITA regulates also the initiation and the elongation of transcription by recruiting components of the transcription factor II D and B (TFIID/B) complexes such as the transcription initiation factor TFIID subunit 1 (TAF1), which can replace, and TATA-binding protein (TBP), phosphorylating the RNA polymerase II and interacting with the positive transcription elongation factor-b complex (P-TEFb) and cyclin-dependent kinase 7 (CDK7) (Kanazawa et al., 2000). Noteworthy, CIITA has acetyltransferase activity and kinase activity but is also itself target of post-translational modification such as acetylation, phosphorylation and ubiquitination in order to increase its functions (Devaiah and Singer, 2013). Distal regulatory elements characterize also MHC-II promoter. These are similar to W/SXY sequence, known as X-like (XL), which are also bound by regulatory factor complex X recruited by another CIITA, which seems to dimerize with the CIITA present in the proximal region of the promoter, after its phosphorylation (Linhoff et al., 2001; Sisk et al., 2001; Tosi, 2002), thanks to chromatin loop formation (Masternak et al., 2003; Krawczyk et al., 2004; Wright and Ting, 2006). Thus, CIITA is fundamental for MHC-II genes expression, whose mRNA appears already after 4–6 h whereas the protein has a half-life of 100 h once complexed with the peptide in the intracellular compartments and transported on the cell surface (Cella et al., 1997; Roche and Furuta, 2015). In addition to IFN-γ, other cytokines such as type-I interferons (IFN-I), granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor-α (TNF-α) can upregulate the expression of MHC-II (Hervas-Stubbs et al., 2011; Lee et al., 2017), whereas TGF-β and IL-10 downregulate it as well as CIITA (Mittal and Roche, 2015). However, the lack of CIITA is primarily responsible for the MHC-II deficiency, followed by the lack of the other factors involved in the formation of the enhanceosome, which depend in turn on the presence of CIITA. Epigenetic silencing contributes also to MHC-II deficiency. HDAC, HMT and DNA methylation are involved in enhanceosome disassembly, chromatin condensation and CIITA hindarance to block MHC-II gene expression in physiological condition (Kaufman, 2018; Chan et al., 2022).

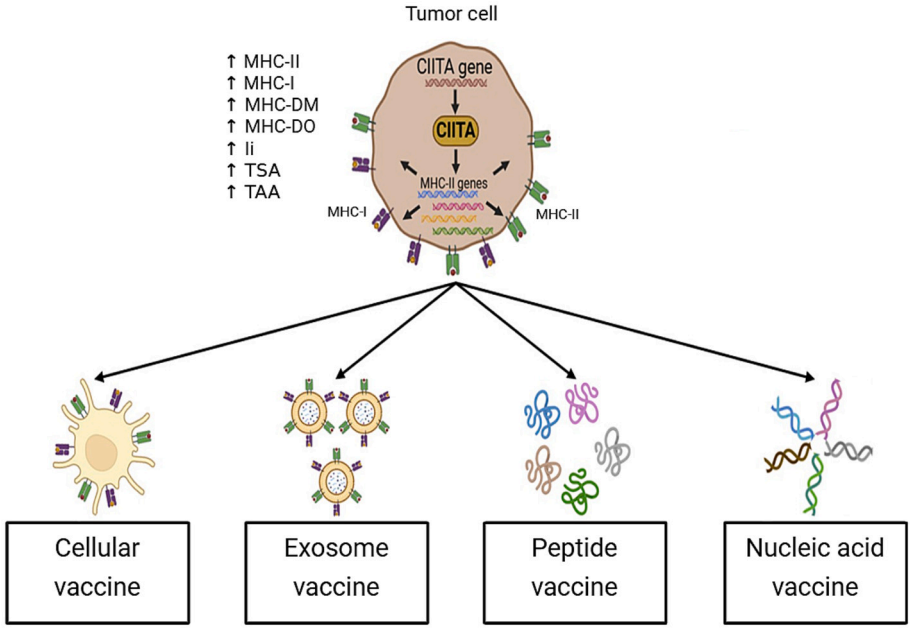


Fig. 3. CIITA-expressing tumor cells as a platform for anti-tumor vaccine development. Tumor cells engineered to express CIITA acquire surrogate APC-like properties through the induction of MHC-II and associated components of the antigen-processing and presentation machinery, including MHC-DM, MHC-DO, and Ii, and may also enhance MHC-I expression, as well as the expression of TSA and TAA. These immunogenic properties provide a rationale for the development of different anti-tumor vaccine strategies, including cell-based, exosome-based, peptide-based, and nucleic acid-based vaccines, with potential applicability into human clinical setting. Created in BioRender.com.

2. Tumor cells as surrogate APC

Since CIITA is the master regulator of MHC-II genes, it plays a crucial role in the adaptive immune responses. In the last decades the hypothesis that tumor cells can act as surrogate APC for their own tumor antigens took place and several studies have been conducted in order to experimentally induce MHC-II expression in tumor cells by inducing CIITA. Generally, tumor cells don't express CIITA which is finely epigenetically regulated, as stated before. However, genetic dysregulation could allow different levels of expression of CIITA as seen in many types of tumors (Axelrod et al., 2019; Tovar Perez et al., 2024). IFN-γ stimulation, as known, is the most common method able to induce transiently CIITA *via* pIV, only if it is not methylated (Muhlethaler-Mottet et al., 1998; Morris et al., 2000; Van Der Stoep et al., 2002; De Lerma Barbaro et al., 2008). If CIITA is epigenetic silenced, theoretically epigenetic drugs could be employed to revert the situation (Zika and Ting, 2005; Wright and Ting, 2006). More simply, gene transfer of a functional copy of CIITA ensures stable expression of MHC-II molecules. There are two classic methods to perform this, by transfection (non-viral-based) or transduction (viral-based) with different advantages and disadvantages (Chong et al., 2021). In particular, using plasmid DNA transfection, it was demonstrated that tumor cells of distinct histological origin were able to stably express CIITA and thus MHC-II. Moreover, these cells were efficiently rejected or retarded in their *in vivo* growth when injected into immunocompetent syngeneic mice (Meazza et al., 2003; Frangione et al., 2010). Stemming from these experiments it was possible to prove that CIITA-tumor "vaccinated" mice develop an immunological response against the CIITA-positive tumor and, most importantly, against a challenge with the parental tumor. The immunological response was studied, highlighting the involvement of Th cells in tumor rejection and stimulating the action of CTL against the tumor cells (Mortara et al., 2006, 2009). Although the exact mechanism underlying the interaction between CIITA-positive tumor cells and immune cells has not yet been reported, these approaches appear to overcome, at least in part, the limitations associated with the lack of professional APC and costimulatory signals in the tumor microenvironment (TME). Most importantly, adoptive cell transfer (ACT) experiments of splenocytes from "vaccinated" mice into naïve recipients have demonstrated the acquisition of protection from tumor growth when challenged with CIITA-negative parental tumor cells, showing the acquisition of a protective memory response (Bou Nasser Eddine et al., 2017; Azzi et al., 2024).

Collectively, these findings support the concept that CIITA-positive tumor cells can acquire APC-like functions and act as potent stimulators of protective adaptive anti-tumor immunity across different tumor histotypes. By functioning as surrogate APC, CIITA-positive tumor cells can contribute to the activation of tumor-specific Th cells, which in turn promote CTL responses and the establishment of a more inflamed and TIL-infiltrated TME, ultimately favoring tumor eradication (Fig. 2). Importantly, the ability of CIITA-positive tumor cells to induce protection against subsequent challenge with the parental tumor demonstrates that this approach can generate a durable immunological memory response, highlighting its potential as a tumor vaccination strategy (Accolla et al., 2019; Forlani et al., 2020, 2023).

3. Implications of CIITA induction in tumor cells

As discussed above, the expression of CIITA enables tumor cells to acquire surrogate APC functions, primarily through the induction of MHC-II expression, thereby enhancing the presentation of tumor antigens, both quantitatively and qualitatively, and facilitating their recognition by the immune system. Moreover, CIITA has also been shown to enhance the constitutive expression of MHC-I molecules (Devaiah and Singer, 2013), suggesting a potential dual role in anti-tumor immunity by promoting both MHC-I- and MHC-II-mediated antigen presentation and consequently supporting $CD8^+$ and $CD4^+$ T-cell responses. This dual regulatory activity makes CIITA an attractive target for the development of novel anti-tumor immunotherapeutic strategies, including different vaccination approaches aimed at enhancing tumor antigen presentation and immune recognition, with potential applicability into human clinical setting (Fig. 3) (Kaczmarek et al., 2023; Low et al., 2026).

3.1. CIITA expression for the development of vaccines

Non nucleic acid vaccines can be divided in cellular and non-cellular based. The first group include DC (Le et al., 2010) and whole tumor cells vaccines (Pérez-Baños et al., 2023), whereas the second include tumor-derived exosomes (TEX) (Naseri et al., 2020), single peptide and multivalent peptide vaccines (Parmiani et al., 2002). All these strategies could be implemented by using CIITA-positive tumor cells *in vitro* and *ex vivo* to identify important tumor-specific antigens (TSA) and tumor-associated antigens (TAA) that, in the absence of CIITA-driven MHC-I and MHC-II expression, would otherwise remain poorly presented or undetectable on the tumor cell surface. A promising antigen is generally tumor specific and highly immunogenic. Finding antigens with these characteristics could be the key to boost the immune system against tumors. For example, TEX derived from CIITA-positive tumor cells, expressing MHC-peptide complexes, were exploited to "vaccinate" challenged mice, demonstrating that modified TEX can retard tumor growth through a Th cells response, even if the exact mechanism has not been clarified (Lee et al., 2011; Fan et al., 2013). Immunopeptidomics coupled with mass spectrometry (MS) is today employed to identify and characterize MHC-I- and MHC-II-peptide complexes expressed on tumor cells, in order to develop effective peptide vaccines able to stimulate a specific and powerful immune response (Shapiro and Bassani-Sternberg, 2023). Recently, a broad MHC ligandome was uncovered in CIITA-positive human glioblastoma (GBM) cell lines, leading to the identification of novel MHC-I- and MHC-II-restricted peptides that could potentially be exploited for vaccine development. Importantly, some of these peptides derive from known GBM antigens that have already been used as targets for different GBM vaccine strategies, further supporting the potential of CIITA-mediated MHC-II expression as a tool for tumor antigen discovery, although its functional implications for direct antigen presentation by GBM cells remain controversial, as discussed in a later section (Forlani et al., 2021). Similar results were also obtained in murine and human colorectal cancer cell lines, in which novel MHC-I- and MHC-II-restricted tumor peptides were identified by MS-based immunopeptidomics and subsequently synthesized for *in vivo* validation. MHC-II-restricetd peptide vaccination effectively controlled tumor growth in mice, demonstrating the ability of these peptides to elicit a specific anti-tumor Th-dependent response (Hos et al., 2022). Noteworthy, tumor peptides discovered with this strategy, reached the clinical practice against hepatocellular carcinoma thanks to the "Cancer Vaccine Development for Hepatocellular Carcinoma: HepaVac", which developed a multipeptide vaccine containing both MHC-I- and MHC-II-restricted peptides, the latter obtained through CIITA-transfected tumor cells strategy. This vaccine known as IMA970A was tested in the phase I/II clinical trial HepaVac-101 (NCT03203005) obtaining Th responses in 10 out of 19 patients, showing favorable safety profile and moderate immunogenicity (Löffler et al., 2022).

Nucleic acid vaccines, based on either DNA or RNA, employ specific antigen-coding sequences that are translated by host cells to elicit a potent immune response (Kozak and Hu, 2024; Lu et al., 2024). In particular, mRNA vaccines have gained increasing attention in cancer research (Lorentzen et al., 2022), especially following the successful development and widespread use of mRNA vaccines during the coronavirus disease 2019 (COVID-19) pandemic (Gote et al., 2023). Building on this strategy MHC-I- and MHC-II-restricted tumor-derived peptides identified using CIITA-positive tumor cells could potentially be exploited to develop specific mRNA vaccines capable of inducing anti-tumor immunity. This approach may be particularly relevant for poorly immunogenic tumors such GBM, which is characterized by a relatively low tumor mutational burden (TMB), potentially offering a basis for personalized immunotherapy.

4. CIITA itself as vaccine

In a more sophisticated approach, nucleic acid vaccines could also be designed to deliver CIITA directly to tumor cells *in vivo*, thereby bypassing the limitations associated with gene transfer *in vitro* and *ex vivo*. This strategy could induce MHC-II genes expression while enhancing MHC-I genes expression for a window of time potentially sufficient to stimulate an adaptive anti-tumor immune response. Different delivery systems, including transfection- and viral vector-based approaches, could potentially be employed to deliver the CIITA coding sequence directly to tumor cells *in vivo*, each with distinct characteristics (Nayerossadat et al., 2012). However, experimental evidence supporting direct *in vivo* CIITA delivery to tumor cells is currently lacking, with previous *in vivo* studies mainly involving transfection of DC with CIITA to increase antigen processing and presentation and enhance immunity (Kim et al., 2008). By contrast, direct CIITA delivery to tumor cells using viral transduction has been investigated predominantly *in vitro*, where it showed an efficiency comparable to that achieved by transfection. For example, lentiviral vectors (LV) containing CIITA were efficiently used to transduce MHC-II-negative B cells derived from patients with bare lymphocyte syndrome type II (BLS-II) in order to restore MHC-II expression (Matheux et al., 2002). Likewise, LV was also used to efficiently transduce tumor cells and primary human skin cells with CIITA, inducing a strong MHC-II expression (Palma et al., 2017). The same was obtained in breast cancer cell lines, which were able to present endogenously synthesized tumor antigens to Th cells (Thompson et al., 2006). Also, adeno-associated virus (AAV) vectors were employed for this purpose. In particular, a chimeric construct named DD-335-CIITA, containing a N-terminal domain deleted form of CIITA substituted with the N-terminal domain of NOD-like receptor family CARD domain containing 5 (NLRC5), known to be the master regulator of MHC-I (Meissner et al., 2010) with analogue functions to CIITA (Neerincx et al., 2012), was inserted into an AAV vector and used to transduce murine melanoma cell line. Tumor cells showed enhanced expression of MHC-I and MHC-II after transduction, leading to a more efficient killing by CTL (Neerincx et al., 2014). Recently, the efficiency of this construct to specifically induce MHC-I expression was confirmed. Renamed as NLRC5-superactivator (NLRC5-SA), it was able to increase the repertoire of MHC-I-ligandome identified by immunopeptidomics (Santharam et al., 2023).

Based on these studies, viral vector transduction represent a potentially translatable strategy for delivering CIITA to tumor cells and inducing MHC-II expression, thereby promoting the presentation of a broader repertoire of tumor antigens. An even more promising approach may be the incorporation of CIITA into oncolytic viral vectors, which could combine the direct oncolytic activity of the virus with enhanced presentation of relevant immunogenic tumor antigens, thereby potentially eliciting a stronger and more effective anti-tumor immune response (Shallak et al., 2026).

4.1. Challenges of in vivo CIITA delivery

Despite their potential for direct *in vivo* CIITA delivery, viral vector-based approaches present several challenges that may limit their clinical translation, including immunogenicity, the risk of insertional mutagenesis, packaging constraints, and off-target transduction (Bulcha et al., 2021). First, viral vectors can themselves activate innate and adaptive immune responses, which may limit transduction efficiency, promote rapid clearance, and complicate repeated administration. This issue is particularly relevant for AAV- and adenoviral-based approaches, in which pre-existing or treatment-induced neutralizing antibodies can interfere with vector uptake and restrict systemic delivery (Lopez-Gordo et al., 2024). Second, integrating vectors such as LV raise concerns regarding insertional mutagenesis and the possibility of altering the expression of host genes, even though the use of self-inactivating and other next-generation vector designs has substantially reduced, but not completely eliminated, this risk (Milone and O'Doherty, 2018). A further limitation is represented by vector packaging capacity, which leaves limited space for a full-length CIITA expression cassette together with

the promoter and regulatory elements required for efficient expression. The use of compact regulatory sequences, split-vector systems, or truncated/synthetic CIITA constructs may partially address this constraint, but these approaches can introduce additional complexity and may compromise expression efficiency or biological activity (Bennett et al., 2017). In addition, systemic viral administration may result in transduction of non-tumor cells according to the intrinsic and engineered tropism of the vector. Consequently, off-target transduction represents critical safety considerations, particularly when CIITA is expressed ectopically in tissues in which MHC-II induction could alter local immune interactions. Strategies based on capsid engineering, tumor-selective promoters, or other transcriptional control elements may improve specificity, but their effectiveness needs to be established in relevant *in vivo* models (Lopez-Gordo et al., 2024).

These limitations provide a strong rationale for investigating non-viral delivery systems for *in vivo* CIITA delivery (Nayerossadat et al., 2012). Among these, lipid nanoparticles (LNP) carrying CIITA mRNA represent a particularly attractive strategy. Unlike DNA-based approaches and integrating viral vectors, mRNA does not require nuclear entry or integration into the host genome and therefore enables transient protein expression for a window of time potentially sufficient to stimulate an adaptive anti-tumor immune response. LNP can efficiently encapsulate and protect mRNA and have emerged as clinically relevant platforms for nucleic acid delivery. However, LNP-based delivery still presents several limitations. LNP may induce innate immune activation and inflammatory responses, while their biodistribution may lead to preferential accumulation in non-tumor tissues and organs. In addition, limited tumor penetration, inefficient endosomal escape, nucleic acid instability, and insufficient or heterogeneous transgene expression may further compromise their therapeutic efficacy. Nevertheless, optimization of physicochemical properties and lipid composition, surface functionalization with tumor-targeting ligands, and the development of tissue- or cell-selective nanoparticles may enhance tumor-specific delivery while reducing systemic and organ-specific off-target exposure (Xu et al., 2025). Other non-viral approaches, including polymeric and inorganic nanoparticles, as well as extracellular vesicle- and exosome-based systems, may provide additional opportunities to improve payload protection, cellular targeting, and intracellular delivery. Such platforms may accommodate diverse genetic payloads while avoiding genomic integration and potentially reducing some of the immunogenicity and other constraints associated with viral vectors (Wang et al., 2025b; Yang et al., 2024). However, these systems are generally less clinically established than viral vector-based approaches and still face important translational challenges, including payload stability, delivery efficiency, tumor penetration, cell-type-specific targeting, endosomal escape, and the achievement of sufficient and reproducible CIITA expression within tumor cells (Sharma et al., 2021).

Overall, viral and non-viral platforms offer complementary opportunities for the development of direct *in vivo* CIITA delivery strategies. While viral vectors currently provide higher and more established gene-transfer efficiency, non-viral systems may offer advantages when transient, repeatable, and spatially controlled CIITA expression is required. The development of tumor-targeted CIITA-LNP or related delivery platforms could therefore provide a means to extend the CIITA-based vaccine concept from *ex vivo* genetically modified tumor cells to direct *in vivo* tumor reprogramming (Wang et al., 2023). Future studies should directly compare these strategies in relevant tumor models, with particular attention to tumor-selective biodistribution, magnitude and duration of CIITA expression, induction of MHC-II and MHC-I molecules, safety and systemic immune activation, and, ultimately, the magnitude and durability of the resulting anti-tumor immune response.

5. Contradictory preclinical evidence in GBM

Despite the compelling evidence supporting the immunostimulatory potential of CIITA-driven MHC-II expression in different tumor models, preclinical studies in GBM have yielded more complex and, in some cases, contradictory results. GBM is the most common, aggressive, and lethal primary malignancy of the central nervous system (CNS), characterized by marked molecular and cellular heterogeneity, a highly immunosuppressive TME, and a relatively low TMB. In this context, studies using orthotopic murine models have provided divergent evidence regarding the ability of tumor cells to acquire or exhibit surrogate APC functions. This question is particularly relevant given that GBM cells are generally characterized by low or absent expression of MHC-II molecules, which may not always be inducible by IFN-γ (Soos et al., 2001; Takamura et al., 2004). Supporting a surrogate APC function, intracranial injection of CIITA-positive murine glioma GL261 tumor cells cultured under 2D adherent conditions resulted in markedly impaired *in vivo* tumor growth compared with parental GL261 tumor cells and conferred protection against subsequent challenge with parental tumor cells in C57BL/6 mice (H-2^b genotype). Most importantly, analysis of tumor-infiltrating immune cells in these "vaccinated" mice demonstrated an increase in tumor-infiltrating lymphocytes (TIL), including both CD4+ and CD8+ T cells (Celesti et al., 2023). These findings were subsequently extended to CT-2A tumor cells, another murine glioma model that more closely recapitulates key features of human GBM. Intracranial injection of CIITA-positive CT-2A tumor cells cultured under 2D adherent conditions resulted in markedly impaired *in vivo* tumor growth compared with parental CT-2A tumor cells in C57BL/6 mice (H-2^b). Moreover, cross-protective immunity against subsequent challenge with parental CT-2A tumor cells was observed in C57BL/6 mice (H-2^b) previously "vaccinated" with GL261-CIITA cells, suggesting the presence of shared tumor antigens between these two GBM models (Gatta et al., 2025). In contrast, Tan et al. (2023) addressed the potential immunizing effect of parental GL261 tumor cells by performing subcutaneous "vaccination" of C57BL/6 mice (H-2^b) with irradiated either parental or CIITA-positive GL261 tumor cells prior to a subsequence intracranial challenge with parental tumor cells. Comparable protection was observed in both groups, consistent with previous evidence that parental GL261 cells can also elicit anti-tumor immunity in C57BL/6 mice (H-2^b), although the rapid growth of the parental tumor limited further investigation of this immunogenic effect. This finding was further supported by ACT experiments in which splenocytes were adoptively transferred into C57BL/6 mice (H-2b) bearing intracranial parental GL261 tumors. Specifically, splenocytes were isolated from C57BL/6 mice (H-2^b) previously "vaccinated" by intracranial injection of either CIITA-positive GL261 tumor cells or from "non-vaccinated" mice that had received intracranial injection of parental GL261 tumor cells. Both tumor cell types were cultured under 2D adherent conditions. These splenocytes were subsequently adoptively transferred by intraperitoneal injection into mice bearing intracranial parental GL261 tumors. The comparable protective effect observed following the transfer of splenocytes from "vaccinated" and "non-vaccinated" mice did not support a role for CIITA-positive tumor cells in enhancing GBM immunogenicity. Furthermore, they demonstrated a lack of TIL activation by CIITA-positive tumor cells in *in vitro* human syngeneic co-culture experiments, using primary human GBM cell lines cultured under 2D adherent conditions and TIL isolated from the same patient biopsies. These findings do not support a major immunomodulatory effect of CIITA on the TME but instead suggest potential MHC-II-independent, non-immunogenic antiproliferative effects. This hypothesis was subsequently confirmed using athymic nude mice and NOD scid gamma mice (NSG), which are immunodeficient due to the absence of T cells and of virtually all immune cells, respectively. Tumor growth was delayed in both immunodeficient mouse models following intracranial injection of CIITA-positive GL261 cells cultured under 2D adherent conditions, compared with the parental tumor cells. These findings confirm that immune mechanisms are not solely responsible for CIITA-mediated GBM rejection. Indeed, subsequent *in vitro* experiments showed that CIITA-positive murine and primary human GBM cell lines exhibited slower proliferation than their parental counterparts when cultured under 2D

adherent, 3D spheroid, and 3D Matrigel® conditions. Finally, molecular analyses demonstrated the upregulation of cyclin dependent kinase inhibitor 1B (P27KIP1) and the inhibition of cell-cycle pathways in CIITA-positive tumor cells, both *in vivo* and *in vitro* (Tan et al., 2024). Similar conclusions were reported in bladder cancer (Redelman-Sidi et al., 2022) and in gastric cancer, where CIITA was shown to limit tumor growth by promoting ferroptosis through the upregulation of acyl-CoA synthetase long chain family member 4 (ACSL4) (Zhang et al., 2025c). Moreover, using a replication-defective adenoviral serotype 5 (Ad5) vector containing CIITA, Salvato et al. (2025) successfully transduced murine and primary human GBM cell lines cultured under 2D adherent conditions *in vitro* and induced MHC-II expression for at least six days post-infection. These findings were subsequently extended to 3D primary human GBM organoid models. To evaluate the ability of CIITA-transduced organoids to elicit adaptive immune responses, organoids were co-cultured with allogeneic, MHC-matched human peripheral blood mononuclear cells (PBMC) from healthy donors. Co-culture resulted in organoid disruption and tumor cell killing, demonstrating increased GBM immunogenicity following CIITA expression in the presence of either $CD4^+$ or $CD8^+$ T cells. However, this effect appears to be at least partially independent of MHC-II expression and antigen presentation. This was first suggested by co-culture experiments using CIITA-transduced GL261 tumor cells and T cells from C57BL/6 OT-II mice ($H\text{-}2^b$) and was subsequently confirmed in co-culture experiments involving PBMC and 3D primary human GBM organoids, stimulated with ovalbumin-derived peptides and an antigenic peptide pool, respectively. Most importantly, expression of a mutant form of CIITA impaired in nuclear translocation and therefore accumulating in the cytoplasm, and consequently unable to induce MHC-II expression, was sufficient to promote contact-dependent tumor cell killing by T cells in the absence of conventional costimulatory signals in the TME. This effect was observed using a two-layer transwell system with 3D primary human GBM organoids and occurred in the absence of canonical T cell degranulation or activation of known cell-death signaling pathways. Overall, these findings suggest that CIITA may enhance GBM immunogenicity through mechanisms that are at least partly independent of its canonical role in MHC-II regulation and antigen presentation. However, the precise mechanisms underlying this phenomenon remain to be elucidated and warrant further investigation.

Taken together, the available evidence supports a role for CIITA-positive GBM cells in promoting adaptive anti-tumor immunity, although their immunostimulatory activity may involve both MHC-II-dependent and MHC-II-independent mechanisms. These findings underscore the importance of interpreting the available preclinical evidence in the context of GBM cell lines, experimental models, culture conditions, and TME composition.

6. CIITA induction by epigenetic drugs

Since CIITA is a key player in the adaptive immune response and its role to make tumor cells as surrogate APC, as well as its ability to enhance the constitutive expression of MHC-I, are well established, more feasible strategies could be developed to induce CIITA expression into human clinical setting and thereby elicit specific anti-tumor Th-dependent responses. CIITA, and consequently MHC-II expression, are finely regulated in a tissue-specific manner, even if in tumor cells gene expression is often altered as stated before (Axelrod et al., 2019; Tovar Perez et al., 2024). Nevertheless, epigenetic mechanisms involved are reversible and could be reverted by specific drugs. For example, when the inducible pIV of CIITA is methylated, tumor cells are MHC-II negative, despite the stimulation with IFN-γ (De Lerma Barbaro et al., 2008), as previously seen in embryonic and fetal tumor cell lines (Morris et al., 2000; Van Der Stoep et al., 2002) and later in colorectal and gastric tumor (Satoh et al., 2004), breast carcinoma (Shi et al., 2006), hepatocellular carcinoma (Ramia et al., 2019), pancreatic carcinoma (Tao et al., 2014) and melanoma (Meyer et al., 2021) cell lines. However, treatment with DNMT inhibitors (DNMTi) can restore CIITA expression and induce MHC-II expression in these settings. Among DNMTi, DNA hypomethylating agents (DHA) induce global DNA hypomethylation and can consequently promote the re-expression of epigenetically silenced genes, including tumor suppressor genes and CIITA. For this reason, DHA have been widely investigated in preclinical setting (Zhang et al., 2022), reaching the Food and Drug Administration (FDA) approval for hematological tumors treatment (Stomper et al., 2021). Most importantly, DHA act also as immunomodulatory agents since they are demonstrated to induce and/or upregulate the expression of different immune-related genes in tumor cells, with particular attention to MHC-I, costimulatory molecules, TAA such as cancer testis antigens (CTA) and human endogenous retroviruses (HERV) (Coral et al., 2013; Fazio et al., 2018). Recently, epigenetic remodeling of human GBM cells by using DHA has also demonstrated the activation of immune pathways involved in the MHC-II-dependent antigen processing and presentation and the activation, proliferation and migration of T and B cells (Lofiego et al., 2024). Moreover, the comparison of different epigenetic drugs has demonstrated that DHA are the most promising immunomodulatory agent, alone or in combination, at least in the tested tumor histotypes (Lofiego et al., 2021; Anichini et al., 2022), laying the rationale for a combinatorial strategy with immunotherapies, such as immune checkpoint inhibitors (ICI) (Covre et al., 2015; Amaro et al., 2023), reaching the clinical phase (Noviello et al., 2023). However, the efficacy of DHA in terms of induction of MHC-II is less strong compared to that of other epigenetic drugs such as HDAC and HMT inhibitors (HDACi and HMTi). These drugs are involved in the maintenance of histone acetylation and hypomethylation to permit uncoiling and accessibility of chromatin, in order to induce TSG and immune-related gene expression, gaining great success and approval for cancer treatment (Marzochi et al., 2023; Shi et al., 2024). In fact, when pIV is not methylated and IFN-γ is not able to induce CIITA, other epigenetic mechanisms repress its expression, as seen previously, causing chromatin condensation. For example, it was possible to distinguish four phenotypes in melanoma cell lines based on MHC-II expression and thus CIITA promoter methylation: phenotype I totally lacking but inducible by IFN-γ, phenotype II having low basal expression and inducible by IFN-γ, phenotype III totally lacking and non IFN-γ inducible, but inducible by epigenetic drugs and phenotype IV totally lacking and not recovering by epigenetic drugs (Meyer et al., 2021). The first three phenotypes were also found in glioma cell lines (Takamura et al., 2004). Therefore, when promoter methylation is not involved, it was demonstrated that trichostatin A, belonging to the class of HDACi, is able to induce CIITA and MHC-II expression in solid and hematological tumor cells (Holtz et al., 2003; Kanaseki et al., 2003; Chou et al., 2005; Chou and Tomasi, 2008; Cycon et al., 2013). A selective HDACi known as CXD101, has demonstrated in murine and human colorectal tumor cells to stimulate the expression of genes involved in MHC-I and II-dependent antigen processing and presentation as well as natural killer (NK) cell-mediated cytotoxicity, showing also *in vivo* efficacy in combination with ICI (Blaszczak et al., 2021). Another selective HDACi known as QAPHA is able to induce MHC-II in lung cancer cells and elicit a Th cells response *in vivo* (Ducellier et al., 2024). Likewise, HMTi acting on the enhancer of zeste homolog 2 (EZH2), a member of the lysine methyltransferases (KMT) and a component of the polycomb repressive complex 2 (PRC2), have been shown to induce MHC-II expression in tumor cells. For example, GSK126 was able to induce MHC-II in colorectal and lung cancer organoid models. In the first case, the effect was also amplified in combination with another HDACi known as entinostat, although with greater toxicity (Pickles et al., 2023), in the second case the use of tazemetostat obtained equivalent effect (DuCote et al., 2024). The same efficacy was proven in melanoma models treated with GSK343 or tazemetostat (James et al., 2023), in anaplastic thyroid cancer models and acute myeloid leukemia (AML) models treated with tazemetostat (Gambacorta et al., 2022; Tiedje et al., 2025), and in urothelial carcinoma models treated with EPZ011989 (Piunti et al., 2022), demonstrating the involvement of

Table 1
Translational comparison of epigenetic drugs for CIITA induction and MHC-II expression in tumor cells.

Epigenetic approach	Mechanism relevant to CIITA	Evidence for CIITA/MHC-II restoration	Translational/clinical maturity	Evidence supporting combination with ICI	Main limitations for a CIITA-directed strategy
DHA	Reversal of DNA methylation, particularly when CIITA pIV is methylated	Restoration of CIITA/MHC-II reported in multiple tumor models; broad induction of MHC-I, costimulatory molecules, CTA and HERV	Highest among the discussed approaches; extensively investigated and clinically approved in hematological malignancies	Strong immunomodulatory rationale; epigenetic–immunotherapy combinations have reached clinical investigation	Global hypomethylation and broad transcriptional effects; MHC-II induction may be weaker than with HDACi/HMTi; CIITA-specific biological dose undefined
HDACi	Increased histone acetylation and chromatin accessibility when CIITA repression is independent of promoter methylation	Induce CIITA/MHC-II expression in multiple tumor models; enhance MHC-I- and MHC-II-dependent antigen processing and presentation; promote Th-cell responses.	Several HDACi have advanced clinically, although the agents specifically demonstrating CIITA induction are largely supported by preclinical evidence	Shows *in vivo* efficacy in combination with ICI	Broad transcriptional effects; response depends on the mechanism of CIITA repression; optimal immunological dose/schedule unknown
HMTi	Reversal of repressive histone methylation at the CIITA promoter	Induce CIITA/MHC-II expression in colorectal, lung, melanoma, thyroid, AML and urothelial models	Clinically relevant drug class, but CIITA-directed application remains preclinical	Strong mechanistic rationale; potential for combination with other epigenetic agents and immunotherapy	Context-dependent activity; CIITA response depends on HMT-mediated repression; optimal ICI combination undefined
Combined epigenetic treatment	Simultaneous targeting of multiple mechanisms repressing CIITA	DHA + HDACi show additive CIITA/MHC-II induction; HMTi + HDACi can further enhance MHC-II	Predominantly preclinical in the specific context of CIITA restoration	Provides rationale for subsequent ICI treatment	Increased toxicity may offset enhanced CIITA/MHC-II induction; requires careful dose and sequence optimization

EZH2 in CIITA silencing and MHC-II repression. These results were obtained after having previously demonstrated, by using chromatin immunoprecipitation (ChIP) approaches, that EZH2 is located on pIV promoter of CIITA, blocking its expression thanks to the trimethylation of histone H3 lysine 27 (H3K27me3) (Holling et al., 2007). Furthermore, the inhibition of the ring finger protein 2 (RNF2), an ubiquitin ligase component of the PRC1, using the small inhibitor RB-3, restores the expression of CIITA in B-cell lymphoma deficient of the deubiquitinase BRCA1 associated protein 1 (BAP1), rebalancing the ubiquitination of histone H2 lysine 119 (H2K119Ub) and thus promoting IRF-1 expression (Zhang et al., 2025a). Recently, targeting the interaction between menin (MEN1) and KMT2A in AML models, with the inhibitor bleximenib, was able to induce CIITA and thus MHC-II. This prevents KMT2A to interact indirectly with CIITA promoter through MEN1, a scaffold protein, which binds CIITA as seen in ChIP. This inhibition induces general trimethylation of histone H3 lysine 4 (H3K4me3) and acetylation of histone H3 lysine 27 (H3K27ac) on CIITA as well as on several immune genes, increasing tumor immunogenicity and T cell killing (Hogeling et al., 2024). Moreover, the inhibition of several PRMT is related to the induction of CIITA and MHC II-related genes, as seen in AML by using a 3-alkenylindol-2-one-based inhibitor (Dong et al., 2025).

In light of these findings, the translational use of epigenetic drugs for CIITA induction should not rely on a single therapeutic approach, but rather on the identification of the molecular mechanism responsible for CIITA silencing in each tumor context. As summarized in Table 1, the main epigenetic approaches discussed differ in their mechanisms of CIITA reactivation and MHC-II induction, clinical maturity, dose-related limitations, off-target epigenetic effects, and available evidence supporting combination with ICI. DHA may be particularly relevant when CIITA pIV methylation represents the dominant repressive mechanism, whereas HDACi or HMTi may be more effective when CIITA repression is sustained by a closed chromatin configuration and repressive histone modifications. Accordingly, although DHA currently display the most advanced clinical development and broadest immunomodulatory activity, HDACi and HMTi may produce stronger induction of CIITA and MHC-II in selected tumor settings. Combinations of epigenetic agents may further increase CIITA expression by simultaneously targeting different repressive mechanisms, as demonstrated by the additive activity of DHA and HDACi in rhabdomyosarcoma, pancreatic, and ovarian cancer models (Londhe et al., 2012; Turner et al., 2017; Ramia et al., 2019), or by the combination of HDACi and HMTi, although enhanced activity may be accompanied by increased toxicity (Pickles et al., 2023). Additional regulatory mechanisms may also contribute to CIITA silencing, including microRNA (miRNA) and long non-coding RNA (lncRNA) (Asirvatham et al., 2008; Codolo et al., 2020; Toker et al., 2023; Yin et al., 2024), which remain largely unexplored in this context. Such epigenetic combinations may result in robust CIITA and MHC-II expression, together with enhanced MHC-I expression, thereby broadening the repertoire of MHC-I- and MHC-II-restricted tumor-derived peptides available for T cell recognition. These observations also have important implications for the combination of epigenetic therapy with ICI. DHA and other epigenetic drugs have broad immunomodulatory properties and epigenetic-ICI combinations have already been investigated in preclinical and clinical settings (Covre et al., 2015; Amaro et al., 2023; Noviello et al., 2023). However, these studies should be distinguished from a specifically CIITA-directed therapeutic strategy. Based on the preclinical evidence discussed above, we propose that epigenetic treatment could be exploited as an immunological priming step to restore tumor-intrinsic CIITA and MHC-II expression, thereby promoting an APC-like tumor phenotype and MHC-II-restricted tumor antigen presentation to Th cells. Subsequent or concomitant checkpoint blockade could then sustain and amplify the resulting adaptive anti-tumor response. At present, however, neither the optimal epigenetic agent nor the dose, treatment duration or sequence with ICI required to achieve this goal has been clinically defined. Because epigenetic drugs induce broad transcriptional changes beyond CIITA, future studies should therefore determine the minimum biologically effective dose capable of restoring CIITA and MHC-II expression in tumor cells while limiting nonspecific epigenetic effects and toxicity. Prospective assessment of this molecular axis before and after epigenetic treatment may consequently represent an important pharmacodynamic readout of future clinical trials aimed at evaluating CIITA-directed epigenetic priming in combination with ICI.

7. CIITA and MHC-II as predictive markers for immunotherapy

The therapeutic relevance of restoring tumor-intrinsic CIITA expression is further supported by growing evidence linking the CIITA/MHC-II axis to the response to immunotherapy. Indeed, in recent years, the potential of CIITA and downstream MHC-II expression as predictive markers of response to immunotherapy has been increasingly investigated (Zeng et al., 2022; Huang et al., 2026; Liu et al., 2025; Zhou et al.,

2025). It is important to emphasize that the objective of this section was to collect and analyze exclusively studies investigating the expression of these molecules in tumor cells and their influence on immunotherapy, particularly ICI. The literature search was conducted on PubMed and Scopus using a combination of key words such as CIITA; MHC class II transactivator; MHC-II; MHC class II; immunotherapy; ICI and immune checkpoint inhibitor. The search results underwent two-stage screening: initial evaluation of titles and abstracts, followed by full-text assessment. Only sources containing data relevant to surrogate APC, immunotherapy, and ICI were included, excluding other works addressing the role of professional APC or other IFN-γ-stimulated cells on immunotherapy. Since CIITA expression and the consequent induction of MHC-II can enable tumor cells to function as surrogate APC capable of stimulating Th cells and, indirectly, CTL involved in tumor eradication, their expression could potentially serve as predictive markers. However, their predictive significance appears to be highly context-dependent rather than uniformly favorable or unfavorable. In particular, this context dependency may be shaped by several interconnected factors, such as the baseline immune status of the TME, ranging from T cell inflamed to exhausted, excluded, or immunosuppressive phenotypes, the tumor immunogenicity, as reflected by TMB and the resulting repertoire of potentially presented antigens, the abundance and spatial localization of MHC-II-positive tumor cells, and the oncogenic background of the tumor, including viral etiology. Collectively, these variables may determine whether MHC-II-positive tumor cells primarily supports productive Th cell-mediated anti-tumor immunity or, conversely, contribute to adaptive immune resistance through inhibitory MHC-II receptors and chronic inflammatory signaling (Wardell et al., 2021). Thus, CIITA and MHC-II expression should not be considered as an isolated binary biomarker, but rather as one component of a multidimensional stratification framework integrating tumor-intrinsic and microenvironmental features. Therefore, further studies are needed to clarify their biological and predictive significance and to establish how their assessment, in combination with other relevant tumor and immune parameters, may contribute to more accurate patient stratification and prediction of response to immunotherapy (Yang et al., 2022; Li et al., 2025).

7.1. Favorable predictive response

The scientific literature highlights the favorable predictive value of response to ICI of CIITA-driven MHC-II. In fact, many studies have demonstrated that the expression of these molecules correlates with a better outcome for anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death protein 1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) treatment in patients with different tumor histotypes such as melanoma (Johnson et al., 2016; Rodig et al., 2018; Liu et al., 2019; Amrane et al., 2024; Claeys and Van Den Eynden, 2024), lung cancer (Wang et al., 2019; Johnson et al., 2020; Redin et al., 2025), colorectal tumor (Sconocchia et al., 2014; Dunne et al., 2020), breast cancer (Forero et al., 2016; Gonzalez-Ericsson et al., 2021; Li et al., 2025), hepatocellular cancer (Wang et al., 2026), head and neck squamous cell carcinoma (Zhang et al., 2025b; Mints et al., 2026), bladder cancer (Yi et al., 2022), laryngeal cancer (Heng et al., 2023), and lymphoma (Roemer et al., 2018; Takeuchi et al., 2019; Nagasaki et al., 2020; Taylor et al., 2022). In these settings, MHC-II expression in tumor cells is frequently associated with a pre-existing T cell-inflamed TME characterized by increased immune infiltration and IFN-γ-related immune activation. Within such an immunological context, CIITA-driven MHC-II expression may further promote tumor antigen presentation to Th cells and sustain both helper and cytotoxic anti-tumor responses, thereby favoring ICI efficacy. Thus, the favorable predictive value of MHC-II may reflect both its functional contribution to anti-tumor immunity and its role as a marker of an already immunologically active TME. Beyond the baseline immune status of the TME, tumor immunogenicity may provide an additional layer influencing the predictive value of MHC-II. In particular, TMB may reflect the overall repertoire of potentially presented tumor antigens and may therefore influence responsiveness to ICI. Accordingly, MHC-II expression and TMB may provide complementary rather than redundant information, as the former reflects antigen-presentation-related immune competence whereas the latter captures a distinct genomic dimension of tumor immunogenicity. These observations support the integration of MHC-II expression in tumor cells with genomic biomarkers such as TMB when stratifying patients for immunotherapy. Recently, it has been shown that the inhibition of mouse double minute 2 homolog (MDM2) in murine and human melanoma cells induces tumor protein P53 (TP53), followed by the expression of MHC-II and IL-15. Moreover, the combination with anti-PD1 improved the survival of metastatic melanoma mice due to an increase of $CD8^+CD73^+TCF\text{-}1^+IFN\gamma^+TNF^+$ T cells, underlining once again the importance of MHC-II as well as IL-15, both correlated to a better prognosis for metastatic melanoma (Langenbach et al., 2023). Similar results were also obtained after the inhibition of nucleophosmin (NPM1) and REST corepressor 2 (RCOR2), two nuclear proteins highly expressed in different solid tumors, promoting tumor progression and immune evasion. NPM1 seems to repress CIITA and NLRC5 expression by binding IRF-1, whereas RCOR2 appears to exert a similar effect by binding to HDAC1/2 and lysine-specific histone demethylase 1A (KDM1A), leading to MHC downregulation. The inhibition of both induces MHC expression and TIL infiltration in murine cancer models, thus promoting tumor retardation (Wang et al., 2024; Bao et al., 2025). Differently, the presence of microtubule associated protein 1 light chain 3 gamma (MAP1LC3C), a non-canonical autophagy protein with TSG function, regulates CIITA expression and is associated with tumor-infiltrating immune cells in lung cancer (Barbeau et al., 2025). In breast cancer, it was demonstrated that PCAF is involved in inducing chromatin accessibility and expression of the CIITA promoter *via* acetylation, promoting MHC-II expression and predicting the efficacy for immunotherapy (Wang et al., 2025c). By contrast, a "cold" tumor is characterized by an immunosuppressive microenvironment with a reduced percentage of TIL, mainly $CD4^+FoxP3^+$ regulatory T cells (Treg) or with an exhausted profile. MHC-II and in particular MHC-I, which role in activating CTL is widely known, are often downregulated or missing, representing an important mechanism of immune evasion (Dhatchinamoorthy et al., 2021). For example, in a murine melanoma model, administration of the Astragalus compound, commonly known for its immune-boosting properties, caused the downregulation of CIITA and MHC-II on tumor cells and DC, reducing TIL and the efficacy of anti-PD-1 (Lei et al., 2025). Moreover, it was demonstrated that the expression of MHC-II on professional APC is fundamental to prevent dysfunction of CTL also in brain tumor, further emphasizing the importance of MHC-II-dependent immunity (Kilian et al., 2023). Thus, in such immunosuppressive landscape, immunotherapy is not effective and for this reason researchers are turning their attention to novel combinatorial strategies in order to increase immunotherapy efficacy (Galon and Bruni, 2019; Zhu et al., 2021). However, it is important to point out that CTL depend on Th cells for their optimal functions and, most importantly, that Th cells are now known to exert cytotoxic functions (Poncette et al., 2022) by expressing granzymes A, B, H, and K (GZMA/B/H/K), perforin-1 (PRF1), natural killer cell granule protein 7 (NKG7), and granulysin (GNLY), which contribute to target-cell killing (Oh and Fong, 2021). These cytotoxic $CD4^+$ T cells have been characterized in different types of tumors and in particular in melanoma (Quezada et al., 2010; Xie et al., 2010). For example, after being isolated using MHC-II tetramers, cytotoxic $CD4^+$ T cells specific for CTA such as NY-ESO-1 and MAG*E*-A3 were able to kill tumor cells stimulated with IFN-γ or subjected to gene transfer of CIITA. Moreover, killing activity was enhanced after stimulation of signaling lymphocyte activation molecule family 7 (SLAMF7), a common surface antigen of immune cells, which deserves further attention for future therapeutic perspectives (Cachot et al., 2021). Recently, it has been demonstrated that, in tumors with low MHC-II expression, $CD4^+$ T cells can adopt an immunosuppressive profile that

promotes tumor growth, thereby representing a potential target for depletion therapy (Wang et al., 2025a). Overall, these findings suggest that CIITA and MHC-II expression in tumor cells may favor ICI responsiveness particularly when occurring within a pre-existing immune-inflamed microenvironment in which MHC-II-dependent antigen presentation can efficiently engage tumor-reactive $CD4^+$ T cells and support $CD8^+$ T cell responses. These observations support the evaluation of CIITA and MHC-II together with complementary immune and genomic biomarkers rather than as isolated determinants of ICI sensitivity.

7.2. *Unfavorable predictive response*

In contrast, some evidence suggests that CIITA-driven MHC-II expression may contribute to adaptive resistance to immunotherapy by fostering immunosuppressive mechanisms, thereby impairing the efficacy of ICI and promoting tumor progression. For example, in MHC-II-positive melanoma and lung cancer, it was seen that the initial efficacy of immunotherapy may lead to resistance to anti-PD-1 through the upregulation on TIL of Fc receptor-like 6 (FCRL6) and lymphocyte-activation gene 3 (LAG-3). Both molecules are immunosuppressive checkpoints with higher affinity for MHC-II than CD4, thus representing new possible targets (Johnson et al., 2018). Moreover, 3D high-resolution microscopy and spatial transcriptomics on primary melanoma samples have shown the presence of MHC-II-positive tumor cells along the invasive tumor front, highlighting the importance of the spatial localization of MHC-II expression within the tumor (Nirmal et al., 2022). These findings indicate that the predictive significance of MHC-II-positive tumor cell cannot be inferred from its overall abundance alone, as its spatial localization and intratumoral heterogeneity may determine the immune cell populations with which MHC-II-positive tumor cells interact. Thus, diffuse *versus* spatially restricted MHC-II expression, as well as its proximity to activated, exhausted, or regulatory immune populations, may contribute to divergent associations with ICI response. A similar unfavorable effect was observed in nasopharyngeal carcinoma, where the interaction between MHC-II-positive tumor cells and LAG-3 expressed on $CD8^+$ T cells was associated with immune evasion and reduced anti-PD-1 efficacy (Meng et al., 2026). Importantly, viral oncogenic background represents an additional layer of complexity in this setting. In Epstein-Barr virus (EBV)-associated tumors, MHC-II upregulation may not reflect the same biological state observed in non-virally driven malignancies, as viral factors can reshape antigen-presentation pathways and immune-checkpoint interactions. Therefore, EBV status and, more broadly, viral oncogenic background should be considered when interpreting MHC-II expression on tumor cells as a predictive biomarker. Other studies further support the context-dependent predictive value of MHC-II-positive tumor cells. In advanced metastatic melanoma, MHC-II expression was associated with response to ICI monotherapy, whereas it was not required to predict benefit from combination therapy, suggesting that its predictive relevance may also depend on the specific immunotherapeutic regimen (Shklovskaya et al., 2020). Other studies suggest that the expression of MHC-II predicts a positive response to monotherapy in advanced metastatic melanoma but is not required for combination therapy (Shklovskaya et al., 2020). Overall, these findings suggest that the unfavorable predictive value of CIITA and MHC-II expression in tumor cells may emerge in specific biological contexts in which their expression contributes to immunosuppressive signaling rather than effective anti-tumor immunity. Moreover, spatial localization of MHC-II-positive tumor cells, viral oncogenic background, and the specific immunotherapeutic regimen may also contribute to adaptive resistance and reduced ICI efficacy.

Taken together, these apparently divergent observations indicate that CIITA and MHC-II should not be regarded as intrinsically favorable or unfavorable predictive biomarkers. Rather, their predictive significance should be interpreted within a context-dependent framework integrating the baseline immune status of the TME, tumor immunogenicity and TMB, the abundance and spatial localization of MHC-II-positive tumor cells, and tumor-intrinsic or etiological factors such as viral oncogenesis. The integration of these immunological, genomic, spatial, and etiological features may therefore improve the predictive value of CIITA and MHC-II for ICI response.

8. Discussion and conclusion

Different strategies have been explored to induce the expression of CIITA, the master regulator of MHC-II genes (Steimle et al., 1994), thereby enabling them to function as surrogate APC. Accordingly, CIITA-driven MHC-II-positive tumor cells may directly present their own tumor antigens to TCR on Th cells in an MHC-II-dependent manner, while also enhancing MHC-I-dependent antigen presentation to CTL (Devaiah and Singer, 2013). These approaches appear to overcome, at least in parr, the limitations associated with the lack of professional APC and costimulatory signals in the TME. Thus, by inducing MHC-II expression while simultaneously enhancing constitutive MHC-I expression, CIITA may exert a dual role in anti-tumor immunity, promoting the optimal activation of a tumor-specific adaptive immune response. This response is primarily mediated by Th cells, which, in turn, promote the clonal expansion and activation of CTL, the major effectors of anti-tumor immunity, as extensively demonstrated in preclinical settings (Meazza et al., 2003; Mortara et al., 2006, 2009; Frangione et al., 2010; Bou Nasser Eddine et al., 2017; Celesti et al., 2023; Azzi et al., 2024). Thus, rather than replacing professional APC, CIITA-expressing tumor cells may complement their activity by increasing the local availability and presentation of tumor-derived antigens that might otherwise remain poorly accessible to tumor-reactive T cells. Nevertheless, the immunogenic properties of CIITA-driven MHC-II-positive tumor cells have been questioned in GBM models, as MHC-II independent mechanisms have also been implicated. Taken together, recent preclinical studies have challenged the view that the anti-tumor effects of CIITA expression in GBM are solely attributable to its canonical role in MHC-II induction and antigen presentation. While Celesti et al. (2023) and Gatta et al. (2025) demonstrated that CIITA-positive GL261 and CT-2A glioma cells can promote protective adaptive anti-tumor immunity in orthotopic murine models, other studies provided evidence for a substantial MHC-II-independent component. In particular, Tan et al. (2023, 2024) showed that CIITA expression can directly impair GBM cell proliferation through cell-cycle inhibition and P27KIP1 upregulation, thereby contributing to tumor growth retardation independently of an intact immune system. Conversely, Salvato et al. (2025) reported that CIITA expression can enhance T cell-mediated tumor cell killing in human GBM organoids even when CIITA is unable to induce MHC-II expression, further supporting the existence of non-canonical immunomodulatory functions. Thus, although current evidence supports an overall tumor-suppressive and potentially immunostimulatory role for CIITA in GBM, the relative contributions of MHC-II-dependent *versus* MHC-II-independent mechanisms remains unresolved. These apparently divergent findings may reflect differences in experimental models, cellular contexts, culture conditions, and TME composition, highlighting the need to further elucidate the context-dependent mechanisms underlying the anti-tumor activity of CIITA in GBM.

The capacity of CIITA to increase tumor immunogenicity nevertheless creates several opportunities for therapeutic exploitation. CIITA-positive tumor cells can potentially reveal broader repertoires of MHC-I- and MHC-II-restricted tumor-derived peptides, which may facilitate the identification of relevant antigens for cell-based, peptide-based, exosome-based, or nucleic acid-based vaccination strategies. Such approaches may be particularly relevant for poorly immunogenic tumors such as GBM, in which the relatively low tumor mutational burden may limit the repertoire of conventional mutation-derived neoantigens. However, these conventional anti-tumor vaccines have encountered critical difficulties based on the rather limited approach to stimulate and allow to persist anti-tumor immune specific response for long period

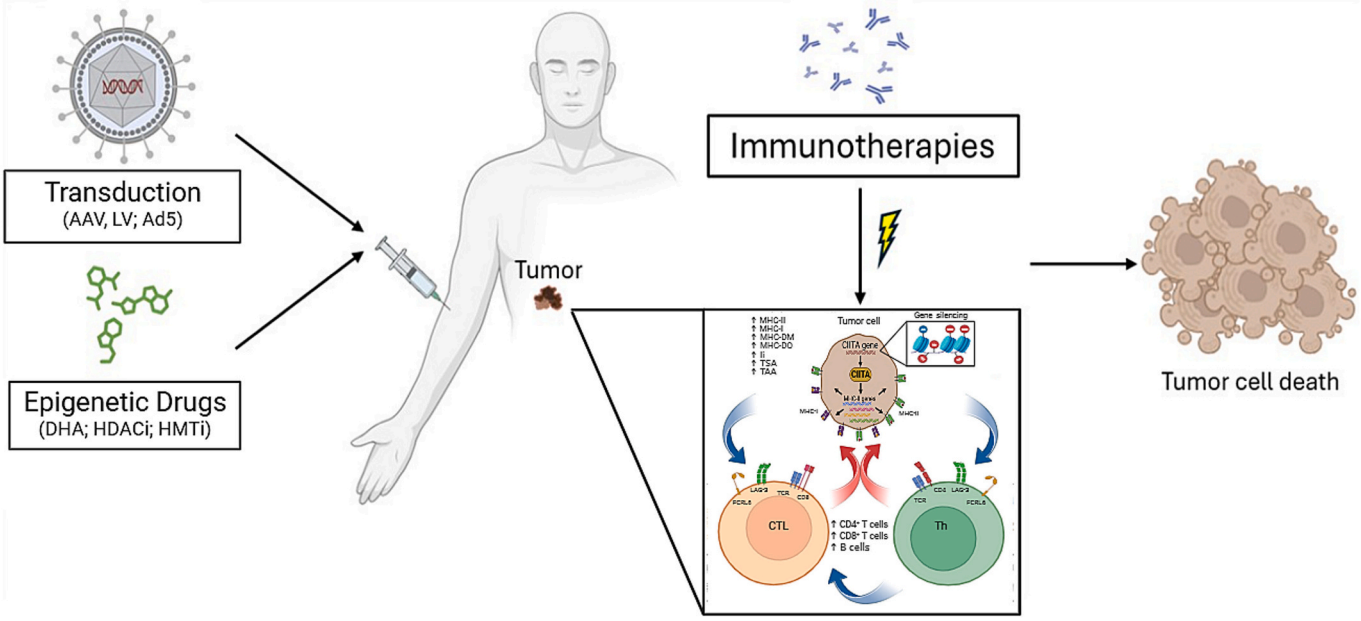


Fig. 4. *In vivo* therapeutic induction of CIITA as a strategy to enhance anti-tumor immunity and support combination immunotherapy. CIITA expression may be induced directly in tumor cells *in vivo* through gene-delivery approaches, such as viral transduction, or indirectly through epigenetic drugs that reverse endogenous CIITA silencing. Restoration of CIITA expression promotes tumor-cell MHC-II induction and activation of the antigen-processing and presentation machinery, thereby increasing tumor immunogenicity and enhancing adaptive anti-tumor immune responses. This provides a rationale for combining CIITA-directed tumor reprogramming with immunotherapeutic approaches, particularly ICI, to sustain and amplify tumor-reactive T-cell responses and promote tumor cell killing. Created in BioRender.com.

(Vermaelen, 2019). In parallel, direct delivery of CIITA to tumor cells could extend the concept of CIITA-based vaccination from *ex vivo* genetically modified cells to *in vivo* tumor reprogramming. Viral vectors currently represent the most established approach for efficient gene transfer and may be further exploited through oncolytic platforms combining direct tumor-cell killing with CIITA-dependent enhancement of tumor antigen presentation (Shallak et al., 2026). However, viral delivery remains limited by several translational challenges, including vector immunogenicity, insertional mutagenesis for integrating vectors, packaging constraints, off-target transduction, and the risk of inappropriate CIITA expression in non-tumor tissues. Emerging non-viral approaches, particularly LNP-mediated delivery of CIITA mRNA, may partially overcome some of these limitations by enabling transient, non-integrating and potentially repeatable CIITA expression and by providing opportunities for tumor-targeted delivery (Wang et al., 2023). Nevertheless, efficient tumor penetration, cell-selective targeting, payload stability, endosomal escape, biodistribution, and the achievement of sufficient and reproducible CIITA expression remain major challenges. Comparative studies should therefore define not only which platform most efficiently induces CIITA *in vivo*, but also the magnitude, cellular distribution, and duration of expression required to elicit effective anti-tumor immunity without unacceptable systemic immune activation.

An alternative and potentially more readily translatable strategy is the pharmacological reactivation of endogenous CIITA through epigenetic drugs acting at multiple regulatory levels, including DNA methylation, histone modifications, and chromatin remodeling. However, the major classes of epigenetic agents are not interchangeable, and their selection should ideally reflect the mechanism underlying CIITA repression. DHA currently have the greatest clinical maturity and broader immunomodulatory activity, including in combination with ICI, and may efficiently restore CIITA and MHC-II expression when silencing is associated with promoter DNA methylation. By contrast, HDACi or HMTi may be more effective when repression is predominantly sustained by repressive histone modifications or chromatin condensation, whereas combination approaches may be required when multiple mechanisms coexist. Thus, the molecular mechanism responsible for CIITA repression should ideally guide the selection of the epigenetic intervention rather than assuming a universal CIITA-inducing strategy across tumor types. This issue is particularly relevant because epigenetic drugs broadly remodel tumor-cell transcription and do not selectively target CIITA. Their therapeutic potential should therefore not be evaluated solely according to doses conventionally used for direct antineoplastic activity. Instead, future CIITA-directed approaches should identify the minimum biologically effective dose capable of restoring sufficient CIITA and MHC-II expression while minimizing off-target epigenetic effects and toxicity. Moreover, the optimal agent, dose, duration of treatment, and sequence or combination with ICI remain to be clinically defined. In this context, epigenetic therapy could serve as an immunological priming step to restore tumor-intrinsic CIITA/MHC-II expression and antigen presentation, followed by or combined with checkpoint blockade to sustain and amplify adaptive immune response (Ghasemi, 2020; Lu et al., 2020; Yu et al., 2024). Prospective evaluation of treatment-induced changes in CIITA/MHC-II expression could therefore provide a useful pharmacodynamic readout in future clinical studies of CIITA-directed epigenetic priming.

The potential clinical relevance of the CIITA/MHC-II axis also extends to its use as a biomarker of immunotherapy response. However, available evidence indicates that neither CIITA nor tumor-cell MHC-II expression appears to represent an intrinsically favorable or unfavorable predictors of ICI efficacy, as their significance is strongly context dependent. In immune-inflamed microenvironment containing pre-existing tumor-reactive lymphocytes, MHC-II-positive tumor cells may enhance $CD4^+$ T cell recognition and support productive anti-tumor immunity and ICI responsiveness. Conversely, MHC-II expression may coexist with adaptive immunosuppressive pathways or dysfunctional immune state and may therefore fail to predict or even associate with reduced therapeutic benefit. CIITA and MHC-II expression should thus be interpreted together with complementary features including the baseline immune status of the TME, tumor immunogenicity and TMB, the abundance and spatial localization of MHC-II-positive tumor cells, and tumor-intrinsic or etiological factors such as viral oncogenesis, and

the specific immunotherapeutic regimen. Such an integrated framework may ultimately provide greater predictive value than assessment of CIITA or MHC-II expression alone and may improve patient stratification for CIITA-directed combination therapies.

In conclusion, CIITA represents a unique link between tumor-cell biology and adaptive anti-tumor immunity and provides a compelling rationale for therapeutically converting poorly immunogenic tumor cells into more immunologically visible targets. Nevertheless, its effects are strongly context dependent and extend beyond MHC-II induction. Future studies should therefore determine, across tumor settings, the mechanisms responsible for CIITA repression, the relative contribution of MHC-II-dependent and MHC-II-independent activities, and the level and duration of CIITA expression required for therapeutic benefit. In parallel, clinically applicable strategies for tumor-selective CIITA restoration will need to balance efficacy with off-target effects and systemic toxicity. Among currently available approaches, epigenetic reactivation may represent the most readily translatable strategy, provided that treatment is tailored to the mechanism of CIITA silencing and administered at biologically effective rather than maximally tolerated doses to limit off-target effects and systemic toxicity. Combining CIITA-directed epigenetic priming with ICI may thereby convert selected MHC-II-negative, poorly immunogenic tumors into a more immune-inflamed and therapeutically responsive state. Ultimately, prospective assessment of CIITA and MHC-II restoration together with immune, genomic, spatial and etiological biomarkers will be essential to identify the patients most likely to benefit and to determine whether pharmacological manipulation of the CIITA/MHC-II axis can ultimately be translated into an effective personalized immunotherapeutic strategy (Fig. 4).

CRediT authorship contribution statement

Fabrizio Celesti: Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization, Writing – review & editing, Writing – original draft.

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