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REVIEW

Concise review: The heterogenous roles of BATF3 in cancer oncogenesis and dendritic cells and T cells differentiation and function considering the importance of BATF3-dependent dendritic cells

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Abstract

The transcription factor, known as basic leucine zipper ATF-like 3 (BATF3), is a crucial contributor to the development of conventional type 1 dendritic cells (cDC1), which is definitely required for priming CD8 + T cell-mediated immunity against intracellular pathogens and malignancies. In this respect, BATF3-dependent cDC1 can bring about immunological tolerance, an autoimmune response, graft immunity, and defense against infectious agents such as viruses, microbes, parasites, and fungi. Moreover, the important function of cDC1 in stimulating CD8 + T cells creates an excellent opportunity to develop a highly effective target for vaccination against intracellular pathogens and diseases. BATF3 has been clarified to control the development of CD8α$^+$ and CD103$^+$ DCs. The presence of BATF3-dependent cDC1 in the tumor microenvironment (TME) reinforces immunosurveillance and improves immunotherapy approaches, which can be beneficial for cancer immunotherapy. Additionally, BATF3 acts as a transcriptional inhibitor of Treg development by decreasing the expression of the transcription factor FOXP3. However, when overexpressed in CD8 + T cells, it can enhance their survival and facilitate their transition to a memory state. BATF3 induces Th9 cell differentiation by binding to the IL-9 promoter through a BATF3/IRF4 complex. One of the latest research findings is the oncogenic function of BATF3, which has been approved and illustrated in several biological processes of proliferation and invasion.

Keywords Basic leucine zipper transcription factor ATF-like 3 · *BATF3* · *BATF3*-dependent dendritic cells · Oncogene

Introduction

One of the unique and common features among the transcription factors of the basic leucine zipper (bZIP) large family, such as c-FOS and c-Jun, is a DNA-binding region and a basic leucine zipper motif. By using their helical leucine zipper motif, they form a heterodimer together. These proteins with heterodimeric structures are parallel and coiled-coil (Ellenberger 1994; Landschulz et al. 1988). Charles Vinson et al. divided b-ZIP proteins into three general groups and 12 families based on dimerization properties. FOS, CNC, and large MAF families have a strong tendency toward heterodimerization instead of homodimerization.

The basic leucine zipper transcription factor ATF-like (BATF) subgroup is part of the FOS family (Landschulz et al. 1988; Vinson et al. 2002). The BATF transcription factor subgroup includes BATF, BATF2, and BATF3. Heterodimer forms of BATF with c-Jun, JunB, or JunD, and BATF2 with c-Jun suppress the activity of AP-1 transcription factors (Dorsey et al.

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1995; Aronheim et al. 1997). BATF3 inhibits FOS/JUN dimer formation by forming a heterodimer with c-JUN, and in competition with c-FOS, reduces IL-2 promoter activity by forming a ternary complex between BATF3, JUN, and nuclear factor of activated T cells (NF-AT) (Iacobelli et al. 2000; Bower et al. 2002). BATF3 is cytogenetically situated on the long arm of chromosome 1 in humans and mice, and is close to the transcription factor ATF3. BATF3 does not have a transactivation domain, which has been shown to have positive transcriptional activity by binding to the interferon-regulatory factor (IRF) family members (Murphy et al. 2013). Apart from mammals, rainbow trout (Oncorhynchus mykiss) also possess two BATF3 homologs known as BATF3a and BATF3b, which could have a regulatory and responsive function in the immune system of fish (Wang et al. 2018). A fundamental study showed various functions of the BATF3 homologue, the so-called ciBATF3, in the grass carp (*Ctenopharyngodon idella*), in immune modulation, which negatively regulates the AP-1 and NF-kB reporter gene transcriptional activity (Zhu et al. 2019).

This concise review study aimed to describe the roles of BATF3 in the differentiation of several immune cells, such as a group of dendritic cells (DCs) involved in cross-presentation and several groups of T cells, and the importance of BATF3-dependent DCs in defense against tumors, viruses, parasites, fungi, and bacteria, as well as various diseases and transplants. We also described the oncogenic role of BATF3 and how targeting the BATF3, whose downstream pathways are involved in several types of cancer, can be a promising treatment in future.

BATF3 and DCs relationship

A brief overview of DCs

DCs are heterogeneous cell populations in the immune system that are divided into three main types based on ontogeny and function: classical or conventional DCs (cDCs), plasmacytoid DCs (pDCs), and monocyte-derived inflammatory DCs (Inf-moDCs). The first two in bone marrow originate from common DC progenitors (CDP), but the latter type originates from monocytes in inflammatory conditions. Dendritic and epithelial cell-205 (DEC-205), C-type lectin domain family 9 member A (CLEC9A), cell adhesion molecule 1 (CADM1), and XC chemokine receptor 1 (XCR1) are markers for human cDC1s (Patente et al. 2018). The major transcription factor in the formation of myeloid cDC1 is BATF3 (Grajales-Reyes et al. 2015). Since human cDC2s express CD1c, CD11c, and signal regulatory protein alpha (SIRPα), they are commonly called blood DCs antigen (BDCA)-1 DCs (Heger et al. 2018). The transcription factors for cDC2s are IRF-4 and IRF8 (Schlitzer et al. 2013). pDCs are characterized by the expression of $CD4^+$, $CD123^+$, $CD303^+$, and $CD45RA^+$ (Cao 2009). pDC transcription factor has been determined to be E2.2 (Reizis 2019). Human Ifn-moDCs exhibit a variety of surface markers, including as BDCA-1, CD1a, CD11c, and CD14 (Collin and Bigley 2018). For moDCs to differentiate in the bone marrow, the transcription factor IRF-4 is necessary (Inaba et al. 1992) (Fig. 1). Immature DCs in tissues, like other antigen-presenting cells, possess a high ability to process and capture antigens. They also have pattern recognition receptors (PRRs) on their surface, which allow them to detect and bind to damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). Mature DCs have high migration power and show high expression of co-costimulatory molecules, proinflammatory cytokines, chemokines, and the chemokine receptor CCR7 (Dalod et al. 2014; Sánchez-Sánchez et al. 2006; Wang et al. 2020). Functionally, mouse cDCs are divided into two distinct lineages: the CD11b + cDC2 lineage and the CD8 α + (CD103 +) cDC1 lineage, with the commitment of DC progenitor cells to the cDC1 or cDC2 lineage occurring in bone marrow (Schlitzer et al. 2015). One of the most important roles of DCs in defense against viruses and tumors is cross-presentation or cross-priming. Once they have taken up and processed extracellular antigens, immature DCs present these antigens to cytotoxic T lymphocytes (CTLs) via the major histocompatibility complex (MHC) class I. This presentation then triggers a cytotoxic response by the CTLs (Wang et al. 2020).

The roles of BATF3 in DCs differentiation

In mice, classical type 1 dendritic cells (cDC1) are major cross-presenting DCs, containing CD8 + DCs in lymphoid tissues and CD103 + CD11b DCs in non-lymphoid tissues, whereas cDC1 are developmentally reliant on the BATF3 transcription factor (Edelson et al. 2010); it has been observed that pDCs can also perform cross-presentation activity (Hoeffel et al. 2007). In mice, the CD8 marker in CD8α + DCs has the form of α/α homodimer, while in typical T cells, it has the form of a heterodimer. To date, no interesting role has been suggested for CD8 in CD8α + DCs differentiation and function (Vremec et al. 1992; Crespo et al. 2013). In the presence of inflammasome activation, BATF3-independent cDCs are responsible for the cross-presentation of intestinal epithelial cells (IECs)-derived antigens to CTLs, whereas in the absence of inflammasomes, BATF3-dependent cDCs are responsible for this task (Deets et al. 2021). Homologous cDC1 are present in humans' blood and are distinguished by the expression of CD141 (known as thrombomodulin and BDCA3) and lymphoid and non-lymphoid tissues, whereas classical type 2 DCs in humans are characterized by CD1c, known as BDCA1 expression (Haniffa et al. 2012; Bachem et al. 2010; Guilliams et al. 2014). cDC1 is developmentally dependent on IRF-8 and BATF3 in mice and humans. BATF3 maintains IRF8 autoactivation via the + 32-kb IRF8 enhancer, which

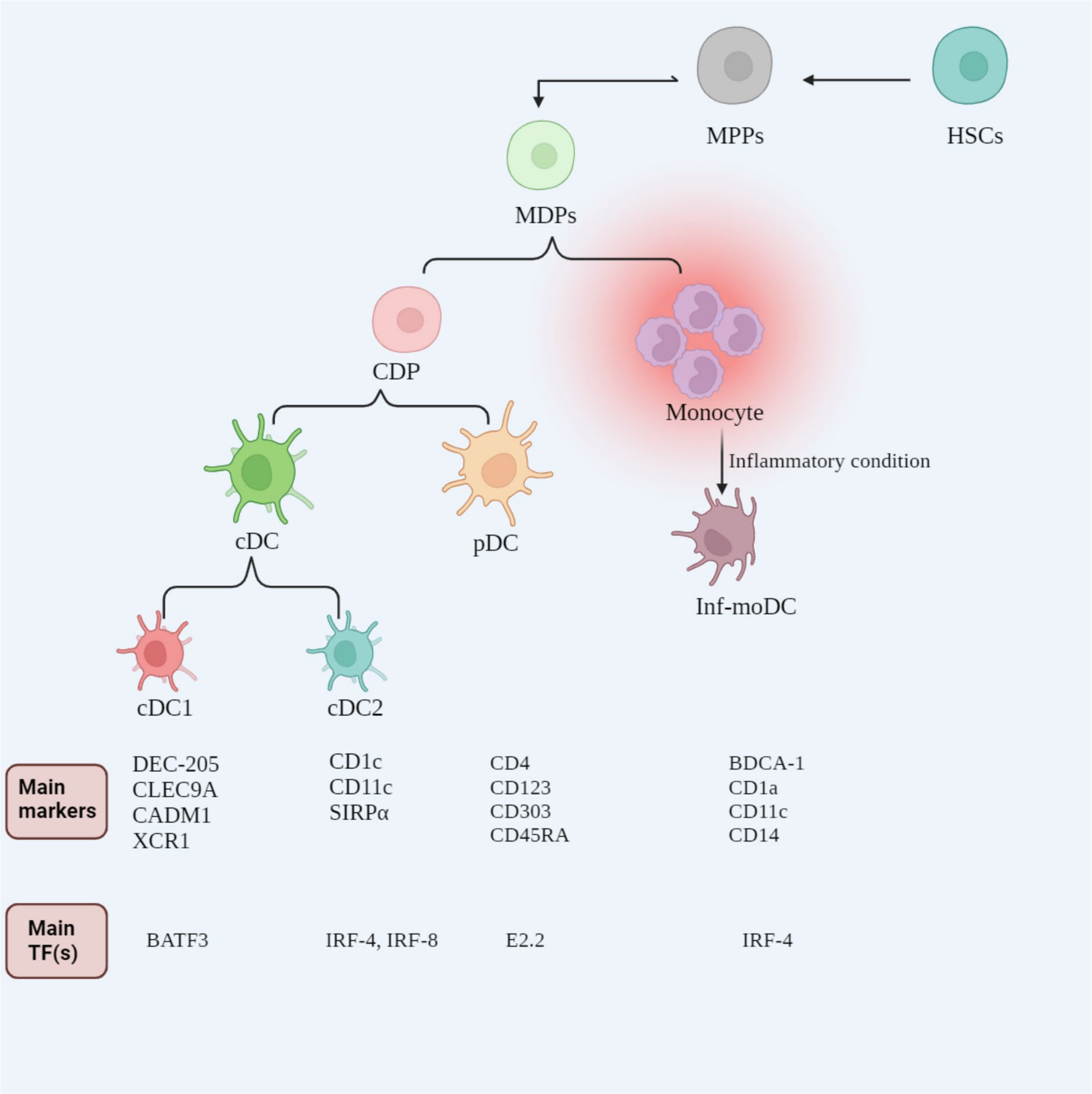

Fig. 1 Different DC subsets and their characteristics. pDC, cDC, moDC, the main subsets of DCs, and their main transcription factors and markers have been shown in this picture. Abbreviations: BATF3, basic leucine zipper transcription factor ATF-like 3; BDCA, blood DCs antigen; CADM1, cell adhesion molecule 1; cDC, conventional dendritic cells; CDP, common DC progenitor; CLEC9A, C-type lectin domain family 9 member A; DC, dendritic cell; DEC-205, dendritic and epithelial cell-205; HSC, hematopoietic stem cells; Ifn-moDC, monocyte-derived inflammatory DCs; IRF, interferon regulatory factor; MDP, macrophage dendritic cell progenitor; MPP, multipotent progenitors; pDC, plasmocytoid dendritic cell; SIRPα, signal regulatory protein alpha; XCR1, XC chemokine receptor 1

consists of numerous AP1-IRF composite motifs with binding capacity to IRF-8 and BATF3, but only IRF8 can bind to the + 41-kb IRF8 enhancer; therefore, in BATF3-deficient mice, CD8α + cDC development is inhibited due to impaired IRF8 autoactivation (Grajales-Reyes et al. 2015). Vivek Durai et al. showed that the + 32-kb IRF8 enhancer, which is active in adult cDC1s, is necessary for the development of cDC1 cells, and the + 41-kb IRF8 enhancer, which is active in plasmacytoid DCs, is also needed for cDC1 specification (Durai et al. 2019). NFIL3 in CDP cells causes cDC1 specification by imposing IRF8 enhancer switching via the Nfil3–Zeb2–Id2 pathway (Bagadia et al. 2019). IRF8, as a major regulator of CD8α + DC development, causes overexpression of transcription factors BATF3 and Id2. Co-expression of IRF8, BATF3, and Id2 has a synergistic impact on inducing CD8α + DC development (see Fig. 1) (Jaiswal et al. 2013). Kuldeep Singh Chauhan et al. demonstrated that upregulation of Pfkfb3 expression in cDC1s is driven by the interaction between IRF8 and BATF3 and not by ID2 (Chauhan et al. 2022). An alternative pathway for the development of CD8α + classical DCs in BATF3-/-mice is a cytokine-dependent rescue that is compensated by BATF and BATF2 transcription factors. The positive function of BATFs in the development of DCs is complexation with IRF-4 and IRF-8 (Tussiwand et al. 2012). The non-essentiality of BATF3 in the evolution of CD8-alpha positive DC cells and their cross-presentation has also been mentioned, although these induced cells have short-term survival, which highlights the essential role of BATF3 in increasing cell survival (Seillet et al. 2013). Specific markers of BATF3-dependent cross-presentation of DCs are expressed through the chemokine receptors XCR1 and DNGR-1 (CLEC9A) (Poulin et al. 2012; Bachem et al. 2012). It is confirmed that the development of cDC1 depends on BATF3, but Samuel W. Lukowski et al. indicated that BATF3-/-mice have a population of cDC1-like cells co-expressing cDC2-associated surface molecules that highlight the existence of heterogeneity in cDCs (Lukowski et al. 2021). In this review, we will mention the importance of BATF3-dependent DCs in antitumor responses and a number of infections and diseases.

The importance of BATF3-dependent DCs in various conditions and immunity

The roles of BATF3-dependent DCs in malignancies

Breast cancer patients with high expression of genes related to CD8 + T cells, CD4 + T cells, cDC1s, and the presence of interferon (IFN) responses tend to have a better prognosis (Mattiuz et al. 2021). Melissa A. Meyer et al. showed that one of the mechanisms of escaping the immune system of localized breast and pancreatic tumors is downregulation of IRF8 by tumor-derived granulocyte stimulating factor. This mechanism is carried out by impaired cDC1 development, impaired CD8 + T cell response, and overcoming immunosurveillance (Meyer et al. 2018). Due to the induction of cellular apoptosis by IL-6 during pancreatic cancer carcinogenesis, the abundance and maturation of cDC1 cells are systematically and progressively impaired. The synergistic effect of CD40 agonist and FMS-like tyrosine kinase 3 ligand (Flt3L) is linked to cDC1 performance and abundance rescue (Lin et al. 2020). Stefani Spranger et al. showed that the presence of intratumoral BATF3-dependent CD103 + DCs results in the trafficking of adoptively transferred CTLs to the tumors through the secretion of CXCL10 and CXCL9; thus, lacking this DC subset within the TME helps the immune escape of cancer cells (Spranger et al. 2017). The major source of interleukin-12 in the body is cDC1s. Interleukin-12 is a pro-inflammatory cytokine that skews the CD4 + T cell response to Th1-immunity and also adjusts T cell and natural killer (NK) cell responses (Trinchieri 2003). Deepak Mittal et al. showed that BATF3-deficient mice are unable to produce IL-12 due to deficiencies in CD103 + DCs, which highlights the imperative role of CD103 + DCs-derived interleukin-12 in the inhibition of tumor metastasis by NK cells (Mittal et al. 2017).

The roles of BATF3-dependent DCs in cancer therapy

Anti-cancer vaccination and various approaches of immunotherapy

In the strategy of anti-cancer vaccination, one of the aims for the superior activation of CD8 + T cells is the maturation of cDC1s, the massive production of IL-12 by these cells, and the fact that cDC1s partially activate NKT and NK cells (Grabowska et al. 2021a). After the ganglioside GM3 liposomal vaccination, the presence of CD169 + macrophages and BATF3-dependent DCs is required for the induction of the CD8 + T cell response (Grabowska et al. 2021b). Production of cDC1-derived IL-27p28 after immunization can be a criterion for estimating CD8 + T cell memory and protective immunity responses (Kilgore et al. 2020). During tumor rejection, the presence of CD40 signaling and major histocompatibility class II molecules in cDC1 cells aids in the early activation of CD4 + T cells (Ferris et al. 2020). Additionally, apart from the role of BATF3 in cDC1 development, it plays a vital role in inducing tumor rejection, as it regulates the expression of various genes independent of cross-presentation (Theisen et al. 2019). The presence of cDC1s and NK cells, as well as bidirectional cross-talk between them in the TME, can improve cancer immunotherapy. NK-cells cause cDC1 recruitment by producing some chemokines, and by producing FLT3L, cause differentiation, survival, recruitment, and the penetration of cDC1s into TME; they also lead to cDC1 maturation by producing some cytokines. In contrast, cDC1s, through CD40/CD40L ligation, induce NK cell proliferation and, by producing certain cytokines, stimulate the production of IFN-γ, TNF-alpha, or GM-CSF by NK-cells (Bödder et al. 2021). Margaux Hubert et al. showed that in breast tumors, selective expression of type III interferon (IFN-gamma) by human cDC1s is associated with good clinical outcome; also, TLR3 stimulation induced IFN-gamma 1 production by cDC1, which can be a good immunotherapy strategy (Hubert et al. 2020). NK cells produce XCL1 and CCL5 chemokines to recruit cDC1 into the tumor microenvironment, which is related to overall patient survival. One of the immune evasion mechanisms of cancer cells is the production of prostaglandin E2 (PGE2) and chemokines to inhibit XCL1 and CCL5, which can also be used in cancer immunotherapy (Böttcher et al. 2018). Nuclear factor κ B(NF-κB) and interferon (IFN) pathways are essential for tumor-infiltrating cDCs to recruit and activate CD8 + T cells, which are disrupted by inactivation of NF-κB and IFN regulatory factor 1 (IRF1) in cDC1s. Upregulation of the NF-κB / IRF1 axis is associated with a better clinical outcome in patients with melanoma, so this axis can be targeted to improve and enhance the efficiency of cancer immunotherapy (Ghislat et al. 2021). Tumor-associated immunosuppressive cytokines, such as interleukin (IL)-10, initiate intracellular signaling that activates signal transducer and activator of transcription 3 (STAT3). This activation of STAT3 results in the suppression of anti-tumor immune responses. In one study, a tumor vaccination method including STAT3 deficient in CD103 + cDC1s constrained tumor growth and effectively raised mouse surveillance compared to STAT3-sufficient CD103 + cDC1s (Chrisikos et al. 2020). Medina BD et al. showed that the inhibition of antitumor property of oncogenic kinase by imatinib in gastrointestinal tumors (GIST) is different in short- and long-term therapy. In the short term, imatinib has positive antitumor effects that are partially dependent on CD103 + CD11b DCs, which are important for raising the cytotoxic response of CD8 + T cells. In the long term, imatinib reduces CD103 + CD11b-DCs via diminishing GM-CSF, which brings about a reduced antitumor response of CD8 + T cells (Medina et al. 2019). Peihong Dai et al. demonstrated that intratumoral delivery of inactivated modified vaccinia virus Ankara (iMVA) has antitumor effects and increases type 1 interferon levels by cDCs, while less anti-tumor properties and IFN-1 production were observed in BATF3-deficient mice, indicating the importance of BATF3-dependent DCs in immunotherapy with iMVA (Dai et al. 2017). The efficacy of immunomodulatory monoclonal antibodies (mABs), such as anti-PD1 and anti-CD137, is dependent on Flt3L- and BATF3-dependent DCs because the cross-priming action of tumor-infiltrating lymphocytes (TILs) depends on the presence of these cells (Sánchez-Paulete et al. 2016). Combined administration of poly I:C and Flt3L results in the activation of CD103 + DCs in the tumor. Tumor-resident CD103 + DCs capture tumor antigens, migrate to draining lymph nodes, and then cross-present to CTLs; therefore, the presence of CD103 + DCs contributes to improving the therapeutic efficacy of PD-L1 and BRAF inhibition (Salmon et al. 2016). However, the accumulation of tumor-infiltrating cDC1s induced by antitumor therapy based on high Flt3L expression is constrained by the presence of DNGR-1. As a result, DNGR-1 blockade can enhance the effectiveness of treatment (Cueto et al. 2021). Man Zhang et al. showed that the efficacy of anti-PD-1 therapy is enhanced by supplementation with CCL7. It means that it acts as an adjuvant and induces recruitment of cDC1 cells to the TME site in a non-small cell lung cancer (NSCLC) mouse model, which leads to the promotion of T cell expansion (Zhang et al. 2020). In patients with advanced melanoma, the number of CD141 + DCs is greatly reduced. A study using a humanized mouse model transplanted with a human melanoma cell line showed that a combination of CD141 + DCs with anti-PD1 therapy was associated with reduced tumor growth (Lee et al. 2021b). Nader El-Sayes *et al.* showed that in mismatch repair-deficient colorectal carcinoma (dMMR CRC), combined administration of oncolytic HSV-1 and low-dose mitomycin C, with immune checkpoint inhibitors (ICI), increased tumor susceptibility to ICI therapy through the infiltration of CTLs, helper T cells, and cDC1s into the tumor, and importantly, the effectiveness of this combination therapy depends on the cDC1s in the tumor (El-Sayes et al. 2022).

Neoadjuvant immunotherapy Neoadjuvant immunotherapy is a strategy where immune checkpoint inhibitors (ICIs) are prescribed individually or in combination before surgery, which is one of the most important ICIs that can be used in resectable tumors, including anti-programmed cell death-1 (PD1) and anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) monoclonal antibodies (Krishnamoorthy et al. 2021). Neoadjuvant immunotherapy with anti-PD1 induces T cell infiltration and cDC1 activation, but the most infiltrating immune cells are a group of macrophages that have immune suppressive activity in recurrent glioblastoma (Lee et al. 2021a). BATF3-dependent DCs play a critical role in enhancing neoadjuvant immunotherapy. A phase Ib clinical trial that compared neoadjuvant versus adjuvant ipilimumab and nivolumab combinations in stage III melanoma patients showed that patients who experienced relapse had low expression of genes associated with BATF3 + DCs in their tumors prior to treatment (Liu et al. 2019).

Chimeric antigen receptor (CAR) T cell therapy

Chimeric antigen receptor (CAR) T cell therapy has shown promise in the treatment of B-cell malignancies. However, progress has been slower in solid tumors due to the absence of a suitable surface target. Therefore, further research and experiments are required in this field (Taefehshokr et al. 2020). Nicholas F. Kuhn et al. demonstrated that CD40L-overexpressing CAR T cell therapy increased the expression of the main gene for cDC1 differentiation, IRF-8, as well as CCR7 in tumor-resident CD11b-CD103- double-negative (DN) cDCs, skewing their differentiation toward CD11b-CD103 + cDC1. They also demonstrated that the presence of endogenous CTLs is required for memory antitumor responses (Kuhn et al. 2020). As a result, ongoing studies achieved promising results regarding the use of these types of DCs in strengthening the immune system to fight tumors in immunotherapy.

The roles of BATF3-dependent DCs in viral immunity

BATF3-/-mice have no response against highly immunogenic syngeneic tumors and West Nile virus due to disruption in the development of CD8α + DCs with subsequent impairment of CD8 + T cell activity, which highlights the importance of cross presentation in antiviral and cancer defense (Hildner et al. 2008). Due to the defects in BATF3-dependent DCs, BATF3-deficient mice are highly prone to respiratory vaccinia virus infection because the accumulation, proliferation, and differentiation of antigen-specific CD8 + T cells in the lungs is compromised (Desai et al. 2018). Rotavirus (RV)-specific IgA response requires BATF3-dependent cDC1, since the activation of TGFβ by the cDC1s-derived αvβ8 integrin pathway is essential for IgA class switching in the gut (Nakawesi et al. 2020). BATF3 dependent DCs are required for CD8 + T cell priming and activation in rotavirus infected-adult and neonatal mice. Adult mice showed a significant amount of CTLs response in the small intestine in the lack of the BATF3 expression, indicating the presence of a compensatory cross-presentation mechanism. However, unlike adult mice, neonatal BATF3-deficient mice showed no CTL response, but local and systemic IgA secretion remained intact. This mechanism may be due to the probable main role of innate immunity in infection controlling (Sun et al. 2017). CD8α + DC plays a critical role in the maintenance and establishment of herpes simplex virus type 1 (HSV-1) latency (Mott et al. 2014). However, in BATF3-/-mice, CD8α + DC are seen and viral latency is normal; so, BATF3 is not a critical factor in the production of CD8α + DCs (Mott et al. 2015). Tracheal cDC1 and cDC2 subtypes are not infected with porcine reproductive and respiratory syndrome virus (PRRSV), but they show differential expression of Toll-like receptors (TLRs) and cytokines (Reséndiz et al. 2018). In BATF3-/-mice with mouse cytomegalovirus (MCMV) infection, the priming of MCMV-specific CTL cells is disrupted due to the reduction in the population of CD8-alpha positive and CD103 positive cells. In these mice, there was a group of normal inflationary T cells, indicating that they are dependent on the direct presentation (Torti et al. 2011).

The roles of BATF3-dependent DCs in bacterial immunity

CTL cells are important for defending against a range of intracellular pathogens, and BATF3-dependent CD8α + DCs play a key role in priming CD8 + T cells. However, in BATF3-deficient mice, the response of CTLs against *Salmonella enterica* serovar *Typhimurium* (ST) infection is impaired (Patel and Sad 2016). Sudhanshu Shekha et al. demonstrated that CD103 + lung dendritic cells (LDCs) skew the immune response toward Th1/Th17 immunity by producing a variety of cytokines such as IFN-γ and IL-17, highlighting the importance of these DCs in respiratory bacterial infections (Shekhar et al. 2018). BATF3-dependent CD103 + DCs shifted the immune response toward a Th-1-mediated response, which induces effector and pTreg cell recruitment to the *Helicobacter pylori* infection site by prompting CXCR3 expression on effector and pTreg cells and stabilizing CXCR3 ligand expression on infected tissues (Arnold et al. 2019). Jessica Nancy Imperato et al. showed that in case of using *Listeria monocytogenes* modified to induce foodborne insufficiency in mice, trafficking of these pathogens from the gut to the mesenteric lymph nodes (MLNs) is not BATF3-dependent, while inducing bacterial accumulation in the MLN and inducing the Lm-Specific CD8 T cell responses are reliant on BATF-dependent DCs, that can be a good target for vaccine design (Imperato et al. 2020). One study found that in LM infection, in response to bacterial P60 protein, NLRP3, a sensor of the inflammasome, is expressed in DCs, triggering the release of IL-18, which also IL-18 signals license to NK-cells to produce IL-10 and more severe systemic LM infection. BATF3-dependent cells are also an important source of IL-18 production; so, BATF3 expression is required to induce systemic LM infection. As a result, the BATF3/NLRP3/IL-18 axis causes the pathogenesis of severe LM infection (Clark et al. 2018).

The roles of BATF3-dependent DCs in parasite infections and fungal immunity

BATF3-dependent CD103 + DCs show a significant role in defending against the acute phase of *Cryptosporidium parvum* infection via secreting the cytokines IFN-gamma and IL-12 and CD8 + T cell priming (Potiron et al. 2019). BATF3-deficient mice with *Schistosoma japonicum* infection also showed improvement in hepatic pathological symptoms, which is associated with a stronger response of CD8 + T cells by a number of CD8α + DCs in the spleen that compensate for cross-presentation (Chen et al. 2017). BATF3-deficient mice infected with *Plasmodium berghei* ANKA (PbA) exhibit defects in the cytotoxic responses of CD8 + T cells. However, they also have high levels of regulatory cells and anti-inflammatory cytokines such as IL-10, which protect them from experimental cerebral malaria (Kuehlwein et al. 2020). Vaccination with attenuated plasmodium sporozoites is associated with the accumulation of BATF3-dependent CD8-alpha positive DCs in the liver, which activates the CD8 + T cell-related response and thus increases vaccine immunogenicity by cross-presenting plasmodium pre-erythrocytic antigens (Montagna et al. 2015). One study found that BATF3-/-mice exposed to *Leishmania major* infection showed severe skin symptoms. CD103 + DCs are the main secretors of IL-12 during *L.*

major infection, and development of these cells is dependent on BATF3. In the case of BATF3 deficiency, local Th-1 immunity is disrupted and the mouse immune system is skewed toward Th-2 and Treg immunity (Martínez-López et al. 2015). BATF3-dependent DCs play an important role in the immune response and resistance against human visceral leishmaniasis, which can be used by targeting these DCs and delivering *Leishmania infantum* parasitic antigens to these DCs for rational vaccine design and targeted immunotherapy (Soto et al. 2020). BATF3 deficient mice are vulnerable to *Toxoplasma gondii* infection due to reduced production of IL-12 by CD8α + DCs, while administration of IL-12 restores resistance against *T. gondii* infection, which highlights the importance role of CD8α + DCs in *T. gondii* infection resistance via IL-12 production (Mashayekhi et al. 2011). Another study revealed that in BATF3-/-mice, innate immune responses against *T. gondii* are delayed due to the absence of CD8-alpha positive DCs, but are able to eliminate the pathogen. In these mice, CD-4 positive T cells replace the response against this pathogen and, by producing IFN-gamma, lead to a severe delayed response against *T. gondii* (Tussiwand et al. 2020). The commensal strain of *Cryptosporidium tyzzeri* (Ct-STL) induces a type 1 T helper cell response to help intestinal immune homeostasis. Inducing the Th1 response requires cDC1 cells, as a lack of cDC1 cells shifts the immune system toward Th17 and regulatory T cells (Russler-Germain et al. 2021). In group 1 innate lymphoid cells (ILC1), expression of T-bet transcription factor induces IFN-γ production, and IFN-γ upregulates the expression of IRF8, and thereby maintains the cDC1 population in *T. gondii* infection. Production of IFN-γ by NK cells also preserves the cDC1 population in *T. gondii* infection (López-Yglesias et al. 2021). Induction of CD103 + DC accumulation by BATF3 gene expression during mucosal and systemic candidiasis infection is also dispensable (Break et al. 2016).

The roles of BATF3-dependent DCs in tolerogenic and autoimmune response

BATF3-dependent CD103 + CD11b DCs are promising targets in immune tolerance promotion and vaccination (Mayer et al. 2014). CD103 + DCs isolated from MLNs, through the expression of endogenous transforming growth factor (TGF) -beta, and exogenous retinoic acid (RA) in the development of FOXP3 T-reg cells as a cofactor induce the development of FOXP3 T-reg cells (Coombes et al. 2007). High expression of integrin αvβ8 by CD103 + DCs isolated from mLNs aids in the expression of TGFβ and the production of FOXP3 T-reg cells to induce immune tolerance (Païdassi et al. 2011). The cross-immune tolerance function of intestinal cDC1 cells is performed by expressing transforming growth factor β (TGFβ), retinoic acid (RA), and programmed death ligand 1 (PD-L1), to produce FOXP3 + CD8 + Tregs. The importance of CD103 in the tologenic activity of FOXP3 + CD8 + Treg has also been expressed (Joeris et al. 2021). One of the mechanisms of immune tolerance to self-antigens is the killing and phagocytosis of autoreactive CD8 + T cells by DCs. However, the role of cDC1 in this process is negligible (MacNabb et al. 2019). The mechanism of immune tolerance against circulatory antigens in the kidney is dependent on renal lymph node BATF3-dependent DCs, which, in addition to cross-presentation of these antigens, express PD-L1 on their surface, and by binding PDL1 to PD-1 on the surface of CTL cells, induce tolerance against these antigens (Gottschalk et al. 2013). BATF3-dependent CD103 + CD11b DCs play an essential function in the recovery of allergic airway inflammation induced by tolerization with *H. pylori* (Engler et al. 2014). Major histocompatibility class II molecules-deficient cDC1s show high expression of CD40 and increased cross-priming of self-antigens in keratinocytes, causing early onset lethal autoimmunity. Execution of tolerogenic function against autoreactive CD8 + T cells requires MHC-II restricted interaction of cDC1 cells with Treg cells (Wohn et al. 2020). Stephen et al. showed that macrophages and CD103-positive DCs are two important cell populations of antigen-presenting cells in the islets of Langerhans in NOD mice (young non-obese diabetic mice) with a concomitant increase in CD103 + DCs and the entry of T cells into islets contribute to autoimmune diabetes, while in BATF3-deficient NOD mice, as a consequence of lacking of CD103 + DCs, and reducing cross-presentation and autoreactive of T cells help to prevent diabetes (Ferris et al. 2014). Brian et al. showed that BATF3-deficient mice are susceptible to experimental autoimmune encephalitis (EAE) following myelin oligodendrocyte glycoprotein (MOG) subcutaneous immunization because the lack of dermal CD11blow/- Langerin + CD103 + DCs has no effect on CD4 + T cells (Edelson et al. 2011). Resistance to collagen-induced arthritis (CIA) has been reported in BATF3-deficient mice, which highlights the importance of CD103 + and CD8α + DCs in the pathogenesis of the disease (Ramos et al. 2020).

The roles of BATF3-dependent DCs in diseases and humoral vaccination

The presence of cDC1s is uncommon in normal kidneys, but the presence of cDC1s increases in some kidney diseases, which may be related to disease severity and clinical-pathological characteristics (Chen et al. 2021). In chronic obstructive pulmonary disease (COPD), human lung cDC1s mediate the priming of the cytotoxic response of lung NK cells (Pallazola et al. 2021). However, in atherosclerosis, the role of BATF3-dependent DCs is insignificant and has no impact on the formation of atherosclerotic lesions in mice (Gil-Pulido et al. 2017). Yalin Li et al. showed that BATF3-/-Apoe-/-mice show abnormal CD8α + DC cell development; so, a decrease in CD8α + DCs is associated with a decrease in leukocyte infiltration and a decrease in the T-helper 1 cell response. BATF3-dependent CD8α + DCs exacerbate atherosclerosis by secreting interferon-gamma (IFN-γ) and interleukin-12 (IL-12), which are associated with the Th-1 response. Also, IFN-γ induces the expression of the chemokine (C–C motif) ligand 5 (CCL5) by macrophages in the aorta (Li et al. 2017). Maintained surface display of naïve antigen by cDC1s can be a good strategy for efficient humoral vaccination, provided that the antigens target Clec9A on the surface of cDC1s and are also available for B cell and T cells (Kato et al. 2020).

The roles of BATF3-dependent DCs in graft immunity

BTAF3-dependent DCs are also involved in histocompatibility antigen-mismatched grafts rejection (Atif et al. 2015). While CD8 + DCs in BATF3-deficient mice maintain skin graft rejection responses and delayed hypersensitivity responses, their phenotype and function are affected, including impaired expression of IRF8, expression of characteristic markers of CD11b + DCs, and their inability to phagocytose dying cells (Chandra et al. 2017). cDCs are not necessary for the induction of acute graft versus host disease (GvHD), a major complication after allogeneic hematopoietic stem cell transplantation (HSCT). Instead, host-derived CD8α + DCs play a crucial role in regulating early immune responses after HSCT, as they induce tolerogenic responses mediated by regulatory T cells (Weber et al. 2014). Megan S Molina et al. in an experimental bone marrow transplantation (BMT) model demonstrated that the combination of bendamustine and total body irradiation (BEN + TBI) could be a safer and more suitable alternative to cyclophosphamide with TBI (CY + TBI). This is because BEN + TBI shifts the differentiation of host DCs in mice toward BATF3-independent pre-cDC1s and subsequently reduces the likelihood of developing GVHD (Molina et al. 2020).Yixuan Wang et al. also showed that mice deficient in BATF3 and BATF show long-term survival after cardiac allografts because the absence of these transcription factors impairs the effector activities of T cells (Wang et al. 2022).

The roles of BATF3 in T-lymphocytes differentiation

Treg cells

Treg cells are important cells in the development of immune system homeostasis. The main regulator of differentiation and maintenance in Treg cells is FOXP3. One study presented that BATF3 expression in naïve CD4 + T was concomitant with the inhibition of differentiation toward Treg. BATF3 inhibits FOXP3 transcription by binding to the CNS1 region at the FOXP3 locus (see Fig. 2(D)) (Lee et al. 2017). Zhang et al. showed that OX40 signaling inhibits its FOXP3 gene expression through two different pathways: the first through upregulation of BATF and BATF3 gene expression, which induces closed chromatin configuration by employing histone deacetylases SIRT1 and 7, and the second by activation of the AKT/mTOR pathway (Zhang et al. 2018).

Memory T cells

BATF3 plays an intrinsic role in acquired immunity by reducing cellular apoptosis and assisting in the formation of memory T cells. Memory T cells lacking BATF3 exhibit a reduced recall response, but their overall function is not impaired (Atif et al. 2015; Qiu et al. 2020). In CD8 + T cells, BATF3 promotes cell survival and the transition to T cell memory by negatively regulating the transcription of the proapoptotic factor BIM (see Fig. 2(C)). BATF3-deficient CTLs undergo normal differentiation and expansion, but their increased BIM expression is associated with a reduced memory response due to decreased cell death. Therefore, BATF3 could be a promising target molecule in the development of adoptive T cell therapies for cancer (Ataide et al. 2020).

Th-9 cells

Th-9 cells, a functional subgroup of naïve CD4 + T cells, have an essential role in several diseases, including allergic responses and immune-related diseases. Th-9 cells require transforming growth factor beta (TGF-β) and IL-4 cytokines, and several transcription factors, including BATF for differentiation, and OX40 signaling for amplification. One study revealed that overexpression of BATF3 through interaction with IRF-4 and complex formation was synergistically associated with increased promoter activity of IL-9 and differentiation of Th-9 cells. In BATF knockout Th-9 cells, increased BATF3 expression led to increased IL-9 expression and differentiation of Th-9 s and induced airway inflammation; so, BATF3 and BATF compensated for each other in the differentiation of Th-9 cells (see Fig. 2(B)) (Lee et al. 2019). Masato Tsuda et al. showed that BATF3 stimulates Th-9 cell differentiation, secretion of IL-9, and T cell-driven mucosal inflammation via the TL1A-BATF3-IL-9 axis. This axis can be a promising axis in Th-9 cell-derived immune-related disease therapy (Tsuda et al. 2019). Figure 1 shows the role of BATF3 in differentiation and function of some immune cells in Fig. 2.

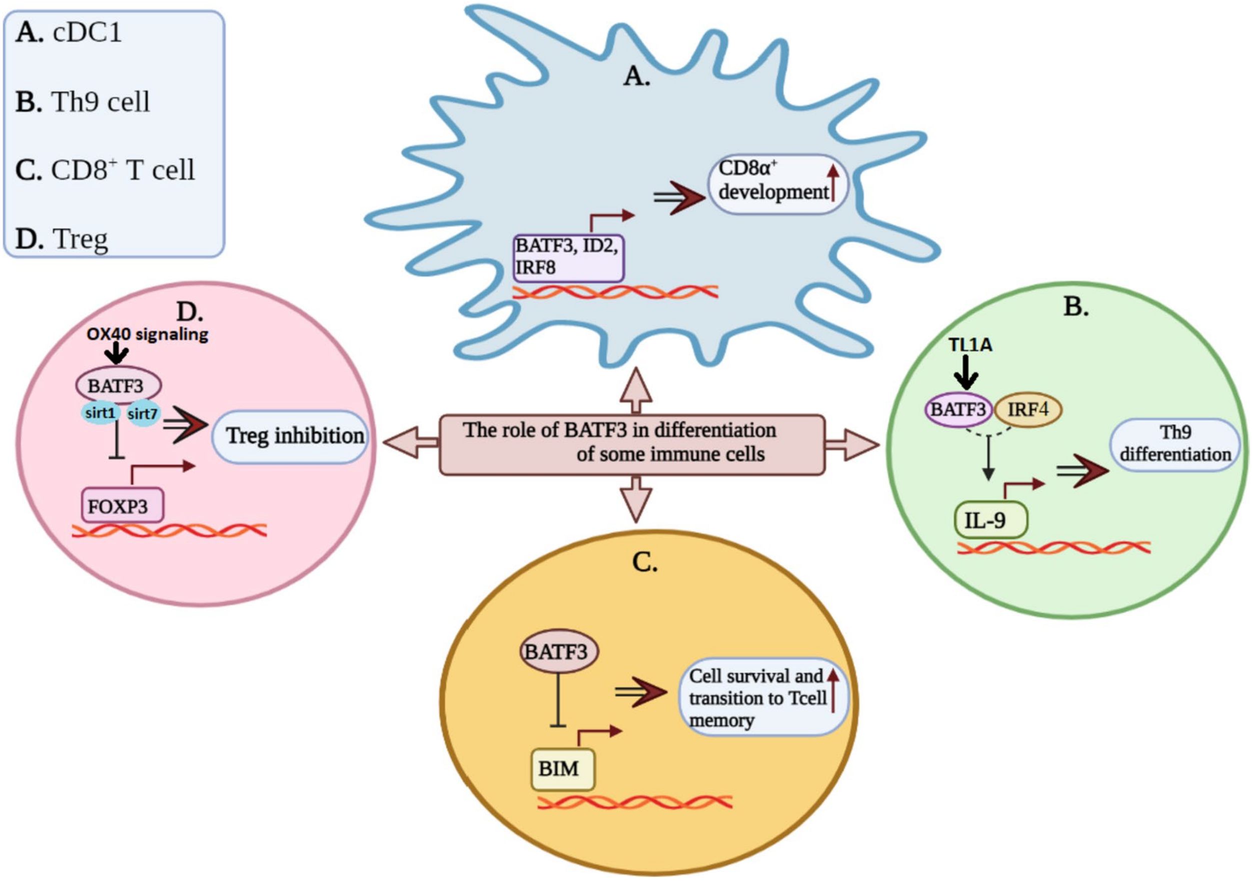

Fig. 2 The role of BATF3 in differentiation of some immune cells. (**A**) Co-expression of IRF8, BATF3, and Id2 has a synergistic impact on inducing the of CD8α$^+$ DC development. (**B**) Overexpression of BATF3 through interaction with IRF-4 and complex formation was synergistically associated with increased promoter activity of IL-9 and differentiation of Th9 cells. (**C**) BATF3 inhibits BIM expression in CD8$^+$ T cell resulting in induction of cell survival and transition to T cell memory. (**D**) The expression of FOXP3 is hampered by BATF3 leading to Treg inhibition. Abbreviations: BATF3, basic leucine zipper transcription factor ATF-like 3; DC, dendritic cell; IL-9, interleukin-9; IRF, interferon regulatory factor; FOXP3, Forkhead box *P3*; Treg, regulatory T lymphocyte

The oncogenic roles of BATF3 in numerous cancer types

Colorectal cancer

Ping Li et al. pointed to the importance of BATF3 upregulation in tumor progression by inducing S1PR1 gene expression. BATF3 exerts oncogenic functions in colorectal cancer (CRC) by targeting the S1PR1/p-STAT3/miR-155-3p/WDR82 axis (Li et al. 2021). Ling Cao et al. showed that decreased miR-760 expression in CRC and low miR-760 tumor levels were considerably correlated with the worst prognosis in CRC patients. One of the direct targets of miR-760 is the BATF3 gene, which is upregulated in CRC. The miR-760 could be a good treatment option for inhibiting malignant cell proliferation by inhibiting BATF3/AP-1/cyclinD1 signaling (Cao et al. 2018). One of the most important stages in the development and progression of inflammation is neutrophil recruitment, which is also seen in colitis-associated colon cancer (CAC). BATF3 transcription factor, by forming a heterodimer with JUND factor, increases CXCL5 transcription, and thus recruits neutrophils at the site of inflammation and causes CAC (Lin et al. 2021). Jiale Tian et al. proved that the expression of histone methyltransferase SETDB1 is significantly augmented. SETDB1 inhibits microRNA-22 (miR-22) by downregulating FOSB, and thus activates the BATF3/PD-L1 axis and aids in the immune evasion of tumor cell (see Fig. 3A) (Tian et al. 2022).

Glioma

Research has indicated that circular RNA circ_0034642 is upregulated in glioma cancer tissues and cell lines, and this increased expression is correlated with a worse prognosis. Circular RNA circ_0034642 functions as a miRNA sponge

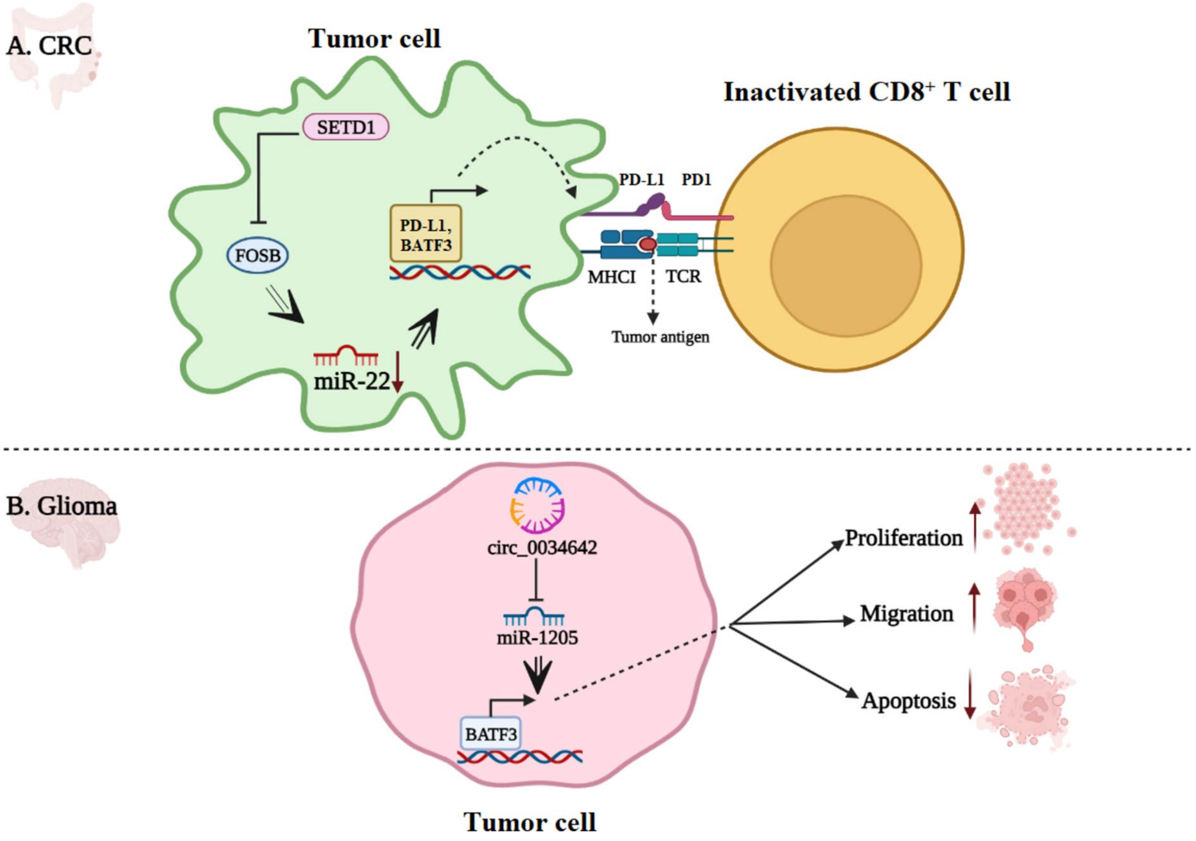

Fig. 3 Some roles of BATF3 in CRC and glioma progression. **A** Histone-lysine N methyltransferase SETDB1 inhibits miR-22 by downregulating FOSB, and thus activates the BATF3/PD-L1 axis and aids in the immune evasion of tumor cells. **B** Circular RNA circ_0034642 acts as a sponge for miR-1205 and the direct target of miR-1205 is the 3′ UTR region of BATF3. Circ_0034642 stimulates invasion, migration, and cell proliferation while inhibiting cellular apoptosis via the miR-1205/BATF3 signal pathway. Abbreviations: BATF3, basic leucine zipper transcription factor ATF-like 3; Circ, circular RNA; CRC, colorectal cancer; miR, microRNA; PD-L1, programmed death-ligand 1; UTR, untranslated region

for miR-1205, and the 3′ UTR region of BATF3 is a direct target of miR-1205. Circ_0034642 stimulates invasion, migration, and cell proliferation while inhibiting cellular apoptosis via the miR-1205/BATF3 signal pathway (see Fig. 3B) (Yang et al. 2019; Yi et al. 2019). Figure 3 shows some roles of BATF3 in CRC and glioma progression.

Laryngeal squamous cell carcinoma

Hang Zhang et al. indicated that in laryngeal squamous cell carcinoma (LSCC), LINC01638 has significant expression and its high expression is associated with clinical severity. LINC01638 induces the expression of BATF3 by miR-523-5p decoy and through this pathway promotes LSCC cleavage (see Fig. 4A) (Zhang et al. 2021).

Lymphoma

Christian Weiser et al. designed a retroviral vector expressing BATF3, then transduced it into adult mouse T and B lymphocytes, and finally transplanted it into a murine transplantation model. According to the results, increased BATF3 expression was associated with the induction of malignancy in murine mature B cells and inhibition of BLIMP-1 expression, which highlights the oncogenic role of BATF3 (Weiser et al. 2018). In Hodgkin/Reed–Sternberg cells of classical Hodgkin lymphoma (HL), the level of Sphingosine-1-phosphate (S1P) increases due to the increase in the expression level of sphingosine kinase 1 (SPHK1), the enzyme that synthesizes S1P, and the decrease in the expression level of sphingosine phosphate phosphatase (SGPP1), which is an enzyme that breaks down S1P. Among cell surface S1P receptors, the expression level of S1PR1 increases and S1PR2 decreases. The PI3-K/Akt signaling pathway is stimulated as a result of the binding of S1P to S1PR1, and activation of this pathway is also associated with upregulation of the BATF3 gene. BATF3 induces aberrant expression of several important genes that contribute to the development of HL cancer. For example, BATF3 inhibits plasma cell differentiation by increasing PRDM1 expression and decreasing BACH2 expression (see Fig. 4B) (Vrzalikova et al. 2018). Lollies et al. showed that in many

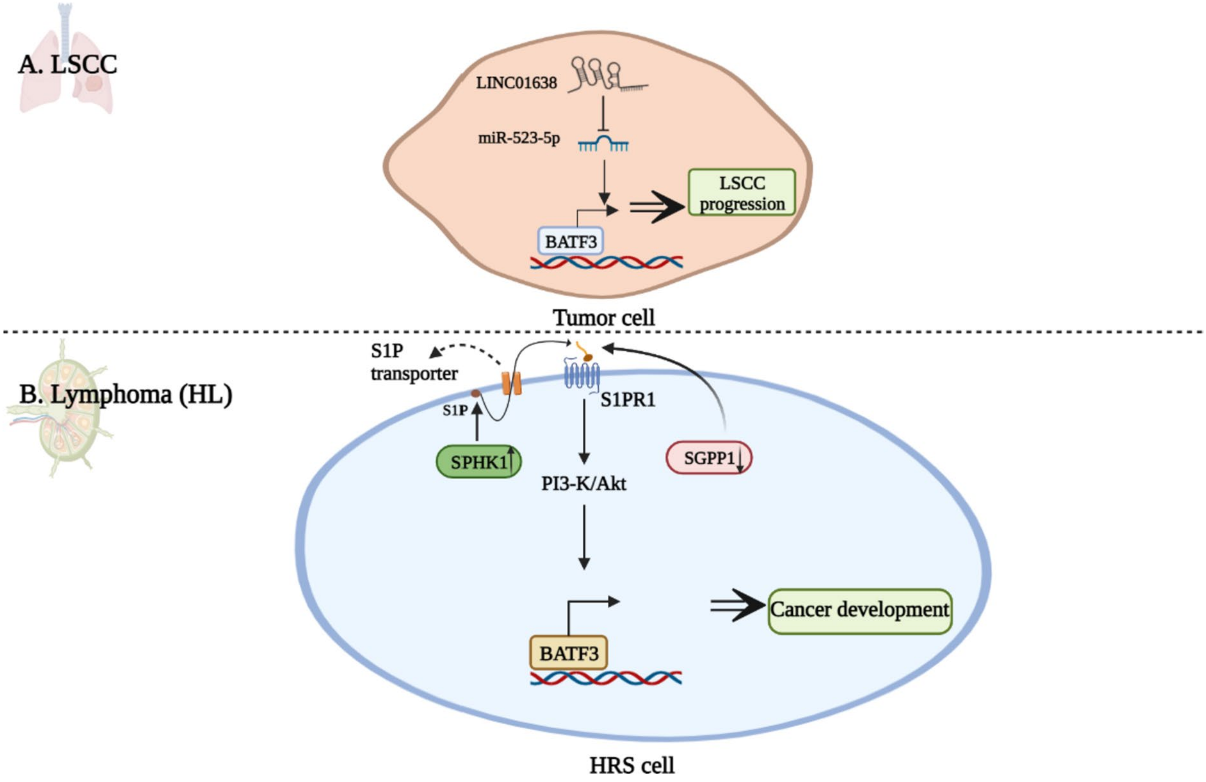

Fig. 4 Some roles of BATF3 in LSCC and lymphoma (HL) progression. **A** LINC01638 induces the expression of BATF3 by miR-523-5p decoy and through this pathway promotes LSCC cleavage. **B** In HL, the level of S1P increases due to the increase in the expression level of SPHK1, the enzyme that synthesizes S1P, and the decrease in the expression level of SGPP1, which is an enzyme that breaks down S1P. Among cell surface S1P receptors, the expression level of S1PR1 increases and S1PR2 decreases. The PI3-K/Akt signaling pathway is stimulated as a result of the binding of S1P to S1PR1, and activation of this pathway is also associated with upregulation of the BATF3 gene. BATF3 induces aberrant expression of several important genes that contribute to the development of HL cancer. Abbreviations: BATF3, basic leucine zipper transcription factor ATF-like 3; HL, Hodgkin lymphoma; HRS cell, Hodgkin/Reed–Sternberg cell; LSCC, laryngeal squamous cell carcinoma; miR, microRNA; PI3-K/Akt, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT); S1P, sphingosine-1-phosphate; S1PR, S1P receptor; SGPP1, sphingosine phosphate phosphatase; SPHK1, sphingosine kinase 1

CD30 + lymphomas, including classical Hodgkin lymphoma (cHL) and anaplastic large cell lymphoma (ALCL), BATF3 is highly expressed, and BATF3 silencing in ALCL and CHL is associated with reduced tumor proliferation and survival, which highlights the oncogenic role of BATF3. Part of the BATF3 oncogenic function is interaction with JUN (B) factors, then binding to the Ap-1 motif on the myc gene promoter, and finally upregulating the myc gene. Also, BATF3 expression is regulated by the JAK/STAT signaling pathway (Lollies et al. 2018). Nikolai Schleussner et al. showed that there is a pattern of gene expression in primary ALCL related to Th-17 and ILC-3 genes, and BATF3 and BATF interacting with JUNB, regulate the expression of these genes, and notably, inhibition of BATFs, or global inhibition of AP-1 factors, inhibits cell growth and induces cell death in ALCL cells (Schleussner et al. 2018). Huan-Chang Liang et al. studied super-enhancer regions and showed that the two main regulators in ALCL named BATF3 and IL-2R are regulatory linked to each other, because BATF3 silencing is associated with reduced IL-2 receptor (IL-2R) expression in ALCL. IL-2Rα-expression in ALCL is also associated with more aggressive clinical presentation. Therefore, IL-2Rα-targeting could be a good treatment strategy for ALCL (Liang et al. 2021). Using BATF3 immunohistochemistry in combination with BATF3-scoring may be an acceptable option in the diagnosis of cHL (Benckendorff et al. 2021). Masao Nakagawa et al. showed that viral oncoprotein HBZ is expressed in adult T cell leukemia/lymphoma (ATLL) cells and binds to the super-enhancer region of the BATF3 gene increases the expression of BATF3 and its downstream genes, and most importantly the MYC gene. The BATF3-IRF4 complex activates the oncogenic HBZ pathway in ATLL (Nakagawa et al. 2018). Figure 3 shows some roles of BATF3 in LSCC and lymphoma (HL) progression.

Discussion

This review provides significant insights into the multifaceted functions of BATF3 in cancer development, dendritic cell (DC) differentiation, and T cell functioning. It underscores the importance of BATF3-dependent dendritic cells (DCs) in immune responses and their potential implications for cancer treatment. The discussion delves into the challenges associated with comprehending BATF3 and its impacts across various biological systems. A pivotal aspect is the involvement of BATF3 in the generation of conventional type 1 dendritic cells (cDC1). The review emphasizes the critical role of BATF3 in cDC1 production, vital for initiating immunological responses mediated by CD8 + T cells against intracellular infections and malignancies. Understanding the processes driving the expansion of BATF3-dependent cDC1 cells is crucial for effectively harnessing their potential in immunotherapy strategies. However, further research is needed to elucidate the precise molecular pathways and components involved in BATF3-mediated cDC1 development. The study also highlights the possibility of BATF3-dependent cDC1 cells in the tumor microenvironment (TME). These cells contribute to the process of monitoring and protecting against foreign substances within the body's immune system and may enhance the efficacy of treatments that augment the immune response. Nevertheless, fully capitalizing on the therapeutic potential of BATF3-dependent cDC1 within the context of cancer therapy presents challenges. The heterogeneous nature of the TME, the immune evasion strategies employed by malignancies, and the inhibitory characteristics of the TME hinder maximizing the therapeutic effectiveness of BATF3-dependent cDC1. Overcoming these obstacles necessitates a comprehensive understanding of the intricate interplay between BATF3-dependent cDC1, tumor cells, and the TME. The present study further explores the oncogenic role of BATF3 in various biological processes, including proliferation and invasion. Notwithstanding the demonstrated oncogenic function of BATF3 in several scenarios, further investigation is warranted to unveil the underlying mechanisms and identify specific downstream targets of BATF3 contributing to cancer development. Understanding these systems will facilitate the development of targeted treatments aimed at suppressing BATF3-mediated cancer-promoting pathways. Challenges related to investigating BATF3 largely stem from the complex nature of its interactions with other transcription factors and signaling pathways. BATF3 engages in heterodimerization with different collaborators, such as c-Jun and IRF4, and modulates gene expression in a context-dependent manner. Unraveling the precise functional consequences of these interactions and their significance across diverse cellular environments poses a challenge. Moreover, there are obstacles in translating BATF3-targeted therapies into clinical use. The main obstacle lies in developing therapeutic strategies that can effectively and safely target BATF3-mediated pathways without causing harm to important body functions. Furthermore, the variability in BATF3 expression among different cancer types and patient groups complicates the development of BATF3-based treatments. In conclusion, this paper provides a thorough examination BATF3's roles in cancer development, DC differentiation, and T cell functioning. By highlighting the potential utility of BATF3-dependent DCs in cancer immunotherapy, it also acknowledges the complexities associated with researching BATF3 and translating these findings into clinical applications. To overcome these limitations, further study is imperative to unravel the intricate molecular mechanisms and formulate precise treatment approaches that harness the full potential of BATF3-dependent pathways effectively.

Conclusion

DCs are one of the most specialized subsets of cells in linking innate and adaptive immunity. Among the heterogeneous subsets of DCs, the cDC1 subset plays a pivotal role in immune responses against infectious, intracellular pathogens and in controlling immune responses against cancer. The cDC1 are distinguished by the expression of CD141 marker in humans and CD8α/CD103 markers in mice. BATF3, with chief role in the development of cDC1, is required for priming of CD8 + T cells. In this regard, BATF3-dependent cDC1 includes opulent functions such as promoting immunosurveillance in the phase of T cell priming. The cDC1, NK cells, and bidirectional cross-talk between them by producing some types of cytokines and chemokines in TME can improve cancer immunotherapy. For instance, CD103 + DCs-derived interleukin-12 is a pro-inflammatory cytokine that regulates T cell and NK cell responses in the inhibition of tumor metastasis. The role of cDC1 in the cross-immune tolerance against circulatory self-antigens is carried out through the killing of autoreactive CD8 + T cells. Binding PD-L1 to the expressed PD-1 on the surface of CTL cells, they induce tolerance against these antigens. In addition to the impact of BATF3 on differentiation of cDC1, it influences differentiation of blood cells such as Tregs, memory T cells, and Th-9 cells. As an interesting point, it has been established that upregulation of BATF3 plays a vital role in tumor progression of some types of cancers such as CRC, lymphomas, glioma, and LSCC.

Future prospective

BATF3-dependent DCs have attracted the attention of researchers due to their vital role in enhancing the cytotoxic response of CD8 + T cells against viral and cancerous cells. In this respect, new approaches to targeting BATF3-dependent DCs can be applied to improve immunotherapy. Specifically, because of the involvement of BATF3 in various cell signaling pathways, in case of overexpression in some cancers, it can lead to exacerbating and progressing cancer. As a result, targeting BATF3 through the novel approaches of gene therapy such as CRISPR/Cas9 brings about promising results in reducing the tumor progression.

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