Protein Cell 2021, 12(3):165–173
https://doi.org/10.1007/s13238-020-00796-6

Protein & Cell

REVIEW

The function and regulation of TET2 in innate immunity and inflammation

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Received July 7, 2020 Accepted September 15, 2020

ABSTRACT

TET2, a member of ten-eleven translocation (TET) family as α-ketoglutarate- and Fe^{2+}-dependent dioxygenase catalyzing the iterative oxidation of 5-methylcytosine (5mC), has been widely recognized to be an important regulator for normal hematopoiesis especially myelopoiesis. Mutation and dysregulation of TET2 contribute to the development of multiple hematological malignancies. Recent studies reveal that TET2 also plays an important role in innate immune homeostasis by promoting DNA demethylation or independent of its enzymatic activity. Here, we focus on the functions of TET2 in the initiation and resolution of inflammation through epigenetic regulation and signaling network. In addition, we highlight regulation of TET2 at various molecular levels as well as the correlated inflammatory diseases, which will provide the insight to intervene in the pathological process caused by TET2 dysregulation.

KEYWORDS TET2, innate immune response, DNA demethylation, inflammatory resolution, inflammatory diseases

INTRODUCTION

Innate immune responses are critical in protecting the host from infection and injury, which are efficiently and timely regulated to maintain the immune homeostasis. Diverse epigenetic mechanisms, referring to dynamic regulation of DNA modifications, histone modifications, chromatin remodeling and non-coding RNAs (ncRNAs), are implicated in precise regulation of innate immune responses through establishing specific gene expression patterns especially at transcriptional and post-transcriptional levels (Zhang and Cao, 2019). As the most canonical epigenetic modification, DNA methylation occurs by transferring the methyl group onto 5-carbon of the cytosine to form 5-methylcytosine (5mC), which plays a vital role in transcriptional silencing and genome stability (Jones, 2012), and is of great importance for mammalian development (Jones, 2012; Smith and Meissner, 2013). Aberrant changes of DNA methylation is associated with various pathological diseases, such as cancer (Klutstein et al., 2016), obesity (Zhang et al., 2017a) and inflammatory autoimmune diseases (Meda et al., 2011).

As the chromosomal translocation partner initailly found in leukemia, TET family members, TET1, TET2 and TET3, have been proved to be a key regulator for DNA demethylation owing to its dioxygenase activity. Specifically, TET enzyme oxidizes the methyl group of 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) (Tahiliani et al., 2009; He et al., 2011; Ito et al., 2011), thereby inducing active and passive DNA demethylation through DNA replication or thymine-DNA glycosylase (TDG) and base excision repair (BER) pathway (Wu and Zhang, 2017). TET protein-mediated dynamic regulation of DNA methylation and its oxidation are largely involved in regulating lymphoid and myeloid differentiation and function (Lio and Rao, 2019). In innate immune cells, especially myeloid cells, the expression of TET2 and TET3 is much higher than TET1, and the expression of TET2 increases, while TET3 decreases after TLR ligands stimulation (Zhang et al., 2015; Xue et al., 2016; Cull et al., 2017), implying that TET2 may act as an activation-induced regulator during innate immune response.

Among the three TET family members, TET2 is identified as an important regulator for normal hematopoiesis

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especially myelopoiesis (Quivoron et al., 2011; Alvarez-Errico et al., 2015). Dysfunction of TET2 is well-proved to be associated with acute myelocytic leukemia (AML), myelodysplastic syndromes (MDS) and other myeloid disorders (Delhommeau et al., 2009; Langemeijer et al., 2009). Recently, numerous studies suggest that TET2 also plays a crucial role in various inflammatory related diseases by regulating innate signaling network and expression of innate effectors during both onset and resolution of immune responses and inflammation. In this review, we provide an overview of the functions of TET2 in innate immunity. In addition, we summarize the regulation of TET2, from transcription, post-transcription, post-translation to gene-specific targeting aspect, and its involvement in inflammatory diseases, thereby implying TET2 as a potential therapeutic target for intervention in inflammatory diseases.

TET2 IN INFLAMMATION INITIATION

Innate immune responses are initiated during pathogen infection and tissue injury by multiple innate immune cells, mainly including macrophages, dendritic cells (DCs), neutrophils, innate lymphoid cells, mast cells, epithelial cells, and endothelial cells (Medzhitov, 2008). Pathogen- or danger-associated molecular patterns (PAMPs or DAMPs) are recognized by germline-encoded pattern-recognition receptors (PRRs) such as Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs), which trigger the intracellular signaling pathways to promote the production of various proinflammatory cytokines and mediators (O'Neill et al., 2013; Cao, 2016).

TET2 is required for the differentiation and proliferation of mast cells in mice (Montagner et al., 2016). Loss of TET2 severely changes the 5mC oxidation and the gene expression pattern, which impairs the differentiation of mast cells and the production of cytokines. And TET2 expression is essential for restraining the proliferation of mast cells, independent of its enzymatic activity. Besides, there is evidence that TET2 is involved in regulating the transduction of innate signaling pathways during inflammation initiation. Epigenetic regulator CXXC finger protein 5 (CXXC5) recruits TET2 to maintain hypomethylation of CpG islands (CGI) in the genome of plasmacytoid dendritic cells (pDCs), a rare subset of DCs that highly produce IFN-α in response to viral infection. Among these CGI-associated genes, transcription of *Irf7* is promoted via TET2-sustained promoter hypomethylation, which is critical for TLR-induced type I IFN production for initiating anti-viral immune response (Ma et al., 2017). Besides DNA, TET2 could also act on RNA and perform oxidation of 5mC on RNA in innate immune cells (Fu et al., 2014). TET2 directly binds to the mRNA 3′-UTR of *Socs3*, a negative regulator of JAK-STAT pathway which is important for cytokine-induced myelopoiesis during pathogen infection, and decreases the 5mC level in this region in an enzymatic activity-dependent manner, therefore promoting the degradation of *Socs3* mRNA through ADAR1 and activating the emergency production of mature innate immune cells during pathogen infection (Shen et al., 2018). Although proved to oxidize the 5-methylcytosine on mRNA, whether TET2 can demethylate 5mC in mRNA is still indeterminate, implying that certain cofactors potentially function in this process.

Furthermore, the roles of TET1 and TET3 in innate immunity are also revealed these years. TET3 recruits HDAC1 to the promoter of *Ifnb1* and negatively regulates type I IFN production independent of DNA demethylation (Xue et al., 2016). TET1 is thought to regulate 5hmC in the promoter regions of pro-inflammatory cytokine genes, thereby contributing to the activation of macrophages (Sun et al., 2019).

TET2 IN INFLAMMATION RESOLUTION

The resolution of inflammation refers to an intricate process in which inflammatory agents are eliminated, inflammatory mediators are catabolized or suppressed, and immune cells including leukocytes are cleared from the inflamed tissue (Buckley et al., 2013). The prompt and effective inflammation resolution is critical for host to maintain the homeostasis and prevent the inflammatory disorders. In recent years, it is increasingly indicated that TET2-involved epigenetic regulation is a key factor for the resolution of inflammation. In an enzymatic activity-independent manner, TET2 binds and recruits HDAC1/2 to facilitate histone deacetylation and suppresses IL-6 and IL-1β expression during the resolution stage of inflammation in innate myeloid cells and macrophages respectively (Zhang et al., 2015; Cull et al., 2017). Loss of TET2 results in upregulation of IL-1β expression and unexpected IL-1β cleavage mediated by NLRP3 inflammasome (Fuster et al., 2017), which confirms the role of TET2 in promoting inflammation resolution. Moreover, tumor-associated macrophages with absent TET2 expression exhibit an immune-active phenotype, including increased expression of inflammatory cytokines and decreased expression of ARG1, which promotes the anti-tumor T cell response (Pan et al., 2017), although another study showed that mutations of DNMT3A and TET2 are most likely associated with the increased expression of ARG1 in bone marrow myelomonocytic cells in MDS/CMML patients (Cull et al., 2018). In summary, these studies indicate that TET2 plays an important role for inflammation resolution by regulating the function of innate immune cells (Fig. 1).

TRANSCRIPTIONAL AND POST-TRANSCRIPTIONAL REGULATION OF TET2

Previous studies have identified many transcriptional regulators of TET2 expression. For example, the transcription factor CCAAT/enhancer binding protein alpha (C/EBPα) induces TET2 expression during pre-B cell to macrophage trans-differentiation through binding to the upstream of *TET2* gene (Kallin et al., 2012). Furthermore, the sulfhydrated

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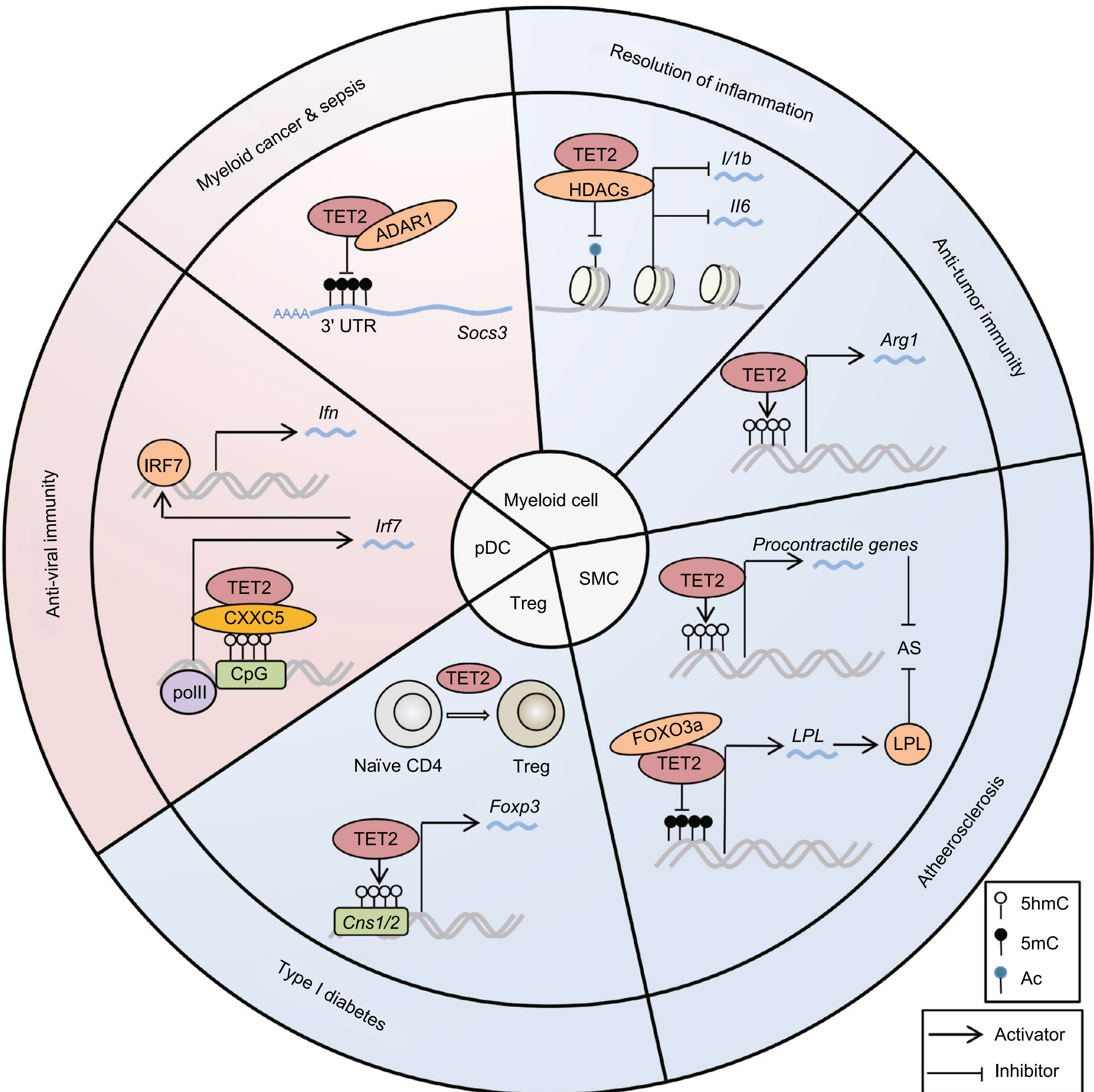

Figure 1. Negative (blue) or positive (pink) regulation of TET2 in the inflammatory immune responses and related diseases. During the onset of innate immune response, CXXC5 recruits TET2 to maintain low 5mC level of CpG islands of *Irf7* gene, which promotes IRF7 expression to activate type I IFN production for initiating anti-viral immune response. Besides, TET2 binds to the mRNA 3′-UTR of *Socs3* and inhibits its 5mC level, which promotes the degradation of *Socs3* mRNA through ADAR1 and thereby facilitates infection-induced myelopoiesis. As to the resolution phase of inflammation, TET2, whose expression is promoted via IL-1R-MyD88 pathway, downregulates the expression of inflammatory cytokines IL-6 and IL-1β through recruiting HDACs for histone deacetylation in innate myeloid cells and macrophages respectively. Loss of TET2 in tumor-associated macrophages results in increased expression of inflammatory cytokines as well as decreased expression of ARG1. In addition, TET2 regulates the differentiation of regulatory T cells (Treg) and smooth muscle cells (SMC), thus acting as the repressor of type I diabetes and atherosclerosis.

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nuclear transcriptional factor Y subunit beta (NFYB) binds to *TET2* promoter and thereby promotes *TET2* gene transcription (Yang et al., 2015).

Expression of TET2 can also be regulated by microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) post-transcriptionally. For instance, miR-125a-5p targets the 3′-UTR of *TET2* mRNA to inhibit TET2 expression during immune responses, thereby activating NLRP3 inflammasome and promoting the expression of proinflammatory cytokine IL-1β and IL-18 (Zhaolin et al., 2019). Let-7a-1/let-7d/let-7f-1 (Let-7adf) microRNA cluster represses TET2 expression or activity through either directly targeting *TET2* mRNA or promoting succinate accumulation by regulating the Lin28a/SDHA axis in LPS-activated macrophages, leading to enhanced production of IL-6 (Jiang et al., 2019) (Fig. 2). Moreover, lncRNA AC016405.3 restrains proliferation and metastasis of glioblastoma multiforme cells through sponging of miR-19a-5p and the subsequent upregulation of TET2 expression (Ren and Xu, 2019).

POST-TRANSLATIONAL REGULATION OF TET2

Degradation

It has been reported that TET2 is degraded via four different pathways. CXXC domain-containing protein IDAX (also known as CXXC4) can promote caspase activation probably via regulating gene transcription. As a TET2 binding partner, IDAX promotes degradation of TET2 protein (Ko et al., 2013). A family member of calcium-dependent proteases, calpain1, mediates TET2 degradation, which is likely to affect global 5hmC level and expression of certain lineage-specific genes in mESCs (Wang and Zhang, 2014). The degradation of TET2 can also be mediated by the ubiquitin-proteasome pathway that poly-ubiquitination of the C-terminal conserved DSBH domain increases the instability of TET2 (Lv et al., 2018). Recently, it was proposed that p53 facilitates the autophagic degradation of TET2 by promoting the shuttling of nuclear TET2 toward the cytoplasmic autophagosome (Zhang et al., 2019a).

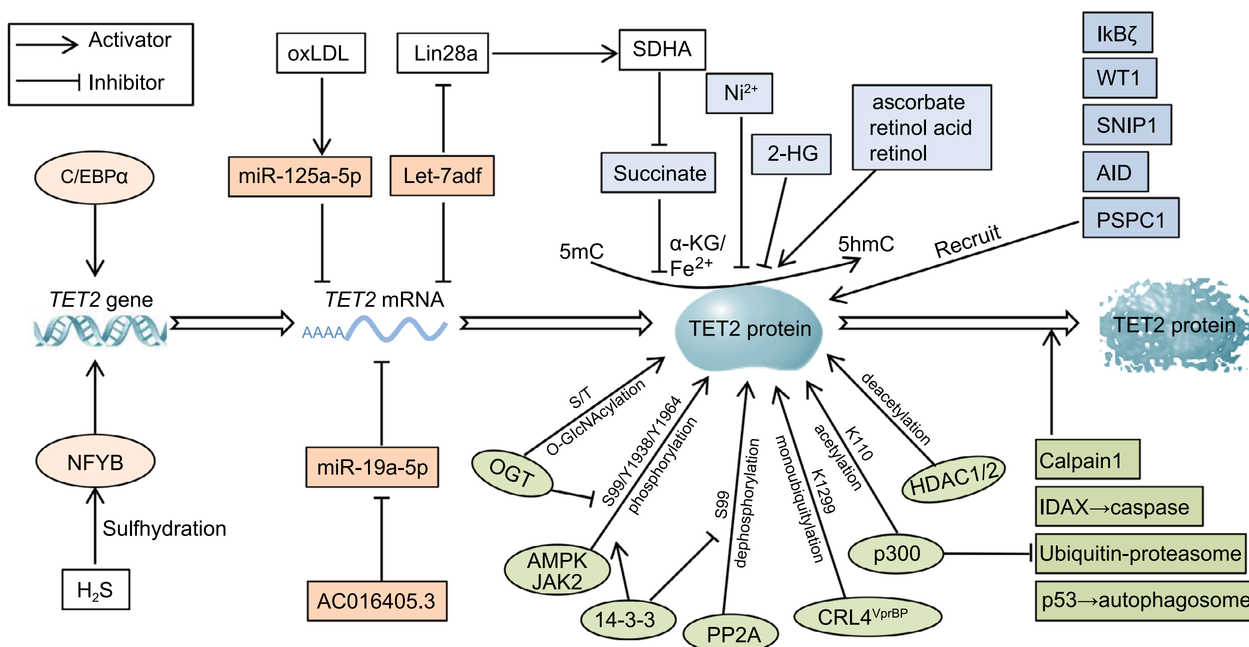

Figure 2. Regulation of TET2 gene expression and protein function. Transcription factors, such as C/EBPα and NFYB, promote TET2 expression at mRNA levels, while certain miRNAs and lncRNAs post-transcriptionally regulate TET2 expression. Post-translational modifications (PTMs), including O-GlcNAcylation, phosphorylation, ubiquitylation and acetylation at specific residues respectively, are also involved in regulating TET2 expression. The degradation of TET2 is mediated by four different pathways, namely calpain1, caspase, ubiquitin-proteasome and autophagosome pathway. For some small molecule metabolites, succinate, 2-HG and Ni^{2+} can inhibit TET2 protein activity, while ascorbate, retinol acid and retinol enhance TET2 activity or expression. Transcription factors including IκBζ, WT1 and SNIP1, as well as proteins AID and PSPC1, are able to recruit TET2 to regulate certain gene expression.

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Monoubiquitylation and acetylation

TET2 binds to VprBP and is monoubiquitylated by the $CRL4^{VprBP}$ E3 ubiquitin ligase on a highly conserved lysine residue, which facilitates TET2 binding to chromatin, although $CRL4^{VprBP}$ also can destabilize TET2 through lysine poly-ubiquitination (Nakagawa et al., 2015; Lv et al., 2018). TET2 is acetylated at lysine 110 by p300, which stabilizes TET2 protein through the inhibition of TET2 ubiquitination. Consequently, the recruitment of TET2 to chromatin during oxidative stress is promoted to prevent abnormal DNA methylation (Zhang et al., 2017b).

O-glcNAcylation and phosphorylation

O-linked GlcNAc transferase (OGT) catalyzes TET2 O-GlcNAcylation and thereby reduces TET2 phosphorylation at the N terminus and low-complexity insert region (Bauer et al., 2015). AMPK phosphorylates TET2 and enhances TET2 stability (Zhang et al., 2019b). Increased glucose levels hinder AMPK-mediated human TET2 phosphorylation at serine 99, resulting in the destabilization of TET2 followed by dysregulation of both 5hmC level and the tumor suppressive effect of TET2 *in vitro* and *in vivo* (Wu et al., 2018). 14-3-3 protein can bind TET2 to maintain AMPK-mediated serine 99 phosphorylation via protecting TET2 from protein phosphatase 2A (PP2A)-mediated dephosphorylation (Kundu et al., 2020). Besides, JAK2 can also phosphorylate TET2 at tyrosine 1939 and 1964 which increases TET2 activity and enhances binding of transcription factor KLF1 with TET2 upon hematopoietic cytokine erythropoietin (EPO) stimuli (Jeong et al., 2019).

Metabolic factors

TET2-mediated oxidation of 5mC can also be regulated during metabolic reprogramming (Yang et al., 2014). TET proteins belong to 2-oxoglutarate oxygenases, employing Fe^{2+} as metal cofactor and α-KG as co-substrate (Tahiliani et al., 2009; Loenarz and Schofield, 2011). α-KG-dependent TET2 enzymatic activity is suppressed due to the accumulation of metabolites that share structural similarity with α-KG, such as succinate which inhibits the oxidation of 5mC to 5hmC (Killian et al., 2013) and 2-HG (Xu et al., 2011). Also, natural Ni^{2+} ion can displace Fe^{2+}, the cofactor of TET2, thus inhibiting TET2 enzymatic activity (Yin et al., 2017). Besides, retinol acid, retinol (vitamin A) and ascorbate (vitamin C) are proved to regulate TET2 activity or expression. Ascorbate is likely to act as a cofactor of TET2 (Minor et al., 2013), which enhances TET2 enzymatic activity and alter DNA methylation so as to regulate the expression of germline genes in ES cells (Blaschke et al., 2013). Another study proposed that ascorbate enhances the catalytic activity of TET2 and the production of 5hmC by reducing Fe^{3+} to Fe^{2+} that participates in the catalytic center of TET2 (Hore et al., 2016). Without affecting TET2 protein stability or catalytic efficiency, retinol acid or retinol (vitamin A) activates TET2 expression probably through affecting *TET2* transcription, and thereby enhances 5hmC production in naive embryonic stem cells (Hore et al., 2016).

RECRUITMENT OF TET2

As to the structural characteristic of TET proteins, both full-length TET1 and TET3 contain a CXXC domain at the amino terminus that helps them bind DNA, whereas TET2 does not (Pastor et al., 2013). Various proteins are reported to be involved in the recruitment of TET2 to target chromatin in different biological processes. Transcription factors, including IκBζ (Zhang et al., 2015), WT1 (Wang et al., 2015), and SNIP1 (Chen et al., 2018), mediate the recruitment of TET2 to specific gene loci to regulate gene transcription. IDAX preferentially binds to CpG-rich regions containing unmodified cytosines in gene promoter regions and CpG islands through its CXXC domain in a DNA sequence-independent manner. IDAX interacts with TET2 catalytic domain and recruits TET2 to DNA (Ko et al., 2013). Besides, activation-induced cytidine deaminase (AID) can recruit TET2 to *FANCA* promoter to induce demethylation for oncogene activation in diffuse large B cell lymphoma (Jiao et al., 2019).

Furthermore, TET2 can potentially be recruited by some RNA-binding proteins, which may lead to a broader regulatory role of TET2, on regulating RNA splicing, stability, localization and degradation. RNA-binding protein Paraspeckle component 1 (PSPC1) recruits TET2 to transcriptionally active loci in an RNA-dependent manner, leading to the RNA 5hmC modification and the destabilization of *MERVL* RNAs through unidentified mechanism. PSPC1-TET2 complex can also recruit HDAC1/2 for transcriptional silencing of *MERVL* transcripts via histone deacetylation (Guallar et al., 2018). A previous study identified a nine-residue peptide adjacent to the catalytic domain of TET2 as the most likely RNA binding site (He et al., 2016), suggesting that TET2 itself acts as a RNA-binding protein and is involved in the post-transcriptional regulation of gene expression. Further study also proved the RNA-binding capacity of TET2 through enhanced crosslinking and immunoprecipitation followed by high-throughput sequencing (eCLIP-seq) (Shen et al., 2018).

TET2 AND INFLAMMATORY DISEASES

Atherosclerosis

As described above, inhibition of TET2 upregulates the production of mature proinflammatory cytokines including IL-1β and IL-18, which activates the inflammation response and subsequently contributes to and accelerates atherosclerosis (Fuster et al., 2017; Zhaolin et al., 2019). TET2 has been identified as a key epigenetic regulator of SMC differentiation and phenotype switch of vascular SMC to a pro-proliferation and migration phenotype (Liu et al., 2013; Li et al., 2020).

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TET2 facilitates the expression of key procontractile genes in SMCs inducing the contractile phenotype of SMCs, thus attenuates vascular injury in human atherosclerotic disease (Liu et al., 2013). Additionally, coiled-coil domain-containing 80 (CCDC80) inhibits the phosphorylation of ERK1/2 and decreases the expression of TET2, which upregulates the methylation level of lipoprotein lipase (LPL) promoter region, and impairs the interaction of TET2 with the transcription factor FOXO3a, causing a reduction of LPL expression and finally the acceleration of atherosclerosis (Gong et al., 2019).

Type I diabetes

Type I diabetes (T1D) is caused by autoimmune damage of pancreatic β cells, and epigenetic regulation has been proposed to involve in the progression of T1D (MacFarlane et al., 2009). As mentioned above, a study revealed a regulatory pathway that links glucose and AMPK to TET2 and 5hmC (Wu et al., 2018). Expression of IFN-α in pancreatic islets during acute or chronic infections, post-transcriptionally increases expression of TET2 through targeting miR-26a for degradation, which in turn increases global 5hmC level of pancreatic β cells, resulting in the initiation of islet autoimmunity in T1D (Stefan-Lifshitz et al., 2019). Moreover, TET2 mediates the demethylation of two intronic enhancers *CNS1* and *CNS2* and stabilizes FOXP3 expression in Treg (Yang et al., 2015; Yue et al., 2016, 2019). The decreased expression of TET2 was demonstrated in Tregs from both mice T1D model and human T1D patients, which impairs Treg stability and function and results in islet autoimmune response (Scherm et al., 2019). In addition, TET2 also plays a role in the pathogenesis of diabetic nephropathy (DN) by activating TGF-β1 expression through demethylation of CpG islands in the TGF-β1 regulatory region (Yang et al., 2018).

Autoimmune diseases

A decreased state of global DNA methylation is verified in patients with rheumatoid arthritis (RA). Correspondingly, the expression of TET2 is increased in the monocytes and T cells of RA patients, which supports that DNA hypomethylation and TET2 enzymes are associated with RA (de Andres et al., 2015). TET2 expression is also a potential prognostic and predictive biomarker in cytogenetically normal acute myeloid leukemia (Zhang et al., 2018). HIV-1 Vpr protein promotes degradation of TET2, thereby attenuating its binding to *Il-6* promoter region, which causes excessive IL-6 expression during resolution phase of inflammation (Lv et al., 2018). A recent study found that loss of TET2 and TET3 upregulates CD86 expression through relieving the gene-specific transcription repression by HDAC1/2, thus leads to hyperactivation of B cells and T cells in mice (Tanaka et al., 2020). Consequently, these mice are prone to develop systemic autoimmunity, which implies the function of TET2 in lupus-like diseases.

CONCLUSIONS AND PERSPECTIVES

Epigenetic regulation plays an important role in modulating immune responses against infection or injury. Numerous studies have well-indicated the significance of TET2 proteins and 5hmC in epigenetic regulation, hematopoietic stem cell development and myelopoiesis. The studies discussed in this review demonstrate the emerging roles of TET2, depending on its enzymatic activity or acting as a scaffold protein, in the homeostatic regulation of immune responses and pathogenesis of inflammatory diseases. We also discuss how TET2 is regulated and recruited, which provides a promising thought to potentially alter the process of immune responses. Despite so many discovered functions of TET2 in immune responses and inflammation, there are still many questions that need to be answered. Are there any other specific mechanisms of TET2 involved in the onset and resolution of inflammation? Can TET2 mutations be detected in other inflammatory diseases? Over the past decades, remarkable progress has been made in exploring the function of TET2 in regulating DNA methylation/demethylation by mediating the oxidation of 5mC. However, can oxidative modifications catalyzed by TET2 directly regulate gene expression as an independent type of epigenetic modifications, not just as the intermediate step of active DNA demethylation process? Besides, because of the distinct structure of TET2 compared to TET1 and TET3, the mechanism of RNA-dependent chromatin targeting of TET2 is still to be further studied. Is there a general regulation mechanism rather than a specific one of how TET2 is recruited to chromatin? Thus, more partner proteins of TET2 need to be identified. On the other hand, the mechanisms of how TET2 regulates gene expression by directly binding RNA are researchable. Combining with multiple epigenomic methods, many novel technologies have been developed and applied to screen the genomic distribution of TET2 catalyzing oxidation modifications and investigate more probable functions of TET2. Most importantly, further studies are required to illuminate the potential therapeutic role of targeting TET2 for the modulation of immune responses and the treatment of relevant inflammatory diseases.

ACKNOWLEDGEMENTS

We thank Dr. Bingjing Wang for helpful discussion. This work was supported by grants from the National Natural Science Foundation of China (81788101, 81922032) and CAMS Innovation Fund for Medical Sciences (2016-12M-1-003).

ABBREVIATIONS

α-KG, α-ketoglutaric acid; 2-HG, 2-hydroxyglutaric acid; 5mC, 5-methylcytosine; 5hmC, 5-hydroxymethylcytosine; 5caC, 5-carboxylcytosine; 5fC, 5-formylcytosine; AML, acute myelocytic leukemia; ARG1, arginase-1; BER, base excision repair; CGI, CpG island; CMML, chronic myelomonocytic leukemia; CXXC5, CXXC finger protein 5; DAMP, danger-associated molecular pattern;

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DC, dendritic cell; DNMT, DNA methyltransferase; HDAC1/2, histone deacetylase 1/2; IFN, interferon; IL, interleukin; lncRNA, long non-coding RNA; MDS, myelodysplastic syndromes; mESC, mouse embryonic stem cell; ncRNA, non-coding RNA; NLR, NOD-like receptor; OGT, O-linked GlcNAc transferase; PAMP, pathogen-associated molecular pattern; pDC, plasmacytoid dendritic cells; PRR, pattern-recognition receptor; RA, rheumatoid arthritis; RLR, RIG-I-like receptor; ROS, reactive oxygen species; SDHA, succinate dehydrogenase subunit A; SOCS3, suppressor of cytokine signaling protein 3; TDG, thymine-DNA glycosylase; TET, ten-eleven translocation protein; TGF-β1, transforming growth factor-β1; TLR, Toll-like receptor; UTR, untranslated region

COMPLIANCE WITH ETHICS GUIDELINES

Boyi Cong, Qian Zhang and Xuetao Cao declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by the any of the authors.

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