

Tet2-mediated responses to environmental stress

Woo Seok Song¹, Meiling Xia¹ (✉)

¹ Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine, Seoul 03080, South Korea

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KEYWORDS

ten-eleven translocation 2; stress; psychiatric disorders; epigenetics

ABSTRACT

The ten-eleven translocation 2 (Tet2) protein, a member of the Tet family, acts as an α -ketoglutarate- and Fe^{2+} -dependent dioxygenase that catalyzes the iterative oxidation of 5-methylcytosine. Tet2 is widely recognized for its involvement in diverse physiological and pathological processes. Herein, we focused on Tet2 changes in stress-related disease models, behavioral changes in response to mutant forms of Tet2, and potential mechanisms underlying the involvement of Tet2 in psychiatric symptoms. This information can contribute to the comprehensive understanding of the role of Tet2 in stress-related disorders and its potential as a therapeutic target.

1 Introduction

The old proverb “the straw that broke the camel’s back” signifies that things have reached a threshold limit and any increase in factors will lead to their collapse. Nowadays, in a pathological context, stress can often be considered that “straw”. According to the World Health Organization, the number of patients with stress-related disorders, such as major depressive disorder (MDD), has surpassed 340 million [1], thus making such disorders a substantial contributor to the global disease burden [2]. MDD represented the second greatest cause of disability in the 2010 “Global Burden of Disease” report and is anticipated to become the leading

cause by 2030 [3]. Furthermore, psychiatric symptoms have been commonly observed in numerous diseases, including Parkinson’s disease [4], Alzheimer’s disease [5], coronavirus disease 2019 [6], and even acne [7]. These associations underscore an urgent requirement for effective interventions targeting stress-related disorders and the associated psychiatric symptoms.

Thus, the effects of diagnosis, prevention, and treatment of stress-related disorders or psychiatric symptoms are inadequate owing to the complexities of their underlying causes and mechanisms. Analyses of epigenetic processes offer a promising avenue for better understanding the development of stress-related disorders through their ability to epigenetically alter gene

Address correspondence to Meiling Xia, Email: lynn_777@naver.com

expression [8]. Such an approach may help gain insights into the mechanisms contributing to stress-related disorders and develop more effective interventions that can mitigate the impact of this global health burden.

DNA methylation, the most typical epigenetic modification, plays a crucial role in transcriptional silencing and genomic stability. This modification is accomplished via the enzymatic transfer of methyl groups to the 5'-carbon atom of cytosine to form 5-methylcytosine (5-mC) [9]. Among the chromosomal translocation partners originally identified in leukemia [10], the ten-eleven translocation (Tet) family members Tet1, Tet2, and Tet3 serve as key regulators of DNA demethylation owing to their dioxygenase activity [11, 12]. For example, Tet2 serves as an important regulator of normal hematopoiesis, particularly myelopoiesis [13]. Recent studies have reported that changes in Tet2 in the brain of stress-model animals and Tet2 mutations cause stress-related phenotypes.

This review focused on the contribution of Tet2, a critical epigenetic protein, to stress-related disorders and explored its potential role in diagnosing, preventing, and treating psychiatric conditions.

2 Structure and function of Tet2

The Tet family includes the isoforms Tet1, Tet2, and Tet3 that are involved in DNA demethylation by catalyzing the conversion of 5-methylcytosine to 5-hydroxymethylcytosine [12]. Tet2, similar to Tet1 and Tet3, contains an N-terminal domain and a C-terminal catalytic domain that comprises a cysteine-rich region and a double-stranded β helix (DSBH) with a large low-complexity insertion. Tet1 and Tet3 contain CXXC zinc finger domains in the N-terminal region that recognize unmodified cytosine, 5mC, and 5-hydroxymethylcytosine (5-mC) in DNA. However, Tet2 requires the interaction with the

IDAX gene product (also known as CXXC4), which is involved in the binding of unmethylated CpG, to catalyze hydroxymethylation [14]. After Tet2 specifically recognizes CpG dinucleotides, 5-mC is inserted into the catalytic cavity owing to the substrate preference of Tet2 for 5-mC, allowing the oxidation of 5-mC to 5-hmC [15].

Recent studies have reported that 5-hmC is present at appreciable levels (~1 per 5000 5-mC residues) in the RNA of mammalian cells and in tissues that express the three Tet enzymes, which catalyze the formation of 5-hmC in RNA [16, 17]. These findings identified Tet2 as an RNA-binding protein with considerable regulatory functions. Specifically, Tet2 hydroxymethylates coding or noncoding RNA. For example, PSPC1 recruits Tet2 transcriptionally active loci, including endogenous retroviruses (ERVs) whose long terminal repeats have been co-opted by mammalian genomes as stage- and tissue-specific transcriptional regulatory modules [18]. Furthermore, Tet2 contributes to myelopoiesis; since these findings offer promising clues regarding the multifaceted roles of Tet2 in the regulation of the epigenetic modifications of diverse molecular targets [19, 20].

3 Functional analysis of Tet2

To identify the functional implications of Tet2, we conducted an analysis of Tet2 expression in diverse cell lines based on the RNA-Seq data obtained from the Human Protein Atlas (HPA) database. The analysis shows that Tet2 mRNA expression levels were higher in cell lines representing the hematopoietic and nervous systems compared with those of other systems (Figure 1a). Numerous studies have reported that the Tet2 gene frequently undergoes microdeletions and copy number-neutral loss-of-heterozygosity and leading to aberrant DNA methylation in diverse hematological malignancies [13, 21].

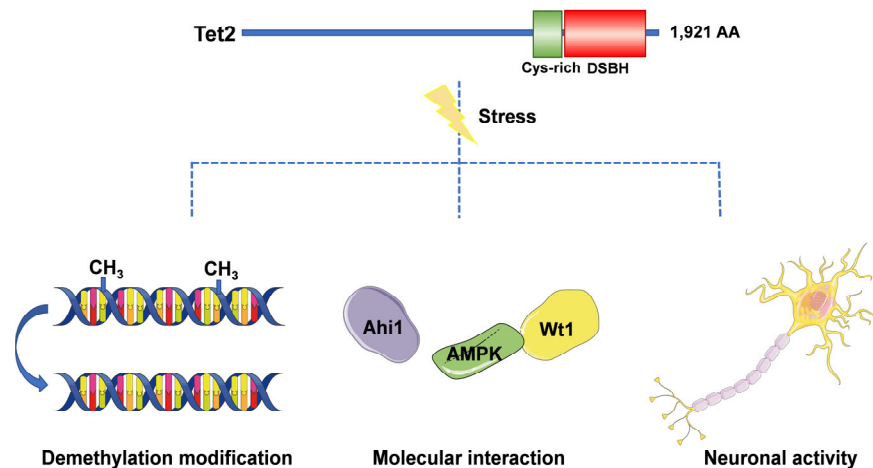


Figure 1 Functional analysis of Tet2. (a) Cell lines that express Tet2 were analyzed using the HPA database. (b, c) Analysis of GO and KEGG pathways (b) and transcription factors (c) associated with Tet2-interacting proteins were analyzed using the NCBI and METASCAPE databases.

However, the role of Tet2 in central nervous system (CNS) disorders, particularly those of psychiatric origin, appears to be underestimated because of the abnormal expression of 5hmC in the brain of patients with psychiatric disorders [22–24].

Furthermore, we identified the Tet2-interacting proteins described in published studies in the NCBI database and identified the functions of these 124 interacting proteins (Supplemental material) using the METASCAPE database. The top 20 clusters of enriched sets are shown in Figure 1b. The interacting proteins of Tet2 mediate pathways such as cellular responses to stress and signaling through Rho GTPases. Notably, the METASCAPE database was also enriched with possible transcription factors or regulators of Tet2 among these validated interacting proteins (Figure 1c), including stimulus-responsive transcription factors such as JUN, FOS, EGR1 [25], HIF1A [26], NF1 [27], SP1 [28], LEF1 [29], ESR1 [30], SIRT1 [31], TP53 [32], WT1 [33], E2F1 [34], and YY1 [35], which participate in psychiatric disorders such as depression, schizophrenia, or bipolar disorder. It will be interesting to identify the transcription factors that act in concert with Tet2 to contribute to

the development and progression of psychiatric disorders.

4 Tet2-mediated responses after stress

4.1 Tet2 expression after environmental stress

As the most well-established animal models of depression, chronic unpredictable mild stress (CUMS) models reproduce classic symptoms of depression such as anhedonia and social deficit [36]. Mice subjected to CUMS exhibit increased Tet2 expression levels in the hippocampus and, in contrast, decreased global 5hmC expression levels [37]. Furthermore, Tet2 and 5hmC levels in mice subjected to chronic social defeat stress (CSDS) exhibit similar responses [37]. Moreover, the induction of these stresses leads to the accumulation of Tet2 in the cytoplasm [37], and the decreased expression of Tet2 in the nucleus explains these contradictory findings.

Furthermore, other studies suggest that reduced Tet2 expression levels serve as a major contributor to stress-related disorders. Poststroke depression (PSD) is a common complication of stroke [38, 39], and decreased Tet2 reduced the 5hmC modification of the inflammatory regulator LEF1 to influence the secretion of IL-18 in mouse

models of PSD [40]. Moreover, Tet2 expression decreases in the hippocampus of socially isolated mice [41]. These findings highlight the importance of Tet2 in stress-related disorders and suggest that targeting Tet2 serves as a potential therapeutic strategy for such conditions. Further research is required to fully identify the mechanisms underlying the role of Tet2 in stress and related disorders.

4.2 Behavioral changes in Tet2-deficient mice

Most studies on Tet2 mutants focus on diseases such as hematopathy and tumors. The established association of epigenetic changes caused by environmental stress includes Tet2 mutations that cause alterations in psychiatric symptoms. Deficiency of Tet2 in the CNS leads to depression-like behaviors, including increased immobility time in the forced swim and tail suspension tests and increased latency to feed in the novelty-suppressed feeding test (NSFT) [37]. Furthermore, Tet2 knockout is associated with increased susceptibility to chronic restraint stress, and these stress-related phenotypes are observed before exposure to the stressor [42].

There has been evidence indicating that stress-related behavioral changes are caused by Tet2 mutations. For example, brain-specific deletion of *Wt1* leads to depressive-like behaviors, including immobility, despair, and anhedonia, in mice via the recruitment of Tet2 to modulate erythropoietin expression [33]. RNA-seq analysis identified 703 genes in neural stem cells that are significantly upregulated and 979 genes that are downregulated because of Tet2 depletion [43]. Gene ontology (GO) analysis revealed specific enrichment of upregulated genes involved in the cell cycle and DNA replication pathways. Conversely, downregulated genes were highly enriched in GO terms related to ion channel changes, synaptic plasticity such as sodium ion

transmembrane transport, synaptic assembly, and dendrite morphogenesis [43]. The expression levels of the gene which participates in psychiatric disorders (including depression and other stress-related illnesses) [44–46] are downregulated after Tet2 deletion and therefore these genes may serve as targets of hydroxymethylation by Tet2.

5 Activities of Tet2 in stress responses

5.1 Tet2 catalyzes hydroxymethylation of DNA and RNA

Tet2 plays a crucial role in 5hmC dynamics (Figure 2). Among the 1,251 stress-induced hydroxymethylation genes, 630 were identified in Tet2 KO mice, suggesting that Tet2 is more likely to cause the stress-induced loss of the 5-hmC loci [42] as revealed by high-throughput sequencing of 5-hmC modified genes [47]. Specifically, decreased Tet2 levels lead to the hypermethylation of PPAR- α in the hippocampus of mice exposed to social isolation-induced stress [41]. Decreased Tet2 levels result in the decreased abundance of differentially hydroxymethylated regions in Wnt signaling pathway genes in PSD mice [40]. In addition, Tet2-modulated DNA demethylation is involved in potential antidepressant therapy in animal models of depression. Caffeic acid regulates the ratio of 5-mC/5-hmC at the promoter regions of the bone-derived neurotrophic factor and catechol-O-methyltransferase (COMT) genes associated with depression-like behaviors in rats [48]. Metformin increases the expression of bone-derived neurotrophic factor to ameliorate depression through the AMPK/Tet2 pathway [49]. Furthermore, Tet2 participates in brain-related traits such as social interaction and risk-taking behavior related to histone H3-K4 methylation [50].

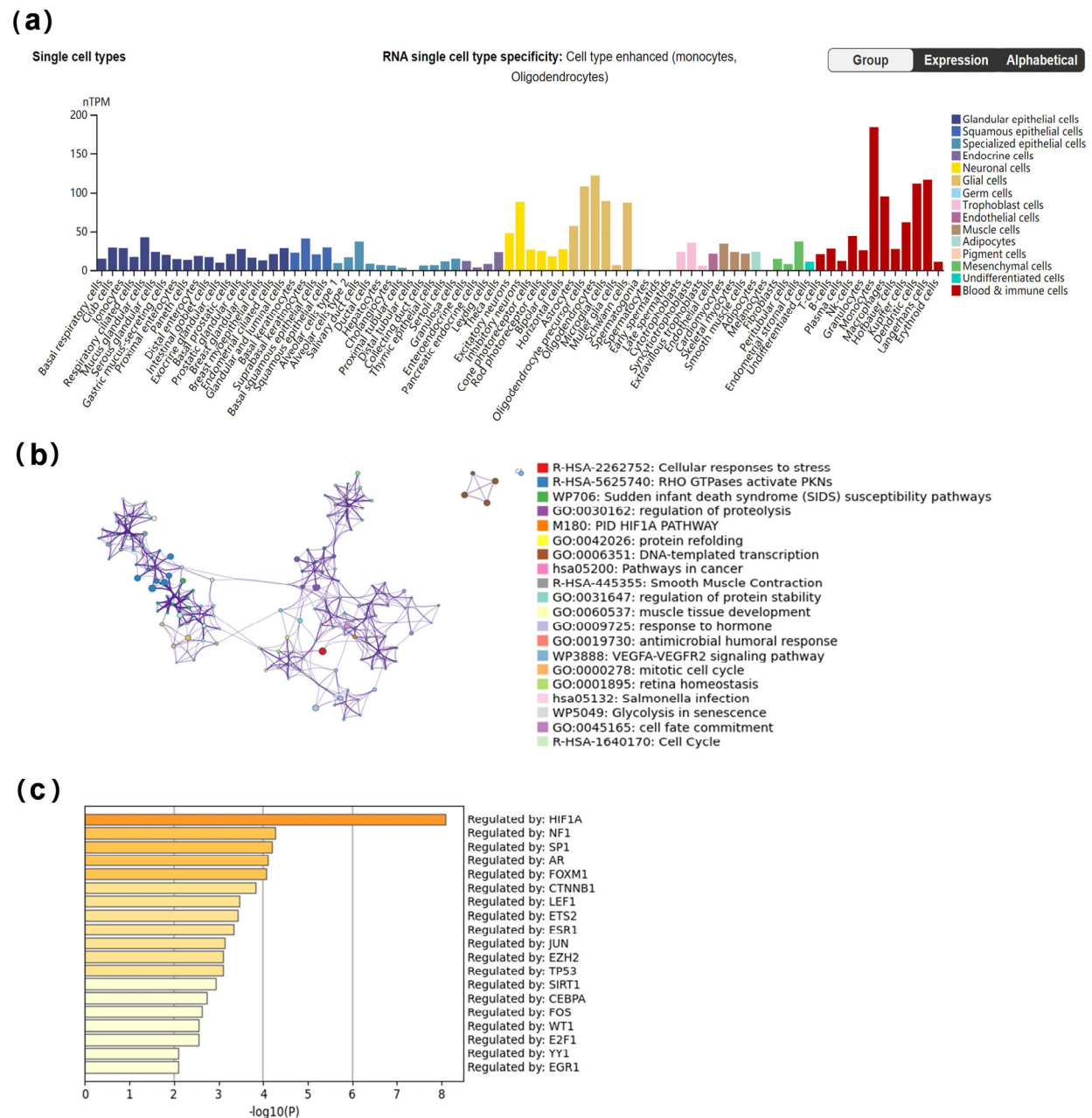


Figure 2 Mechanisms of stress-related behavioral changes induced by Tet2. Tet2 participates in stress-related behavioral changes through demethylation, molecular interaction, and neuronal activity.

5.2 Tet2-interacting proteins in response to stress

In the CUMS model, Tet2 accumulates in the neuronal cytoplasm through interaction with a cellular trafficking protein (Fig. 2) known as Abelson helper integration site-1 (Ahi1), thus preventing Tet2 from entering the nucleus and hydroxymethylating 5mC of DNA [37]. The

exact role of Tet2 accumulation in the neuronal cytoplasm and its potential “cytoplasmic toxicity” remain unclear, although these studies demonstrate that regulating the nuclear translocation of Tet2 serves as a key to treating depression-like behaviors.

As a target for potential antidepressants [51, 52], AMP-activated protein kinase (APMK) phosphorylates and thus stabilizes Tet2 [53]; and

14-3-3 proteins bind Tet2 when phosphorylated at Ser-99 to protect the latter from PP2A-mediated dephosphorylation [54]. Wt1 recruits Tet2 to the promoter of the gene encoding erythropoietin to ameliorate depressive-like behavior in mice [33]. Furthermore, Tet2 interacts with the key nonsense-mediated mRNA decay factor Upf1 to regulate the stability of stress-related genes such as Unc5b mRNA [55].

Significantly more Tet2-interacting partners [56] associated with stress-related disorders were identified, including PU.1 [57], Klf4 [58], Ikzf1 [59], Atrx [60], Cux1 [61], Yy2 [62], Snip1 [63], P300/CBP [64], Hdac1 [65], Hdac2 [66], Phf2 [67], Trapp [68], Chd8 [69], and Runx1 [70]. However, the roles these molecules play in the stress response through Tet2 require further investigation (Table 1).

5.3 Tet2 is involved in the regulation of neuronal activity and neurogenesis

Certain mental state changes are often accompanied by changes in neuronal activity [71, 72]. Although only a few studies have definitively reported the effect of Tet on the electrical activity of neurons, some evidence also pointed to this association (Fig. 2). For example, at least 88% of 5hmC immunostaining-positive cells colocalize with calcium/calmodulin dependent protein kinase II (CaMK II, a marker for excitatory

neurons)-labeled neurons [73]. Neurons express high levels of the three Tet family isoforms [43, 74, 75]. However, the effect of Tet catalytic activity on synaptic transmission in neurons remains unknown.

One study suggests that Tet2 upregulation in neuropathic pain promotes Nfat1 promoter demethylation, resulting in the reprogramming of microglia gene expression while promoting the proliferation of microglia [76]. The activated microglia release more cytokines such as TNF- α and IL-1 β and induce an inflammatory microenvironment that enhances excitatory synaptic transmission [76]. Noticeably, a recent study found that increased Tet2 expression levels in adult hippocampal neurons alter the hydroxymethylation of genes related to synaptic transmission and signaling [77]. Whether the depression-like phenotype induced by Tet2 deficiency or changes in the expression levels of Tet2 in the stress models is related to synaptic transmission or neuronal activity remains to be explored.

6 Conclusions and prospects

Increasing evidence suggests that epigenetic mechanisms offer promising avenues for the study of psychiatric syndromes that arise from the interplay between genetic factors and environmental exposures [78, 79]. As the most studied form of epigenetic modifications, DNA methylation persists throughout life, and demethylation of DNA by Tet2 plays an integral role in stress-induced psychiatric disorders. This review aimed to explore the latest findings regarding Tet2 and its impact on stress responses. Tet2 mutations are present in many patients with cancer, and the role of Tet2 in tumors is well-investigated. Although still in their relatively early stages, recent investigations have revealed that Tet2 expression levels are

Table 1 Stress-related Tet2-interacting proteins

Interacting protein	Mechanism	Reference
Ahi1	Ahi1 mediates the nuclear translocation of Tet2	[37]
AMPK	APMK phosphorylates and stabilizes Tet2	[53]
14-3-3	14-3-3 proteins protect the Ser-99 phosphorylation of Tet2 and stabilize Tet2	[54]
Wt1	Wt1 recruits Tet2 to the promoter of the gene encoding erythropoietin	[33]
Upf1	Tet2 interacts with Upf1 to regulate the stabilities of stress-related genes	[55]

altered in different stress-induced animals and that animals with Tet2 mutations exhibit stress-related behaviors. Furthermore, the hydroxymethylation modifications of DNA and RNA, regulation of RNA stability, and regulation of Tet2 expression are being increasingly researched. Considering the heterogeneous causes and pathophysiologies of neuropsychiatric disorders, more sophisticated techniques are required to investigate the role of Tet2 in stress-related disorders.

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Author Contribution

M.X. analyzed the data and prepared the first draft of the manuscript. M.X. and W.S. participated in the conception and design of the study, M.X. constructively revised the manuscript; M.X. participated in data collection and organization; M.X. and W.S. participated in and supervised the study throughout, and they share corresponding authorship. All authors commented on previous versions of the manuscript and approved the final version.

Declaration of conflicting interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

References

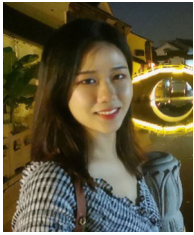
- [1] Chiriță, A. L., Gheorman, V., Bondari, D., Rogoveanu, I. Current understanding of the neurobiology of major depressive disorder. *Rom J Morphol Embryol*, **2015**, 56(2 suppl): 651–658.
- [2] Friedrich, M. J. Depression is the leading cause of disability around the world. *JAMA*, **2017**, 317(15): 1517.
- [3] Mathers, C. D., Loncar, D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, **2006**, 3(11): e442.
- [4] Weintraub, D., Aarsland, D., Chaudhuri, K. R., Dobkin, R. D., Leentjens, A. F., Rodriguez-Violante, M., Schrag, A. The neuropsychiatry of Parkinson's disease: Advances and challenges. *The Lancet Neurology*, **2022**, 21(1): 89–102.
- [5] Kim, B., Noh, G. O., Kim, K. Behavioural and psychological symptoms of dementia in patients with Alzheimer's disease and family caregiver burden: A path analysis. *BMC Geriatrics*, **2021**, 21(1): 160.
- [6] Schou, T. M., Joca, S., Wegener, G., Bay-Richter, C. Psychiatric and neuropsychiatric sequelae of COVID-19—A systematic review. *Brain, Behavior, and Immunity*, **2021**, 97: 328–348.
- [7] Samuels, D. V., Rosenthal, R., Lin, R., Chaudhari, S., Natsuaki, M. N. Acne vulgaris and risk of depression and anxiety: A meta-analytic review. *J Am Acad Dermatol*, **2020**, 83(2): 532–541.
- [8] Peixoto, P., Cartron, P. F., Serandour, A. A., Hervouet, E. From 1957 to nowadays: A brief history of epigenetics. *Int J Mol Sci*, **2020**, 21(20): E7571.
- [9] Jones, P. A. Functions of DNA methylation: Islands, start sites, gene bodies and beyond. *Nature Reviews Genetics*, **2012**, 13(7): 484–492.
- [10] Tahiliani, M., Koh, K. P., Shen, Y. H., Pastor, W. A., Bandukwala, H., Brudno, Y., Agarwal, S., Iyer,

- L. M., Liu, D. R., Aravind, L. et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. *Science (New York, N Y)*, **2009**, 324(5929): 930–935.
- [11] He, Y. F., Li, B. Z., Li, Z., Liu, P., Wang, Y., Tang, Q. Y., Ding, J. P., Jia, Y. Y., Chen, Z. C., Li, L. et al. Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA. *Science*, **2011**, 333(6047): 1303–1307.
- [12] Ito, S., Shen, L., Dai, Q., Wu, S. C., Collins, L. B., Swenberg, J. A., He, C., Zhang, Y. Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. *Science*, **2011**, 333(6047): 1300–1303.
- [13] Quivoron, C., Couronné, L., Della Valle, V., Lopez, C. K., Plo, I., Wagner-Ballon, O., Do Cruzeiro, M., Delhommeau, F., Arnulf, B., Stern, M. H. et al. TET2 inactivation results in pleiotropic hematopoietic abnormalities in mouse and is a recurrent event during human lymphomagenesis. *Cancer Cell*, **2011**, 20(1): 25–38.
- [14] Iyer, L. M., Abhiman, S., Aravind, L. Natural history of eukaryotic DNA methylation systems. *Progress in Molecular Biology and Translational Science*, **2011**, 101: 25–104.
- [15] Lulu, Hu, . Crystal structure of TET2-DNA complex: Insight into TET-mediated 5mC oxidation. *Cell*, **2013**, 155(7): 1545–1555.
- [16] Fu, L., Guerrero, C. R., Zhong, N., Amato, N. J., Liu, Y., Liu, S., Cai, Q., Ji, D., Jin, S. G., Niedernhofer, L. J. et al. Tet-mediated formation of 5-hydroxymethylcytosine in RNA. *J Am Chem Soc*, **2014**, 136(33): 11582–11585.
- [17] Delatte, B., Wang, F., Ngoc, L. V., Collignon, E., Bonvin, E., Deplus, R., Calonne, E., Hassabi, B., Putmans, P., Awe, S. et al. RNA biochemistry. Transcriptome-wide distribution and function of RNA hydroxymethylcytosine. *Science*, **2016**, 351(6270): 282–285.
- [18] Guallar, D., Bi, X. J., Pardavila, J. A., Huang, X., Saenz, C., Shi, X. L., Zhou, H. W., Faiola, F., Ding, J. J., Haruehanroengra, P. et al. RNA-dependent chromatin targeting of TET2 for endogenous retrovirus control in pluripotent stem cells. *Nature Genetics*, **2018**, 50(3): 443–451.
- [19] Shen, Q. C., Zhang, Q., Shi, Y., Shi, Q. Z., Jiang, Y. Y., Gu, Y., Li, Z. Q., Li, X., Zhao, K., Wang, C. M. et al. Tet2 promotes pathogen infection-induced myelopoiesis through mRNA oxidation. *Nature*, **2018**, 554(7690): 123–127.
- [20] He, C. S., Bozler, J., Janssen, K. A., Wilusz, J. E., Garcia, B. A., Schorn, A. J., Bonasio, R. TET2 chemically modifies tRNAs and regulates tRNA fragment levels. *Nat Struct Mol Biol*, **2021**, 28(1): 62–70.
- [21] Lemonnier, F., Couronné, L., Parrens, M., Jaïs, J. P., Travert, M., Lamant, L., Tournillac, O., Rousset, T., Fabiani, B., Cairns, R. A. et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. *Blood*, **2012**, 120(7): 1466–1469.
- [22] Gavin, D. P., Sharma, R. P., Chase, K. A., Matrisciano, F., Dong, E., Guidotti, A. Growth arrest and DNA-damage-inducible, beta (GADD45b)-mediated DNA demethylation in major psychosis. *Neuropsychopharmacology*, **2012**, 37(2): 531–542.
- [23] Gross, J. A., Pacis, A., Chen, G. G., Drupals, M., Lutz, P. E., Barreiro, L. B., Turecki, G. Gene-body 5-hydroxymethylation is associated with gene expression changes in the prefrontal cortex of depressed individuals. *Translational Psychiatry*, **2017**, 7(5): e1119.
- [24] Reszka, E., Jabłońska, E., Lesicka, M., Wiecek, E., Kapelski, P., Szczepankiewicz, A., Pawlak, J., Dmierzak-Węglarz, M. An altered global DNA methylation status in women with depression. *J Psychiatr Res*, **2021**, 137: 283–289.
- [25] Bukowska, B., Woźniak, E., Sicińska, P., Mokra, K., Michałowicz, J. Glyphosate disturbs various epigenetic processes *in vitro* and *in vivo* - A mini review. *Sci Total Environ*, **2022**, 851(Pt 2): 158259.
- [26] Kostyuk, S. V., Ershova, E. S., Martynov, A. V., Artyushin, A. V., Porokhovnik, L. N., Malinovskaya, E. M., Jestkova, E. M., Zakharova, N. V., Kostyuk, G. P., Izhevskaya, V. L. et al. *In vitro* analysis of biological activity of circulating cell-free DNA isolated from blood plasma of schizophrenic patients and healthy controls—Part 2: Adaptive response. *Genes*, **2022**, 13(12): 2283.
- [27] Teksin, G., Sahpolat, M., Kurhan, F., Sesliokuyucu, C., Bayazit, H., . Decreased nesfatin-1 level in overweight depressed patients. *Psychiatria Danubina*, **2022**, 34(4): 682–686.

- [28] Chen, Y. C., Hsu, P. Y., Su, M. C., Chen, T. W., Hsiao, C. C., Chin, C. H., Liou, C. W., Wang, P. W., Wang, T. Y., Lin, Y. Y. et al. microRNA sequencing analysis in obstructive sleep apnea and depression: Anti-oxidant and MAOA-inhibiting effects of miR-15b-5p and miR-92b-3p through targeting PTGS1-NF- κ B-SP1 signaling. *Antioxidants*, **2021**, 10(11): 1854.
- [29] Santos, R., Linker, S. B., Stern, S., Mendes, A. P. D., Shokhirev, M. N., Erikson, G., Randolph-Moore, L., Racha, V., Kim, Y., Kelsoe, J. R. et al. Deficient LEF1 expression is associated with lithium resistance and hyperexcitability in neurons derived from bipolar disorder patients. *Molecular Psychiatry*, **2021**, 26(6): 2440–2456.
- [30] Schneider, M. O., Pretscher, J., Goecke, T. W., Häberle, L., Engel, A., Kornhuber, J., Eichler, A., Ekici, A. B., Beckmann, M. W., Fasching, P. A. et al. Genetic variants in the genes of the sex steroid hormone metabolism and depressive symptoms during and after pregnancy. *Arch Gynecol Obstet*, **2023**, 307(6): 1763–1770.
- [31] Luo, X. J., Zhang, C. Down-regulation of *SIRT1* Gene expression in major depressive disorder. *Am J Psychiatry*, **2016**, 173(10): 1046.
- [32] Gozdziewicz, A. S., Zotti, C. W., de Carvalho, I. A. M., dos Santos, T. C., de Santi Walter, L. R., Ogradowski, K. R. P., Dammski, K. L., Komechen, H., Mendes, M. C., de Souza, E. N. et al. Psychological impact of TP53-variant-carrier newborns and counselling on mothers: A pediatric surveillance cohort. *Cancers*, **2022**, 14(12): 2945.
- [33] Ji, F., Wang, W. W., Feng, C., Gao, F., Jiao, J. W. Brain-specific *Wt1* deletion leads to depressive-like behaviors in mice via the recruitment of Tet2 to modulate Epo expression. *Molecular Psychiatry*, **2021**, 26(8): 4221–4233.
- [34] McGrory, C. L., Ryan, K. M., Kolshus, E., McLoughlin, D. M. Peripheral blood E2F1 mRNA in depression and following electroconvulsive therapy. *Prog Neuropsychopharmacol Biol Psychiatry*, **2019**, 89: 380–385.
- [35] Lu, J., Jin, K., Jiao, J. P., Liu, R. P., Mou, T. T., Chen, B., Zhang, Z. H., Jiang, C. N., Zhao, H. Y., Wang, Z. et al. YY1 (Yin-Yang 1), a transcription factor regulating systemic inflammation, is involved in cognitive impairment of depression. *Psychiatry Clin Neurosci*. **2023**;77(3):149-159.
- [36] Ma, M. X., Chang, X., Wu, H. T. Animal models of stress and stress-related neurocircuits: A comprehensive review. *Stress and Brain*, **2021**, 1(2): 108–127.
- [37] Zhang, Q., Hu, Q. C., Wang, J. J., Miao, Z. G., Li, Z. Y., Zhao, Y. W., Wan, B., Allen, E. G., Sun, M., Jin, P. et al. Stress modulates Ahi1-dependent nuclear localization of ten-eleven translocation protein 2. *Human Molecular Genetics*, **2021**, 30(22): 2149–2160.
- [38] Robinson R. G. Poststroke depression: Prevalence, diagnosis, treatment, and disease progression. *Biological Psychiatry*, **2003**, 54(3): 376–387.
- [39] Morris, P. L., Robinson, R. G., Andrzejewski, P., Samuels, J., Price, T. R. Association of depression with 10-year poststroke mortality. *Am J Psychiatry*, **1993**, 150(1): 124–129.
- [40] Wei, X., Yu, L., Zhang, Y., Li, X., Wu, H., Jiang, J., Qing, Y., Miao, Z., Fang, Q. The role of Tet2-mediated hydroxymethylation in poststroke depression. *Neuroscience*, **2021**, 461: 118–129.
- [41] Matrisciano, F., Pinna, G. PPAR- α hypermethylation in the hippocampus of mice exposed to social isolation stress is associated with enhanced neuroinflammation and aggressive behavior. *Int J Mol Sci*, **2021**, 22(19): 10678.
- [42] Cheng, Y., Sun, M., Chen, L., Li, Y., Lin, L., Yao, B., Li, Z., Wang, Z., Chen, J., Miao, Z. et al. Ten-eleven translocation proteins modulate the response to environmental stress in mice. *Cell Rep*, **2018**, 25(11): 3194–3203.e4.
- [43] Li, X. K., Yao, B., Chen, L., Kang, Y., Li, Y. J., Cheng, Y., Li, L. P., Lin, L., Wang, Z. Q., Wang, M. L. et al. Ten-eleven translocation 2 interacts with forkhead box O3 and regulates adult neurogenesis. *Nat Commun*, **2017**, 8: 15903.
- [44] Licznarski, P., Duman, R. S. Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression. *Neuroscience*, **2013**, 251: 33–50.
- [45] Linden, D. J., Smeyne, M., Connor, J. A. Induction of cerebellar long-term depression in culture requires postsynaptic action of Sodium Ions. *Neuron*, **1993**, 11(6): 1093–1100.

- [46] Murrough, J. W., Abdallah, C. G., Mathew, S. J. Targeting glutamate signalling in depression: Progress and prospects. *Nat Rev Drug Discov*, **2017**, 16(7): 472–486.
- [47] Song, C. X., Szulwach, K. E., Fu, Y., Dai, Q., Yi, C. Q., Li, X. K., Li, Y. J., Chen, C. H., Zhang, W., Jian, X. et al. Selective chemical labeling reveals the genome-wide distribution of 5-hydroxymethylcytosine. *Nat Biotechnol*, **2011**, 29(1): 68–72.
- [48] Hu, J., Cao, S., Zhang, Z., Wang, L., Wang, D., Wu, Q., Li, L. Effects of caffeic acid on epigenetics in the brain of rats with chronic unpredictable mild stress. *Mol Med Rep*, **2020**, 22(6): 5358–5368.
- [49] Wang, Y. F., Liu, B. B., Yang, Y., Wang, Y. M., Zhao, Z., Miao, Z. G., Zhu, J. T. Metformin exerts antidepressant effects by regulated DNA hydroxymethylation. *Epigenomics*, **2019**, 11(6): 655–667.
- [50] Nesbit, N., Wallace, R., Harihar, S., Zhou, M., Jung, J. Y., Silberstein, M., Lee, P. H. Genomewide alteration of histone H3K4 methylation underlies genetic vulnerability to psychopathology. *J Genet*, **2021**, 100(2): 1–10.
- [51] Fang, W. T., Zhang, J., Hong, L. Y., Huang, W. B., Dai, X. M., Ye, Q. Y., Chen, X. C. Metformin ameliorates stress-induced depression-like behaviors via enhancing the expression of BDNF by activating AMPK/CREB-mediated histone acetylation. *J Affect Disord*, **2020**, 260: 302–313.
- [52] Hu, Y., Zhao, M., Zhao, T., Qi, M. M., Yao, G. D., Dong, Y. The protective effect of pilose antler peptide on CUMS-induced depression through AMPK/Sirt1/NF- κ B/NLRP3-mediated pyroptosis. *Frontiers in Pharmacology*, **2022**, 13: 815413.
- [53] Fiedler, E. C., Shaw, R. J. AMPK regulates the epigenome through phosphorylation of TET2. *Cell Metabolism*, **2018**, 28(4): 534–536.
- [54] Kundu, A., Shelar, S., Ghosh, A. P., Ballestas, M., Kirkman, R., Nam, H., Brinkley, G. J., Karki, S., Mobley, J. A., Bae, S. et al. 14-3-3 proteins protect AMPK-phosphorylated ten-eleven translocation-2 (TET2) from PP2A-mediated dephosphorylation. *J Biol Chem*, **2020**, 295(6): 1754–1766.
- [55] Xia, M. L., Yan, R., Wang, W. J., Kong, A. Q., Zhang, M., Miao, Z., Ge, W., Wan, B., Xu, X. S. The Tet2–Upfl complex modulates mRNA stability under stress conditions. *Front Genet*. **2023**;14:1158954.
- [56] Joshi, K., Liu, S. H., Breslin S J, P., Zhang, J. W. Mechanisms that regulate the activities of TET proteins. *Cellular and Molecular Life Sciences*, **2022**, 79(7): 363.
- [57] Weigelt, K., Carvalho, L. A., Drexhage, R. C., Wijkhuijs, A., Wit, H. D., van Beveren, N. J. M., Birkenhäger, T. K., Bergink, V., Drexhage, H. A. TREM-1 and DAP12 expression in monocytes of patients with severe psychiatric disorders. EGR3, ATF3 and PU.1 as important transcription factors. *Brain, Behavior, and Immunity*, **2011**, 25(6): 1162–1169.
- [58] Wang, L., Li, M., Zhu, C. P., Qin, A. P., Wang, J. C., Wei, X. N. The protective effect of Palmatine on depressive like behavior by modulating microglia polarization in LPS-induced mice. *Neurochemical Research*, **2022**, 47(10): 3178–3191.
- [59] Demin, K. A., Krotova, N. A., Ilyin, N. P., Galstyan, D. S., Kolesnikova, T. O., Strekalova, T., de Abreu, M. S., Petersen, E. V., Zabegalov, K. N., Kalueff, A. V. Evolutionarily conserved gene expression patterns for affective disorders revealed using cross-species brain transcriptomic analyses in humans, rats and zebrafish. *Sci Rep*, **2022**, 12: 20836.
- [60] Wille, A., Amort, T., Singewald, N., Sartori, S. B., Lusser, A. Dysregulation of select ATP-dependent chromatin remodeling factors in high trait anxiety. *Behavioural Brain Research*, **2016**, 311: 141–146.
- [61] Sasayama, D., Hiraishi, A., Tatsumi, M., Kamijima, K., Ikeda, M., Umene-Nakano, W., Yoshimura, R., Nakamura, J., Iwata, N., Kunugi, H. Possible association of CUX1 gene polymorphisms with antidepressant response in major depressive disorder. *Pharmacogenomics J*, **2013**, 13(4): 354–358.
- [62] Zambello, E., Zanetti, L., Hédou, G. F., Angelici, O., Arban, R., Tasan, R. O., Sperk, G., Caberlotto, L. Neuropeptide Y-Y2 receptor knockout mice: Influence of genetic background on anxiety-related behaviors. *Neuroscience*, **2011**, 176: 420–430.
- [63] Mulligan, M. K., Dubose, C., Yue, J. M., Miles, M. F., Lu, L., Hamre, K. M. Expression, covariation, and genetic regulation of miRNA Biogenesis genes in brain

- supports their role in addiction, psychiatric disorders, and disease. *Frontiers in Genetics*, **2013**, 4: 126.
- [64] Maurice, T., Duclot, F., Meunier, J., Naert, G., Givalois, L., Meffre, J., Célérier, A., Jacquet, C., Copois, V., Mechti, N. et al. Altered memory capacities and response to stress in p300/CBP-associated factor (PCAF) histone acetylase knockout mice. *Neuropsychopharmacology*, **2008**, 33(7): 1584–1602.
- [65] Li, W. F., Ali, T., Zheng, C. Y., Liu, Z. Z., He, K. W., Shah, F. A., Ren, Q. G., Rahman, S. U., Li, N. N., Yu, Z. J. et al. Fluoxetine regulates eEF2 activity (phosphorylation) via HDAC1 inhibitory mechanism in an LPS-induced mouse model of depression. *J Neuroinflammation*, **2021**, 18(1): 38.
- [66] Wang, S. E., Ko, S. Y., Jo, S., Choi, M., Lee, S. H., Jo, H. R., Seo, J. Y., Lee, S. H., Kim, Y. S., Jung, S. J. et al. TRPV1 regulates stress responses through HDAC2. *Cell Rep*, **2017**, 19(2): 401–412.
- [67] Chris, E., Zheng, T. H., Kennedy Nicholas, A., Ferdinando, B., Anderson Carl, A., Loukas, M., Joanne, H., Jingchunzi, S., Suyash, S., Ioan, V. A. et al. Genome-wide analysis of 53, 400 people with irritable bowel syndrome highlights shared genetic pathways with mood and anxiety disorders. *Nat Genet*, **2021**, 53(11): 1543–1552.
- [68] Mavros, C. F., Brownstein, C. A., Thyagrajan, R., Genetti, C. A., Tembulkar, S., Graber, K., Murphy, Q., Cabral, K., VanNoy, G. E., Bainbridge, M. et al. *De novo variant of TRRAP in a patient with very early onset psychosis in the context of non-verbal learning disability and obsessive-compulsive disorder: A case report. BMC Medical Genetics*, **2018**, 19(1): 197.
- [69] Cherepanov, S. M., Gerasimenko, M., Yuhi, T., Furuhashi, K., Tsuji, C., Yokoyama, S., Nakayama, K. I., Nishiyama, M., Higashida, H. Oxytocin ameliorates impaired social behavior in a *Chd8* haploinsufficiency mouse model of autism. *BMC Neuroscience*, **2021**, 22(1): 32.
- [70] Wuchty, S., Myers, A. J., Ramirez-Restrepo, M., Huentelman, M., Richolt, R., Gould, F., Harvey, P. D., Michopolous, V., Steven, J. S., Wingo, A. P. et al. Integration of peripheral transcriptomics, genomics, and interactomics following trauma identifies causal genes for symptoms of post-traumatic stress and major depression. *Molecular Psychiatry*, **2021**, 26(7): 3077–3092.
- [71] Tunc-Ozcan, E., Peng, C. Y., Zhu, Y. W., Dunlop, S. R., Contractor, A., Kessler, J. A. Activating newborn neurons suppresses depression and anxiety-like behaviors. *Nature Commun*, **2019**, 10(1): 3768.
- [72] Zanos, P., Gould, T. D. Mechanisms of ketamine action as an antidepressant. *Molecular Psychiatry*, **2018**, 23(4): 801–811.
- [73] Zhao, T., Piao, L. H., Li, D. P., Xu, S. H., Wang, S. Y., Yuan, H. B., Zhang, C. X. BDNF gene hydroxymethylation in hippocampus related to neuroinflammation-induced depression-like behaviors in mice. *J Affect Disord*, **2023**, 323: 723–730.
- [74] Antunes, C., da Silva, J. D., Guerra-Gomes, S., Alves, N. D., Ferreira, F., Loureiro-Campos, E., Branco, M. R., Sousa, N., Reik, W., Pinto, L. et al. Tet3 ablation in adult brain neurons increases anxiety-like behavior and regulates cognitive function in mice. *Molecular Psychiatry*, **2021**, 26(5): 1445–1457.
- [75] Greer, C. B., Wright, J., Weiss, J. D., Lazarenko, R. M., Moran, S. P., Zhu, J., Chronister, K. S., Jin, A. Y., Kennedy, A. J., Sweatt, J. D. et al. *Tet1* isoforms differentially regulate gene expression, synaptic transmission, and memory in the mammalian brain. *J Neurosci*, **2021**, 41(4): 578–593.
- [76] Jiang, B. C., Ding, T. Y., Guo, C. Y., Bai, X. H., Cao, D. L., Wu, X. B., Sha, W. L., Jiang, M., Wu, L. J., Gao, Y. J. NFAT1 orchestrates spinal microglial transcription and promotes microglial proliferation via c-MYC contributing to nerve injury-induced neuropathic pain. *Adv Sci (Weinh)*, **2022**, 9(27): e2201300.
- [77] Pratt, K. J. B., Shea, J. M., Remesal-Gomez, L., Bieri, G., Smith, L. K., Couthouis, J., Chen, C. P., Roy, I. J., Gontier, G., Villeda, S. A. Loss of neuronal Tet2 enhances hippocampal-dependent cognitive function. *Cell Rep*, **2022**, 41(6): 111612.
- [78] Guidotti, A., Grayson, D. R. DNA methylation and demethylation as targets for antipsychotic therapy. *Dialogues in Clinical Neuroscience*, **2014**, 16(3): 419–429.
- [79] Akbarian, S. Epigenetic mechanisms in schizophrenia. *Dialogues Clin Neurosci*, **2014**, 16(3): 405–417.



Meiling Xia, got her joint PhD training from Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine. She has published many high-quality papers on journals including *Journal of neuroinflammation*, *Frontiers of medicine*. Her current research interests focus on epigenetic mechanisms of central nervous system disorders. E-mail: lynn_777@naver.com



Woo Seok Song is a PhD candidate from Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine. He has published many high-quality papers on journals including *Neuropharmacology*, *Experimental & molecular medicine*. His research focuses on central nervous system disorders. E-mail: wssong@snu.ac.kr