Involvement of nucleic-acid methylation on biology and evolution: from first hominids to modern humans – Review

Gabriel Dorado [1], Fernando Luque [2], Francisco José Esteban [3], Plácido Pascual [4], Inmaculada Jiménez [5], Francisco Javier S. Sánchez-Cañete [6], Patricia Raya [7], Jesús Sáiz [8], Adela Sánchez [8], Teresa E. Rosales [9], Víctor F. Vásquez [10], Pilar Hernández [11]

[1] Author for correspondence, Dep. Bioquímica y Biología Molecular, Campus Rabanales C6-1-E17, Campus de Excelencia Internacional Agroalimentario (ceiA3), Universidad de Córdoba, 14071 Córdoba (Spain), eMail: <bb1dopeg@uco.es>; [2] Laboratorio de Producción y Sanidad Animal de Córdoba, Ctra. Madrid-Cádiz km 395, 14071 Córdoba; [3] Servicio de Informática, Edificio Ramón y Cajal, Campus Rabanales, Universidad de Córdoba, 14071 Córdoba; [4] Laboratorio Agroalimentario de Córdoba, Consejería de Agricultura y Pesca, Junta de Andalucía, 14004 Córdoba; [5] IES Puertas del Campo, Avda. San Juan de Dios 1, 51001 Ceuta; [6] EE.PP. Sagrada Familia de Baena, Avda. Padre Villoslada 22, 14850 Baena (Córdoba); [7] Dep. Radiología y Medicina Física, Unidad de Física Médica, Facultad de Medicina, Avda. Menéndez Pidal s/n, Universidad de Córdoba, 14071 Córdoba; [8] Dep. Farmacología, Toxicología y Medicina Legal y Forense, Facultad de Medicina, Avda. Menéndez Pidal, s/n, Universidad de Córdoba, 14071 Córdoba; [9] Laboratorio de Arqueobiología, Avda. Juan Pablo II s/n, Universidad Nacional de Trujillo, 13011 Trujillo (Peru); [10] Centro de Investigaciones Arqueobiológicas y Paleoecológicas Andinas Arqueobios, C/. Martínez de Compañón 430-Bajo 100, Urbanización San Andrés, 13008 Trujillo (Peru); [11] Instituto de Agricultura Sostenible (IAS), Consejo Superior de Investigaciones Científicas (CSIC), Alameda del Obispo s/n, 14080 Córdoba.

Abstract

Recent developments in molecular biology, in general, and nucleic-acid sequencing, in particular, have allowed fascinating discoveries. Thus, it is now known that DNA and RNA methylations modulate development of organs, including the brain. That involves both their structure and function, allowing quick adaptation to changing environments. It has been proposed that such epigenetic changes may allow learning and encode memories. Some of these events arose before hominids, but others made us human. Yet, the cerebral cortex evolution not only enhanced learning and memory, but also increased the risk of diseases like cancer and neurodegenerative disorders in humans. Fortunately, technologies like CRISPR have promising potential to edit these epigenetic modifications, to prevent and cure such diseases. The relevance of nucleic-acid methylation is also particularly relevant in bioarchaeology, since both ancient DNA (aDNA) and RNA (aRNA) can be analyzed, revealing unknown paleophysiologies.

Key words: Hominini, paleogenomics, paleoepigenomics, proteomics, metabolomics, gene expression, biomarkers, bioinformatics.

Resumen

Los avances recientes en biología molecular, en general, y secuenciación de ácidos nucleicos, en particular, han posibilitado descubrimientos fascinantes. Así, ahora se sabe que las metilaciones de ADN y ARN modulan el desarrollo de órganos, incluido el cerebro. Eso implica tanto su estructura como su función, lo que permite una rápida adaptación a los entornos cambiantes. Se ha propuesto que tales cambios epigenéticos pueden permitir el aprendizaje y codificar recuerdos. Algunos de estos fenómenos surgieron antes que los homínidos, pero otros nos hicieron humanos. Sin embargo, la evolución de la corteza cerebral no solo mejoró el aprendizaje y la memoria, sino que también incrementó el riesgo de enfermedades como el cáncer y los trastornos neurodegenerativos en humanos. Afortunadamente, tecnologías como CRISPR tienen un potencial prometedor para editar estas modificaciones epigenéticas, para prevenir y curar tales enfermedades. La relevancia de la metilación de ácidos nucleicos también es particularmente importante en bioarqueología, ya que se pueden analizar tanto ADN antiguo (ADNa) como ARN antiguo (ARNa), revelando paleofisiologías desconocidas.

Palabras clave: Hominini, paleogenómica, paleoepigenómica, proteómica, metabolómica, expresión génica, biomarcadores, bioinformática.

Introduction

The study of biological evolution is a fascinating topic, in general, and even more when focused on human evolution. As we have reviewed. developments in molecular biology, in general, and nucleic acid sequencing and amplification, in particular, as well as metabolomics and proteomics, have allowed to gain new insights in such areas, even for extinct species (Dorado et al, 2007-2021b). A key question about the latter is: what made us human? As we have reviewed, developments in nucleic-acid sequencing (Dorado et al, 2021a) has revealed interesting and sometimes surprising facts, including: i) Notch Homolog 2 (*NOTCH2*)-derived gene family, named Notch Homolog 2 N-terminal-Like (*NOTCH2NL*). They were generated from partial duplication, repair and conversion of *NOTCH2* (Dorado et al, 2018); and ii) noncoding RNA (Dorado et al, 2020). Both facts were involved in cortical evolution of human brain from first hominids to modern humans.

Further research has also found that nucleic-acid methylation (epigenetic modification) was also involved in the amazing fact of brain development that made us human (Liu et al, 2021a). It was first discovered the involvement of DNA methylation in regulation of gene expression. Then, it was also found the relevance of RNA methylation in such processes. These facts become even more relevant when considering that not only ancient DNA (aDNA), but also ancient RNA (aRNA) can be sequenced with the new technological advancements (Dorado et al, 2021a).

DNA methylation

DNA methylation in promoter regions typically represses gene expression. Interestingly, DNA methylation and demethylation events take place during human development, being different during gamete generation on males and females (Fig. 1)

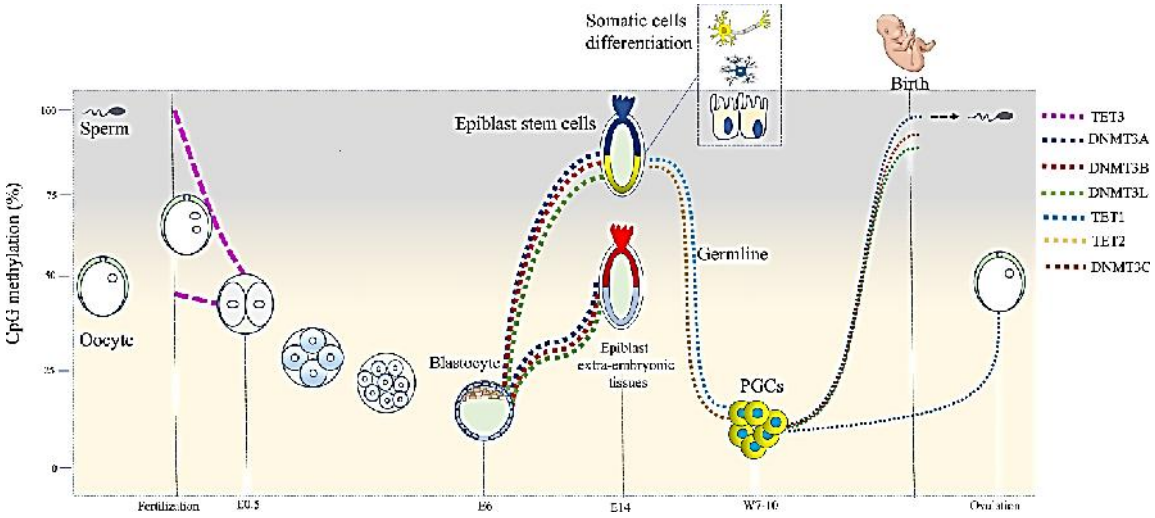

Figure 1. DNA methylation and demethylation events during human development. Such epigenetic changes modulate cellular gene expression, including neurons. Note the significant demethylation after fertilization, methylation after blastocyte, and again significant demethylation in germline and methylation during gametogenesis, with males and females exhibiting different profiles. © Elsevier (Shirvani-Farsani et al, 2021).

(Shirvani-Farsani et al, 2021). On the other hand, neurons are the basis of memories. Indeed, DNA methylation contributes to regulation of brain development, involving structure and function of such organ, allowing quick adaptations to changing environments. Metabolic changes, differences in cellular and synaptic properties, and eventually expansion and reorganization of neural circuits are carried out in the Central Nervous-System (CNS) (Fig. 2) (Sun et al, 2019; Clemens and Gabel, 2020; Pattabiraman et al, 2020; Poon et al, 2020a; Wheater et al, 2020; Yin et al, 2020; Liu et al, 2021a, b; Niiranen et al, 2022).

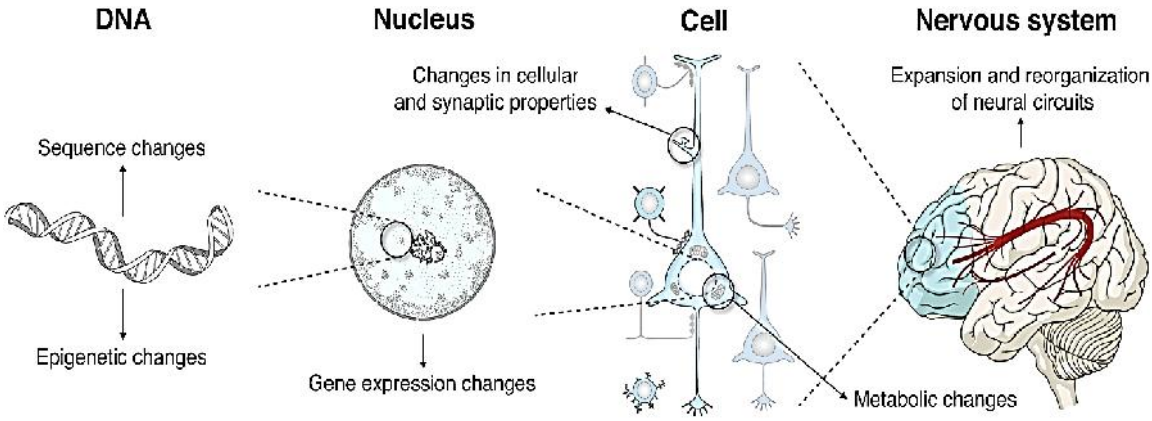

Figure 2. DNA sequence and epigenetic changes in human central nervous-system. Sequence and epigenetic modifications modulate gene expression. That generate changes in cells and CNS. © Elsevier (Pattabiraman et al, 2020).

Thus, human brains show hypomethylated DNA in CG contexts. That way, they upregulate downstream genes. In contrast, DNA hypermethylation of non-CG or CH contexts (H = A, C and T) has increased in human-brain evolution, downregulating genes. It has been proposed that these epigenetic changes may encode memories. Some of such events arose before the segregation of hominoids and catarrhine monkeys, but others arose after separation from chimpanzees. Unfortunately, such human-cortex evolution not only enhanced learning and memory, but also increased the risk of neurodegeneration and neuropsychiatric diseases in humans. They include Alzheimer and Parkinson diseases, schizophrenia, epilepsy and psychosis. Likewise, stroke, ataxia, addiction (including alcohol-use disorder), post-traumatic stress and socio-emotional disorders, depression, suicidality risk and ageing (Hernando-Herraez et al, 2013, 2015; Banerjee et al, 2018, 2019; Pattabiraman et al, 2020; Poon et al, 2020b; Wheater et al, 2020; Coppede, 2021a,b; 2022; Jeong et al, 2021; Liu et al, 2021a,b; Starnawska and Demontis, 2021; Wei et al, 2021; Wigley et al, 2021; Bernstein, 2022; Dragic et al, 2022; Guemri et al, 2022; Kaplan et al, 2022; Kouter et al, 2022; Lei and Wang, 2022; Lionaki et al, 2022; Panariello et al, 2022; Zhan et al, 2022).

Magnetic Resonance Imaging (MRI) has been used to study DNA methylation in the brain (Lam et al, 2022). Additionally, bioinformatics, artificial intelligence (AI), in general, and machine learning (ML), in particular, have also been used to identify methylation signatures in brains of Alzheimer's disease (Li et al,

2022; Chen et al, 2022a, b). Furthermore, DNA methylation profiles have been prosed as biomarkers of neuropsychiatric disorders (Shirvani-Farsani et al, 2021). Besides, aDNA methylation has been used to infer ancient phenotypes, like Neanderthal and Denisovan faces, as we and others have reviewed (Mathov et al, 2020; Dorado et al, 2021b; Niiranen et al, 2022).

RNA methylation

RNA can be also methylated after transcription (epitranscriptomic modification) of messenger RNA (mRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and non-coding RNA (ncRNA). As we have previously reviewer, the latter are sometimes translated into micropeptides (Dorado et al, 2020). As expected, RNA methylation is involved in many physiological and pathological states. Thus, methylation of N6 position of adenosine generates N6-methyladenosine (m^6A or m6A), which plays a key role in brain development. Such epigenetic change is controlled by three types of proteases (writers, readers and erasers), modulating proliferation, differentiation and maturation of neural precursors, including gliogenesis and neurogenesis, allowing brain development. That involves dendritogenesis and axonal growth (axonogenesis), synaptogenesis and synaptic transmission, circadian clock, behavior, learning and memory (Figs. 3 and 4). On the negative side, m6A mRNA methylation is also involved in malignant glioma proliferation (being the most lethal brain tumor) and inflammatory response in microglia (Li et al, 2021; Pan et al, 2021; Sokpor et al, 2021; Yen and Chen, 2021; Sun et al, 2022; Wei et al, 2022; Widagdo et al, 2022; Zhang et al, 2022a, b).

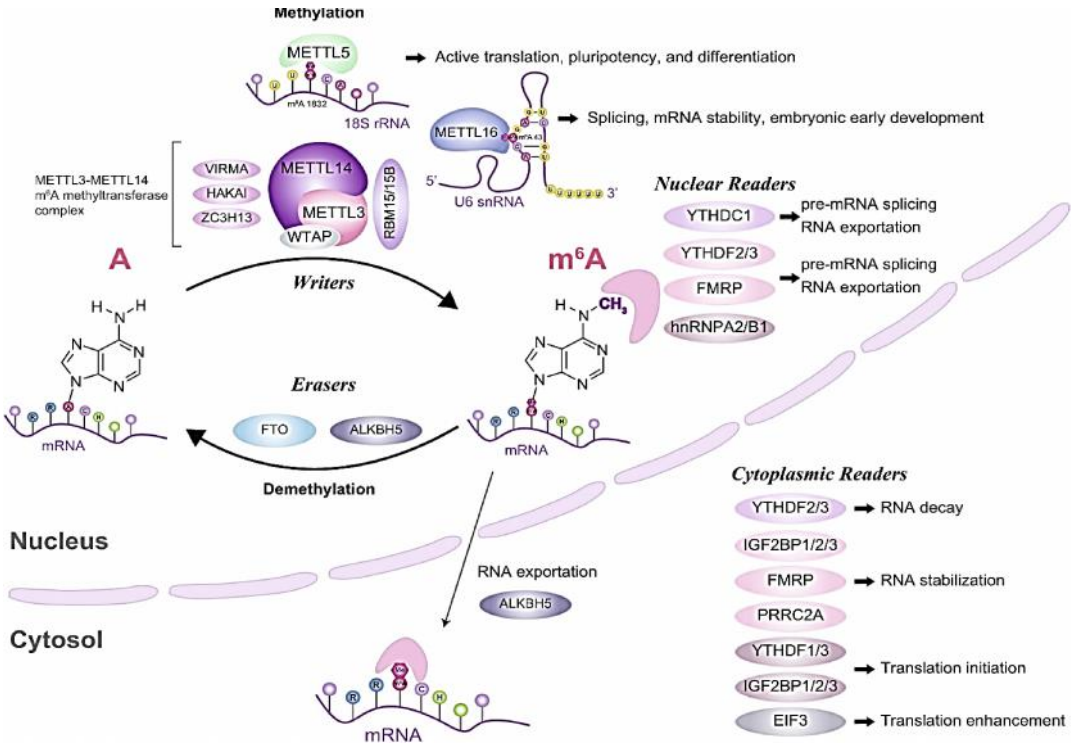

Figure 3. Writers, readers and erasers of m6A mRNA. mRNA is methylated by writers, read by readers and removed by erasers, modulating cell physiology. © BioMed Central (BMC; Yen and Chen, 2021).

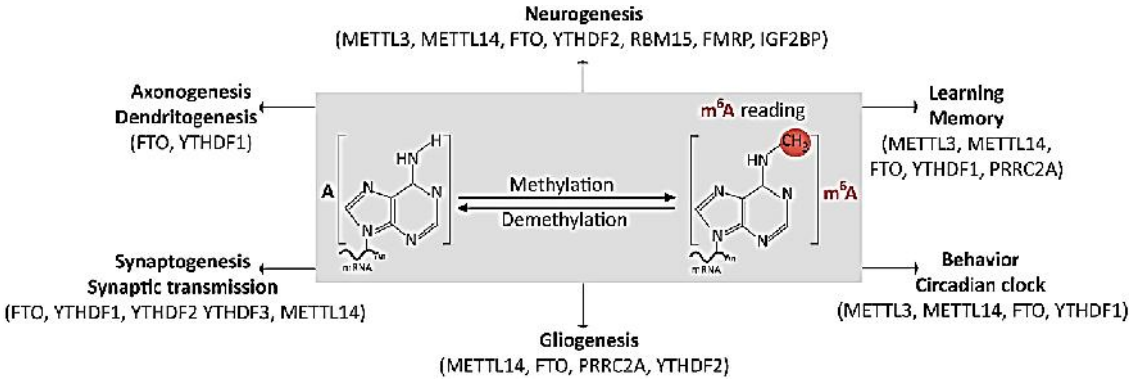

Figure 4. Implication of m6A mRNA in brain physiology. Such epigenetic modifications modulate proliferation and differentiation, including synaptogenesis and synaptic transmission, which are involved in behavior, learning and memory, among other physiological functions. © Frontiers (Sokpor et al, 2021).

It has been found that RNA methylation is involved in learning and long-term memory consolidation, through upregulation of: i) METhylTransferase-Like 3 (*METTL3*); ii) Yeast Two-hybrid 521-B (YT521-B) Homology (YTH) Domain-Family member 1 (*YTHDF1*); and iii) *FTO* [gene name derived from "FaTsO", due to its large size, deleted by the mouse "Fused Toes" (FT) mutation] (Fig. 5) (Zhou et al, 2020; Widagdo et al, 2022).

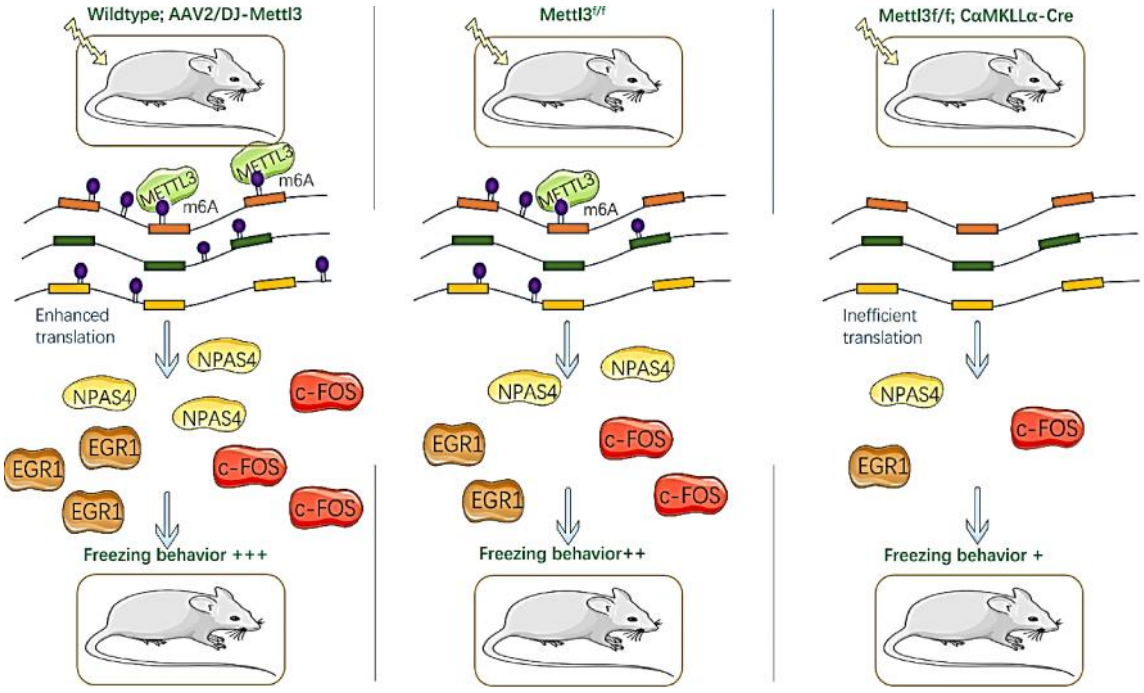

Figure 5. Long-term memory is modulated by *METTL3*. Mice with overexpression (left), normal expression (middle) and knockdown of *METTL3* are shown. The former exhibits increased translation of *EGR1*, *npas4* and *c-FOS*. That enhanced long-term memory ability of such mice, in relation to the ones with normal expression and –mostly– the knockdown ones. © Elsevier (Zhou et al, 2020).

Interestingly, while gene regulation is usually carried out in a binary induction/repression way, m6A methylation fine-tunes it. That is accomplished through different processes, including splicing, export, translation, stability and degradation of mRNA. Curiously, m6A mRNA methylation is highest in the brain than in other human organs. As said before, it modulates neurogenesis, including axonogenesis, and gliogenesis, during brain development. Later on, it is involved in brain health through synaptic plasticity, circadian rhythm, stress response and cognitive function. On the other hand, m6A methylation imbalance and dysregulation may lead to different pathologies, like chronic neurodegeneration, acute brain injury, neuropsychiatric disorders and brain cancer (Fig. 6) (Chokkalla et al, 2020, 2022; Park et al, 2020; Sokpor et al, 2021; Yen and Chen, 2021; Sun et al, 2022; Wei et al, 2022; Zhang et al, 2022a, b).

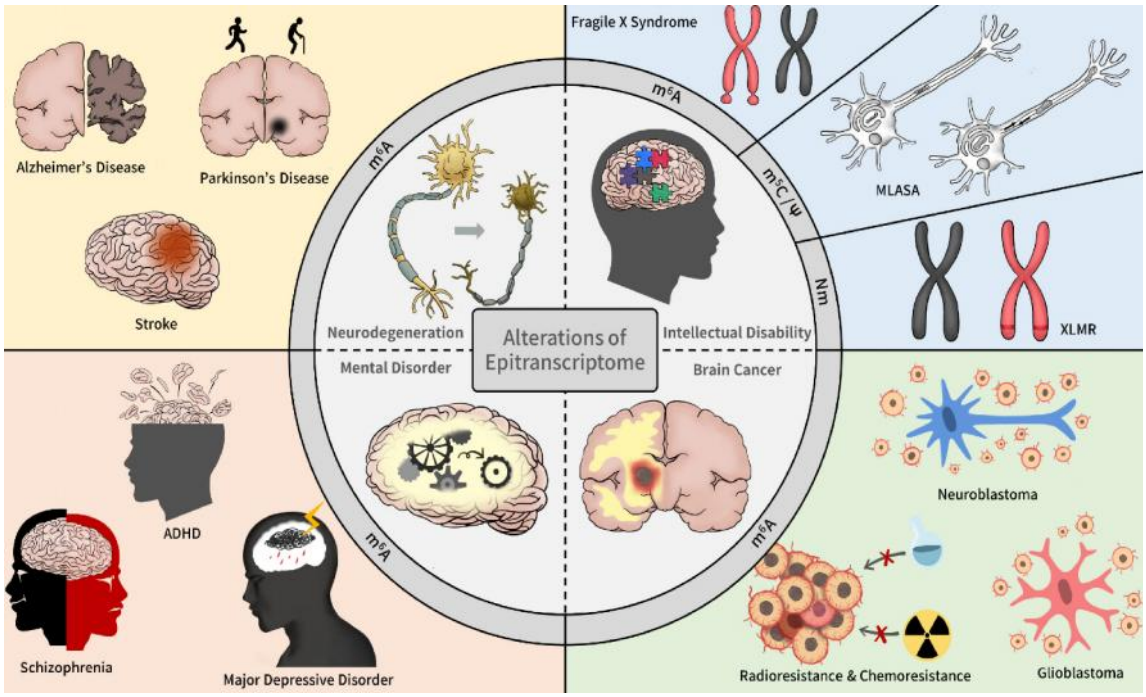

Figure 6. RNA epitranscriptomic alterations and brain disorders. Such diseases may involve neurodegeneration, intellectual disability, mental disorder and brain cancer. © The Korean Society for Biochemistry and Molecular Biology (Park et al, 2020). See also the modulation of brain physiology by m6A mRNA at <https://img.inotgo.com/imagesLocal/202208/10/220208101553342913_6.jpg> or <https://pic4.zhimg.com/80/v2-582705027d88c88525ca79e182d37eef_1440w.jpg>. Such epitranscriptomic modification is involved in brain development, its health and disease (Chokkalla et al, 2020).

Concluding remarks and future prospects

Developments in nucleic-acid sequencing have allowed to discover new biological processes. Among them are nucleic-acid (DNA and RNA) methylation. Identifying individual methylation sites can be expensive and labor intensive. Therefore, bioinformatics approaches have been proposed (Li et al, 2022; Chen et al, 2022a, b). Such epigenetic modifications are involved in regulation of gene expression, including brain development. In summary, partial

duplication, repair and conversion of *NOTCH2* into *NOTCH2NL* genes, *as well as* noncoding RNA and nucleic-acid methylation were involved in cortical evolution of human brain from first hominids to modern humans. Although there are limitations (Non, 2021; Smith and Non, 2022), these studies have an even greater relevance, when considering that new sequencing technologies allow to sequence aDNA and aRNA, as we and others have reviewed (Dorado et al, 2007, 2009, 2011, 2016, 2021; Lindqvist and Rajora, 2019). Last but not least, Clustered Regularly-Interspaced Short-Palindromic Repeats (CRISPR), that we have also reviewed (Dorado et al, 2017), has promising potential to edit m6A and cure neurological diseases like Alzheimer and Parkinson, increasing incorporation, stability and translation, or activating decay and degradation of specific mRNA molecules (Fig. 7) (Sokpor et al, 2021).

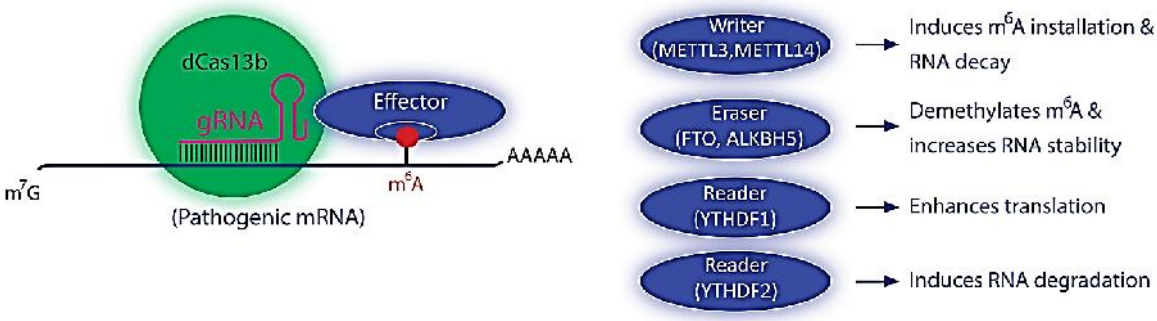

Figure 7. Editing of m6A mRNA by CRISPR. mRNA can be modified, either increasing or decreasing its incorporation, stability and activity. © Frontiers (Sokpor et al, 2021).

***Acknowledgements*.** Supported by "Ministerio de Economía y Competitividad" (MINECO grant BIO2015-64737-R) and "Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria" (MINECO and INIA RF2012-00002-C02-02); "Consejería de Agricultura y Pesca" (041/C/2007, 75/C/2009 and 56/C/2010), "Consejería de Economía, Innovación y Ciencia" (P11-AGR-7322) and "Grupo PAI" (AGR-248) of "Junta de Andalucía"; and "Universidad de Córdoba" ("Ayuda a Grupos"), Spain.

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