Arch Iran Med. October 2018;21(10):478-485

http www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

Mini Review

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tRNA Methyltransferase Defects and Intellectual Disability

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Abstract

In all organisms, transfer RNA (tRNA) molecules are required to undergo post-transcriptional modifications at different levels in order to convert into mature tRNAs. These modifications are critical for many aspects of tRNA function and structure, such as translational efficiency, flexibility, codon–anticodon interaction, stability, and fidelity. Up to now, over 100 modified nucleosides have been identified in tRNAs from all domains of life. Post-transcriptional modifications include different chemical processes such as methylation, deamination, or acetylation, with methylation reactions as the most common. tRNA methyltransferases are a family of enzymes involved in the post-transcriptional methylation of tRNA bases. Recent studies have reported different human diseases resulting from defects in tRNA methyltransferase activity, including cancer, diabetes and neurological disorders such as intellectual disability (ID). In this article, we focused on biological function and characterization of tRNA methyltransferases associated with ID in order to explain how functional disruption of tRNA methyltransferases could lead to ID phenotype.

Keywords: Intellectual disability, Methylation, tRNA methyltransferase, tRNA modification

Cite this article as: Abedini SS, Kahrizi K, de Pouplana LR; Najmabadi H. tRNA methyltransferase defects and intellectual disability. Arch Iran Med. 2018;21(10):478–485.

Received: January 14, 2018, Accepted: May 30, 2018, ePublished: October 1, 2018

Introduction

Transfer RNAs (tRNAs) are small molecules (70–100 nucleotides) that play a central role in protein translation, and are highly abundant in the cell (up to 5% of the total RNA).[1-3] In all organisms, during their biogenesis and maturation, primary tRNA transcripts are processed by a sequence of post-transcriptional modifications which are required for their proper function as translation adaptors. Post-transcriptional modifications regulate the structure and function of tRNAs, and influence all aspects of tRNA biology.[2-5] The nature of base modifications is very variable among different tRNAs, but some of them are ancestral and have remained conserved during evolution throughout the tree of life.

The position of specific base modifications in the tRNA body is not fixed,[4,6,7] and the biochemical pathways that generate them also show large functional variations among species.[1,4,6] In general, however, the anticodon loop is the domain of tRNA that accumulates greater modification diversity, in particular, at the wobble position where modified bases directly affect codon recognition and modulate codon–anticodon interactions.[3,7-9]

More than 100 chemically modified nucleosides have been reported in different residues of tRNA molecules.[3,4,7,10-13] Among numerous types of chemical modifications, methylation reactions catalyzed by methyltransferases are relatively more frequent than others.[14-16] To date, more than 30 methylated nucleotides have been found at different positions in tRNAs in all organisms, while the enzymes responsible for several of them have not yet been described.[13,15,16] The functional importance of tRNA methyltransferases (Trms) is illustrated by the fact that any changes and perturbations in methylation patterns are linked to defects in tRNA structure and function, with observable effects on cell development, proliferation, and metabolism. Accordingly, the functional disruption of Trms is associated with different human diseases including cancer, immunodeficiencies, neurodegeneration, cardiopathies, and mitochondria-related conditions.[8,12,13,15-20]

Several reports have linked defects in tRNA methyltransferase activity to various types of neurological disorders such as intellectual disability (ID).[12,17,18] Here we would like to review the current understanding of the role that different tRNA methyltransferases play in the development of human neurological disorders.

Biological Function of tRNA Methyltransferases and Their Effects on Neural System

Transfer RNA methyltransferases are a diverse group of tRNA modification enzymes involved in methylation. Methylation is one of the most important processes for regulation of tRNA functionality and it is known as a marker of its

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maturation. In addition, it is involved in formation of the correct tRNA structure and its stability, and the prevention of base-pairing errors during translation.[13,16,20-23] Other activities for methylation reactions that have been reported in recent studies include controlling tRNA transportation from cytoplasm to mitochondria, tRNA localization and their quality control system.[15,16,24,25]

Methylation can happen at any canonical bases (A, C, G, and U) of tRNA, but the sites of methylation are conserved during the evolution of living organisms. Different sites have been detected for methylation including C5 of prymidine, endocyclic or exocyclic nitrogens of purines and pyrimidines and the 2'-oxygen of ribose.[16,20-23] The biochemical structure of some common methylated nucleosides has been illustrated in Figure 1.

Diversity in chemical reactions among Trms is related to the cofactor used during methylation process. tRNA methyltransferases may use S-adenosylmethionine (SAM/AdoMet) or 5,10-methylenetetrahydrofolate as cofactor and methyl donor groups for methylation. But, based on their consumption, almost all of them belong to the SAM superfamily, and exclusively employ AdoMet as a universal donor.[15,16,26,27] Five structural classes have been identified for AdoMet dependent enzymes, which tRNA methyltranferases based on their catalytic domain, are categorized in two classes (Class I and IV). Class I and IV are detected in the presence of Rossmann-fold domain and deep trefoil knot structure, respectively.[15,16] Regardless of methyl group donors, in their absence or depletion, methylation reactions will be incomplete and other tRNA modifications will be disrupted.[15-17,23]

It has recently been reported that some Trms catalyze methylation reactions in various residues of tRNAs while one nucleotide can be methylated by different Trms. For more details about methylated nucleosides and their corresponding tRNA methyltransferases, some good reviews are available.[1,13,15,16,28,29]

The modification especially methylation plays a crucial role in protein synthesis, so any deficiency can probably cause a genetic disorder. By improving the identification of tRNA methyltransferase enzymes, different human genetic diseases such as mitochondrial defects, metabolic dysfunctions, diabetes, cancers and neurodegenerative and neurological diseases have been detected resulting from mutations and disruptions in these enzymes.[16,17,20,30-32] In most cases, neurological disorders due to Trms defects are associated with ID.[12,17,20]

Table 1 summarizes the genes responsible for tRNA methyltransferases, the position of methylated nucleosides within tRNA and their related neurodevelopmental dysfunction.

Different deleterious changes and mutations in tRNA methyltransferases can impact on the neural system, because the human brain is very sensitive to tRNA methyltransferase deficiency and oxidative stress resulting from Trms disruption.[1,3,12,13,17,18,33-35]

Intellectual Disability and Trms Genes

ID, as a deficiency in the development of cognitive and adaptive abilities, is one of the most common heterogeneous disorders with a prevalence of approximately 1%–3% in general population.[61-64] The etiology of ID varies from environmental factors to single gene defects. It is estimated that genetic causes are involved in 25%–50% of ID cases.[63-66] Among genes known to be responsible for ID, some of them encode tRNA methyltransferase enzymes and are described in this section.

The tRNA methyltransferase 10A (*TRMT10A*) or human RNA (guanine-9) methyltransferase domain containing 2 (*HRG9MTD2*) encodes a protein that modifies a single

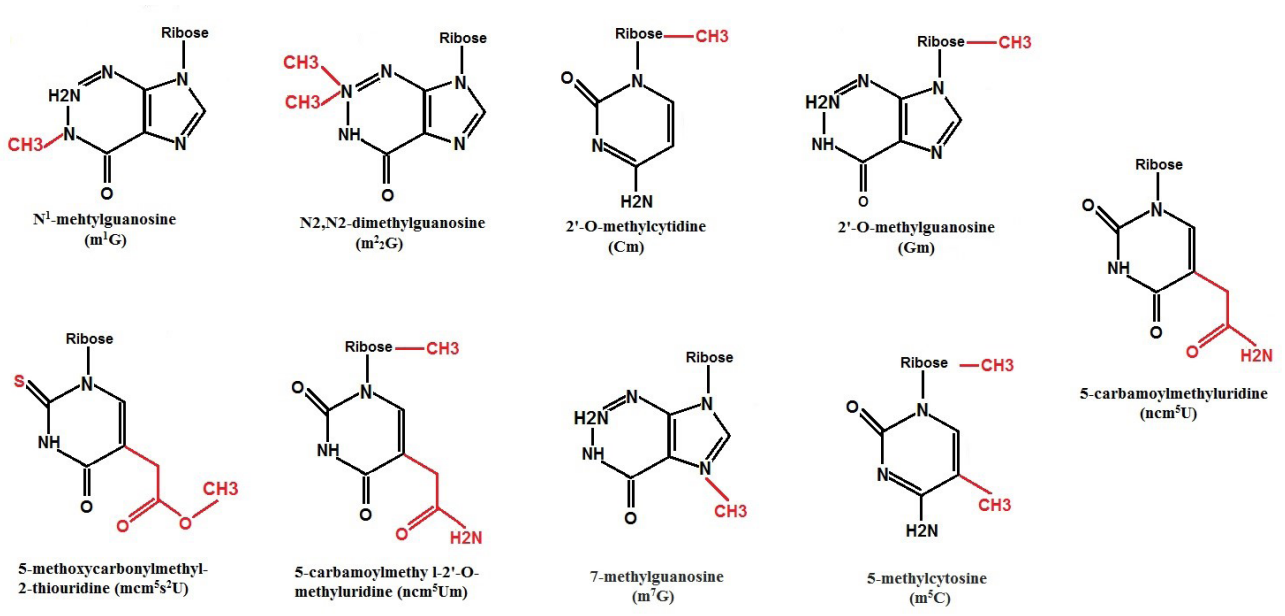

Figure 1. Some Methylated Nucleosides in tRNAs. Methylation sites are colored in red.

Table 1. tRNA Methyltransferases and Their Associated Neurological Disorders

Methyltransferases/ Gene	tRNA Modification and Residues Affected	Neurological Disorders	Patients#	Ethnicity	References
TRMT10A (HRG9MTD2)	m^1G9; Several tRNAs	ID, microcephaly, developmental delay, epilepsy	9	Moroccan, Jewish, Uzbekistani, Israeli Muslim, Caucasian	36-38
TRMT1	m^2_2G26 (m^2G26); several tRNAs	Cognitive disorders and ID	9	Iranian	39, 40
FTSJ1	Cm 32,Cm34, Gm34, ncm^5Um 34; $tRNA^{Leu}$, $tRNA^{Trp}$, $tRNA^{Phe}$	Non-syndromic X-linked ID	18	Belgian, Japanese, Australian	41-45
ELP1(IKBKAP), ELP2, ELP3, ELP4 (Elongator Complex)	mcm^5s^2U34, ncm^5U 34, and derivatives; several tRNAs	ID, Familial dysautonomia, atypical rolandic epilepsy, amyotrophic lateral sclerosis	Many	Ashkenazi Jewish, Iranian, Caucasian, Belgian, USA, UK	39, 46-53
WDR4	m^7G46, several tRNAs	Down's syndrome, brain malformation, microcephaly, encephalopathy, seizures	3	Saudi Arabia	54, 55
NSUN2	m^5C34; $tRNA^{Leu}$ m^5C48, m^5C49, m^5C50; several tRNAs	Autosomal-recessive ID, Microcephaly, Dubowitz-like syndrome	18	Iranian, Pakistani, Lebanese, German, Emirati	56-60

Abbreviations: m^1G, N^1-mehtylguanosine; m^2_2G, N2,N2-dimethylguanosine; Cm, 2′-O-methylcytidine; Gm, 2′-O-methylguanosine ; ncm^5Um, 5-carbamoylmethyl-2′-O-methyluridine; mcm^5s^2U, 5-methoxycarbonylmethyl-2-thiouridine; ncm^5U, 5-carbamoylmethyluridine; m^7G, 7-methylguanosine; m^5C, 5-methylcytosine; Leu, leucine; Trp, tryptophan; Phe, phenylalanine; ID, intellectual disability.

guanosine residue at position 9 of numerous tRNAs by methylation (Figure 2). This modification is highly conserved and is catalyzed by a SAM-dependent methyltransferase.[36,67] Northern blot analysis has shown that *TRMT10A* is expressed in all tissues, but the highest expression is detected in brain and pancreatic islets.[36]

Three different mutations have been identified for *TRMT10A* which are associated with ID, primary microcephaly, epilepsy, short stature and early-onset diabetes.[36-38] TRMT10A protein can have an effect on the development of neural progenitor cells, and may also play a role in the neural differentiation process in the cortical marginal zone and cerebellum, so any defects in this gene can have an influence on brain size and intellectual efficiency.[36] In addition to these effects, the loss of activity of TRMT10A may lead to a dramatic acceleration of β cell apoptosis.[36,37]

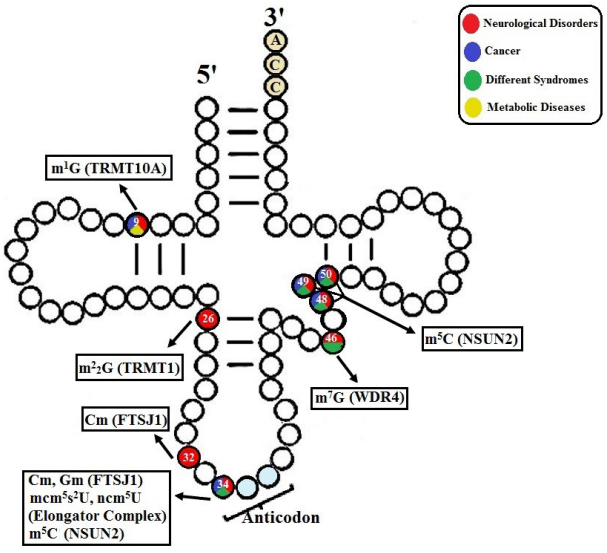

Figure 2. Schematic Representation of the Secondary Structure of tRNA and Methyltransferases Discussed in This Article. The color inside the circle shows the different phenotype identified with Trms deficiency.

In vitro methyltransferase assay has demonstrated that the mutant enzyme shows a dramatic reduction (at least 10^4-fold) in methylation activity and the inability to bind the SAM group.[36,38] It also seems that perturbations in methylation at position 9 can result in structural defects and protein instability by a deficiency in folding.[38]

Mutations in another Trms gene, *TRMT1* or tRNA methyltransferase 1, is known to be a genetic cause of autosomal recessive ID.[39,40] *TRMT1* encodes an enzyme that dimethylates a specific guanosine (m^2_2G) at position 26 and modifies it to N^2,N^2-dimethylguanosine in several tRNAs by using the AdoMet methyl group (Figure 2).[68-71] This gene is ubiquitously expressed in all human tissues and is localized in the nucleus, cytoplasm and mitochondria.[71-73] TRMT1 contributes to tRNA folding and inhibition of Watson-Crick base pair formation (base-pairing stability) in different tRNAs.[15,73,74]

Different homozygous frameshifts of *TRMT1* have been reported in three Iranian families with cognitive impairment and facial dysmorphism. All identified mutations are located in the catalytic domain of TRMT1 which is conserved during evolution.[39,40] It was predicted that these mutations resulted in the production of a truncated protein, and hence led to loss of enzyme activity, although it had previously been identified that any mutation in conserved regions of *TRMT1* can abrogate tRNA methyltransferases, proper RNA binding and stability.[40,68,75]

A recent study by Dewe and colleagues confirmed that a deficiency in m^2_2G modification reduces the proliferation rates and perturbs the translation of specific homeostatic proteins involved in the cellular oxidative stress response. They also showed that the loss of activity of TRMT1 affects the levels of reactive oxygen species (ROS), cellular response to oxidative stress that increases endogenous ROS levels, and sensitivity of cells to oxidizing products.[74] Numerous studies have shown that there is a correlation between excessive ROS levels and apoptosis.[76-81]

According to these results, and the extreme sensitivity of the brain to alterations of ROS levels, it has been proposed that homozygous mutations in the *TRMT1* gene can disrupt neural cell growth, proliferation and survival of especially neural stem cells that play a crucial role in cognitive ability. Therefore, ID can be a clinical symptom in the absence or dysfunction of TRMT1 enzyme.[33-35,74,82-84]

Mutations in another tRNA modification enzyme, FtsJ RNA Methyltransferase Homolog 1 (*FTSJ1*), homologous to the yeast methyltransferase 7 (TRM7), have been identified in families with non-syndromic X-linked ID (NSXLID).[41-44,85] FTSJ1 protein contains an AdoMet-binding domain which can methylate nucleosides at positions 32 and 34 on $tRNA^{Trp}$, $tRNA^{Leu}$ and $tRNA^{Phe}$ (Figure 2).[17,45] Some experimental data have demonstrated that FTSJ1 is highly expressed in the fetal brain, specifically in central nervous system, in comparison to adult brain and other tissues, which emphasizes the potential role of FTSJ1 in brain development and cognitive skills.[41,45] Different deleterious mutations of *FTSJ1* have been identified in families with NSXLID and young males of the Han Chinese population with cognitive disorders.[43,44]

Reduced levels of tRNA methylation, protein dysfunction and instability were observed in NSXLID families, which were caused by *FTSJ1* mutations. Notably, new findings from human cell lines obtained from NSXLID patients implicate a significant reduction in peroxywybutosine (o2yW37 is dependent on Cm32 and Gm34 modification) levels in $tRNA^{Phe}$, and disruption of 2'-O-methylation of N32 and N34 of the anticodon loop of tRNAs.[45] These results indicate that 2'-O-methylation deficiencies may cause ID. Consistently, cell growth deficiencies were observed in organisms with $tRNA^{Phe}$ insufficiency resulting from mutant *TRM7*.[45,85]

Intriguingly, overexpression of *FTSJ1* can also be deleterious, because some cases with mild or moderate ID were associated with chromosomal duplication of the region containing *FTSJ1*; however, the pathogenic pathway has not yet been demonstrated.[86,87]

Elongator Protein Complex (ELP) is another tRNA methyltransferase whose deficiency has been linked to ID. Elongator complex modifies uridine at position 34 in the anticodon of several tRNAs via SAM mechanism (Figure 2).[48,88] This complex consists of multiple subunits which are highly conserved among eukaryotes, and plays different roles including regulation of tRNA modification with SAM-binding domain, transcription elongation, microRNA (miRNA) biogenesis, and α-tubulin and histone acetylation.[48,88-90]

Different variants of elongator complex genes have been reported as the cause of neurological disorders.[20] For example, *ELP3* mutations are associated with amyotrophic lateral sclerosis (ALS). Because this gene is involved in histone and alpha tubulin acetylation, so its defects influence axonal biology and motor neuron stability.[46,47,91]

Allelic variants in *ELP1* and *ELP4* are associated with Familial dysautonomia (FD) and Rolandic epilepsy, respectively. Some experiments have shown that *ELP1* is necessary for accurate formation and function of neural cells and cell motility. Other studies have shown that *ELP4* variants can perturb brain development via interruption of elongator complex interaction with essential genes for the brain.[49,50,52,89]

ID has been reported in four families with a homozygous mutation in *ELP2*. Two of the reported families have missense mutations at the same amino acid position, albeit their origin is completely different.[39,53] Involvement of the *ELP2* gene in signal-transducing platform and histone acetyltransferase activity is linked to a neurodevelopmental disorder.[48,53]

Interestingly, all disorders that have been identified with ELP deficiency are because of failure of 5-methoxycarbonylmethyl-2-thiouridine (mcm^5s^2U) formation at position 34 of tRNAs. It has been demonstrated that this modification is essential for appropriate function of neural cells.[48,90,92,93]

In general, elongator protein complex regulates transcriptional elongation of almost all genes that are involved in neurodevelopmental processes such as axon growth, neuronal signaling and cell motility. In addition, this complex controls neurotransmitter release, synapse formation, and neural cell migration by interaction with filamin A, and is involved in vesicular trafficking and exocytosis.[48,89,94,95] These functions show the crucial role of the elongator complex in nervous system, although the mechanisms and neuropathogenic effects of ELP have not yet been clarified completely.

ID has been identified in families with mutations in Human WD repeat domain 4 (WDR4), a homolog to yeast *TRM82*.[13,55] The product of this gene is a subunit of a methyltransferase enzyme that modifies a highly conserved guanosine to 7-methylguanosine (m^7G) at position 46 of several tRNAs (Figure 2).[54,59] This gene contains two different transcripts encoded the same protein. The smaller transcript is highly expressed in some fetal tissues such as heart, kidney and brain, while the larger transcript is weakly expressed in all adult tissues. The expression pattern suggests that the smaller transcript plays a crucial role in developmental processes.[55]

WDR4 was reported as a candidate gene for Down's syndrome by Michaud and colleagues, although the exact correlation between this gene and disease was not revealed.[55] Recently, a missense mutation in *WDR4* has been linked to a distinct form of microcephalic primordial dwarfism (PD) with different neurological symptoms such as severe microcephaly, facial dysmorphism, severe encephalopathy, and seizure.[54]

Defective WDR4 impairs m^7G methylation and decreases m^7G level which can lead to tRNA degradation, reduction in specific tRNA species, and abnormal translation resulting in perturbation of protein synthesis.[14,22,54,96] A reduction in m^7G46 modification can cause severe growth deficiency or impaired protein translation. However, it has not been clarified whether decreased proliferation, accelerated apoptosis, or both, could have an effect on cell growth in patients with *WDR4* variants.[14,54]

Finally, some reports showed mutations in highly

conserved NOP2/Sun RNA methyltransferase family member 2 (*NSUN2*) gene as a causative link to autosomal recessive ID.[56,59,60] Deletion of the ortholog of *Nsun2* in flies was associated with severe short-term memory deficiency.[56]

Position 34 (wobble position) of $tRNA^{Leu}$ and also position 48–50 on several tRNAs are modified to 5-methylcytosine (m5C) by an enzyme encoded by NSUN2 gene (Figure 2). This modification is needed for proper translation, cellular stress response, cell division, spindle assembly and chromosome segregation.[35,56,97-99]

ID with additional features has been observed in some patients with *NSUN2* mutations.[56-60] In one family with three children, phenotypes were similar to Dubowitz syndrome, and in another family, only one affected male had Noonan syndrome.[57] Moreover, different clinical manifestations such as short stature, dysarthria, dysmorphic features, microcephaly, and developmental delay have been reported in other families.[56,60]

A reduction in mRNA levels due to nonsense-mediated mRNA decay (NMD) degradation has been identified in almost all allelic variants of *NSUN2*. In other cases, mutations in *NSUN2* result in aberrant localization of protein to nucleoli, aggregation in the nucleoplasm, and loss of enzyme activity.[35,60,99]

Loss of *Nsun2* function have several different effects such as impaired tRNA-protein binding, elevated cleavage of 5'tRNA fragments mediated by angiogenin, and increased cell sensitivity to oxidative agents.[35] Angiogenin catalyzes stress-induced cleavage of tRNAs to prevent translation and rescue cells in different stress conditions. Emerging evidence indicates that angiogenin acts as a preserver of neural cells during the stress response as well as playing a key role in cell proliferation and survival.[35,100-102] Aberrant accumulation of 5'tRNA fragments leads to decreased protein synthesis and elevated cell sensitivity to stress in human and mouse cells.[35,101-103] Therefore, inhibition of cytosine-5 methylation can cause neurological diseases and different phenotypes.

Conclusion

This review summarizes our current understanding of the molecular mechanism linking tRNA methyltransferases to human neurological disorders, especially ID.

Although the specific molecular mechanisms explaining how some Trms affect neurological functions remain unclear, recent discoveries indicate that Trms play a critical role in development of the nervous system and its functions. Also any perturbation in these enzymes can impact on neurodevelopmental processes and cognitive abilities.[12,13,17,19,20,30,35]

On the other hand, different experimental data have shown that neural cells are highly sensitive to defects in tRNA methyltransferases as a result of impaired protein translation and/or their regulation. Also, they have revealed that any alteration in tRNA methylation status may have an effect on several basic biological processes including apoptosis, cell growth, and cell response to stress.[17,19,35,74]

Now, we need to promote research on the maturation pathways of tRNA and their functions for a better understanding of diagnosis and prognosis of different disorders and the effect of tRNA on diseases as well as providing potential treatment strategies for rectifying hypomodified tRNAs. In this context, developments in various technologies such as tRNA sequencing, mass spectrometry-based approaches, advances in transcriptomics-proteomics approaches, and animal models will be helpful.

Finally, it will be necessary to improve our insight with regard to the potential role of other genes in tRNA function whose disruptive influence can lead to neurodevelopmental diseases by different pathways.

Authors' Contribution

All authors have been personally and actively involved in the work presented in this paper.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

The manuscript is currently being considered for publication has not been published in whole or in part in another journals.

Acknowledgements

We thank all the Genetic Research Center and Gene Translation Laboratory members for their invaluable support. This work was supported by the Iranian National Science Foundation under grant No. 92038458 and 92035782, Iran's National Elites Foundation and National Institute for Medical Research Development, grant no. 958715. Additional support was received from the Spanish Ministry of Economy and Competitiveness, grant BES2013-064551 and BIO2015-64572.

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