Short Conceptual Overview

Hari Manev* and Svetlana Dzitoyeva

Progress in mitochondrial epigenetics

Abstract: Mitochondria, intracellular organelles with their own genome, have been shown capable of interacting with epigenetic mechanisms in at least four different ways. First, epigenetic mechanisms that regulate the expression of nuclear genome influence mitochondria by modulating the expression of nuclear-encoded mitochondrial genes. Second, a cell-specific mitochondrial DNA content (copy number) and mitochondrial activity determine the methylation pattern of nuclear genes. Third, mitochondrial DNA variants influence the nuclear gene expression patterns and the nuclear DNA (ncDNA) methylation levels. Fourth and most recent line of evidence indicates that mitochondrial DNA similar to ncDNA also is subject to epigenetic modifications, particularly by the 5-methylcytosine and 5-hydroxymethylcytosine marks. The latter interaction of mitochondria with epigenetics has been termed ‘mitochondrial epigenetics’. Here we summarize recent developments in this particular area of epigenetic research. Furthermore, we propose the term ‘mitoepigenetics’ to include all four above-noted types of interactions between mitochondria and epigenetics, and we suggest a more restricted usage of the term ‘mitochondrial epigenetics’ for molecular events dealing solely with the intra-mitochondrial epigenetics and the modifications of mitochondrial genome.

Keywords: DNA hydroxymethylation; 5-hydroxymethylcytosine; DNA methylation; 5-methylcytosine; mitochondrial DNA (mtDNA).

*Corresponding author: Hari Manev, The Psychiatric Institute, Department of Psychiatry, University of Illinois at Chicago, 1601 West Taylor Street, M/C912, Chicago, IL 60612, USA, e-mail: hmanev@psych.uic.edu
Svetlana Dzitoyeva: The Psychiatric Institute, Department of Psychiatry, University of Illinois at Chicago, 1601 West Taylor Street, M/C912, Chicago, IL 60612, USA

Introduction

It has been about a year since we first reviewed the emerging research on mitochondrial epigenetics (1). Although many publications in the field of DNA methylation still keep perpetuating the statement ‘the mammalian mitochondrial DNA (mtDNA) is not methylated’, evidence for the presence of both 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) in mammalian mtDNA continues to accumulate.

Epigenetic mechanisms that shape the expression of the mammalian genome encompass various modifications of nuclear DNA (ncDNA) and its associated proteins (e.g., histones), as well as a family of noncoding RNA transcripts. Within the mitochondrion, which according to the current knowledge does not contain histones, the circular mtDNA (typically present in multiple copies within a single mitochondrion) appears to be susceptible to 5mC and 5hmC modifications but not to a direct action of other epigenetic mechanisms operative in chromatin remodeling (1).

The first inference to the possibility that 5mC may be present in mammalian ncDNA was made in 1948 [for a review, see (2)]. In 1971, it was found that animal (i.e., loach embryo) mitochondria contain DNA methyltransferase (DNMT) activity necessary for the formation of 5mC, and it was proposed that not only ncDNA but also mtDNA may contain 5mC (3). In 1973, two independent studies were submitted for publication [(4) in April and (5) in October; the latter was delayed due to a technical fault] that documented the presence of 5mC in mammalian mtDNA. In addition to demonstrating the presence of 5mC in mtDNA, these and other early studies (6, 7) reported additional evidence for the association of DNMT activity with mammalian mitochondria. It was suggested that mitochondrial DNMT may differ from nuclear DNMT. For example, mitochondrial DNMT was more sensitive to inhibition by mercaptoethanol (4); mitochondrial and nuclear DNMTs exhibited differential pH dependence (6); and it was suggested that they recognize different DNA sequences (6, 7). Thus, since the mid-1970s, it has been known that mammalian mitochondria are capable of methylating their own genome. Nevertheless, this knowledge had been generally neglected except for the occasional confirmatory publications (8–10) (Figure 1).

The recent resurrection of interest in mammalian mtDNA methylation can be traced to the 2011 discovery...
of a mitochondrial isoform of nuclear-encoded DNMT1 (mtDNMT1) and the confirmation of its role in the synthesis of 5mC in mtDNA (11). Interestingly, these authors also found evidence of a significant amount of 5hmC in mammalian mtDNA. Hence, it appears that the history of reluctant acceptance of the evidence for mammalian DNA methylation is repeating itself in the case of DNA hydroxymethylation (Figure 1). Namely, the presence of 5hmC in mammalian ncDNA was discovered as early as 1972 (12). Hence, it was shown that among different tissues, 5hmC is particularly abundant in the DNA samples extracted from mouse brain. However, this finding was generally neglected until it was rediscovered in 2009 (13). Again, the mouse brain was found to be a good source of hydroxymethylated DNA. The putative physiological origin of 5hmC in mammalian DNA was further emphasized by the finding of an enzymatic pathway, the ten-eleven translocation (TET) family of enzymes, responsible for the oxidation of 5mC to generate 5hmC (14). Subsequent to the recent discovery of 5hmC in mtDNA extracted from cell cultures (11), 5hmC was found in mouse brain mitochondria along with the evidence for the association of TET immunoreactivity with the mitochondrial fraction (15). In addition, it was observed that, in mouse DNA, the 5hmC site density was significantly greater in mtDNA compared with ncDNA (16).

Hence, in a relatively short period since the publications by Shock et al. (11), the renewed interest in mtDNA methylation and hydroxymethylation has given impetus to studies aimed at elucidating the physiological and possibly pathological roles for mitochondrial epigenetics and at characterizing possible differences between nuclear and mitochondrial epigenomes.

**Why the term ‘mitochondrial epigenetics’?**

The bidirectional type of interactions between mitochondria and nuclei has been long recognized. Regarding epigenetics, the standard view has been that only nuclear epigenetic mechanisms (i.e., ncDNA methylation and hydroxymethylation, histone modifications, and nuclear noncoding RNAs) are at play in these interactions (17). There are at least three types of mitochondrial interaction with these nuclear epigenetic mechanisms (Figure 2).

First, epigenetic mechanisms that regulate the expression of nuclear genome also influence mitochondria by modulating the expression of nuclear-encoded mitochondrial genes. Namely, mammalian mtDNA encodes only 13 proteins (all members of the oxidative phosphorylation complexes), 2 ribosomal RNAs (rRNAs), and 22 transfer RNAs (tRNAs). All other proteins (perhaps thousands) necessary for mitochondrial structure and function are encoded by nuclear mitochondrial genes (18). These mitochondrial genes are susceptible to epigenetic regulation. A recent example of such epigenetics-mitochondria interaction is the nuclear-encoded DNA polymerase γA. This mitochondrial enzyme, which regulates mitochondrial genome by influencing the mtDNA copy number, is regulated by ncDNA methylation within its exon 2 (19). This exemplifies how, in mammalian cells, mitochondrial genome can be regulated by nuclear epigenetics. Another
example involves the nuclear noncoding small RNAs. It appears that mitochondria are one of the destinations of micro-RNAs (miRNAs; involved in gene silencing) (20). It has been suggested that these nuclear encoded miRNAs may epigenetically regulate both ncDNA- and mtDNA-encoded genes.

Second, a cell-specific mtDNA copy number and mitochondrial activity are capable of determining the methylation pattern of nuclear genes. For example, the removal of mtDNA from cells in culture causes dramatic alterations in ncDNA methylation (both hypomethylation and hypermethylation). These epigenetic changes in ncDNA are reversible, as they can be corrected by the reintroduction of mtDNA (21). A possible mechanism involved in this interaction between mitochondria and nuclear epigenetics appears to involve the mtDNA copy number-dependent expression of DNMT1 (22), an enzyme crucial for DNA methylation.

Third, mtDNA haplotypes modulate the pattern of nuclear gene expression and the levels of global ncDNA methylation. This is just one example of important functional consequences of the mitochondrial genome polymorphisms. Hence, it was shown that in the European population, in which mtDNA has nine different haplotypes (i.e., H, J, U, X, T, I, K, W, and V), subjects carrying the J haplogroup had higher global DNA methylation levels than the non-J carriers (23). Furthermore, in vitro experiments have confirmed the ability of various mtDNA haplotypes to alter nuclear gene expression and ncDNA methylation (24).

In addition to the above three examples of mitochondrial interactions with nuclear epigenetics, a fourth and most recent line of evidence indicates that mtDNA similar to ncDNA is also subject to direct intra-mitochondrial epigenetic modifications (1).

Until recently, no consideration was given to these intra-mitochondrial epigenetic mechanisms. Instead, mitochondrial epigenetics has been generally assumed to encompass the epigenetic regulation of nuclear-encoded mitochondrial genes and, as discussed above, the mitochondrial impact on nuclear epigenetics. To emphasize the complexity of the mitochondria-epigenetics interactions, we propose the term ‘mitoepigenetics’ to include all four above-noted types of interactions between mitochondria and epigenetics (both the intra-nuclear and the intra-mitochondrial epigenetics) (Figure 2). Furthermore, we suggest a more restricted usage for the terms mitochondrial epigenetics and mitochondrial epigenomics, i.e., solely in reference to molecular events dealing with epigenetics within the mitochondrion and involving the mitochondrial genome.

Currently, mitochondrial epigenetics focuses on mtDNA methylation and hydroxymethylation. In the nucleus, epigenetic mechanisms involve both ncDNA and nuclear proteins, i.e., chromatin remodeling – mostly via modifications of histone proteins. The present view is that mitochondria do not contain histones and may not be susceptible to epigenetic machinery involved in chromatin remodeling. Nevertheless, several histone family members have recently been identified within mitochondria (25). In addition, mtDNA is protein-coated and packaged into aggregates called nucleoids or mitochromosome. Hence, it is possible that epigenetic mechanisms would emerge that are operative in these structures, i.e., in nucleoid remodeling (1). Finally, although the epigenetic research on noncoding RNAs focuses almost exclusively on nuclear encoded RNAs, it appears that mitochondrial genome may be involved in this type of regulation by generating the mitochondrial long (26) and small (27) noncoding RNAs. For example, in experiments with mice trained to execute a nose-poke in a port containing various test odors in order to obtain a reward, it was found that two hippocampal mitochondrial RNAs (tRNA and Mt-1) gave rise to small RNAs (25–30 nucleotides) that showed a dramatic and specific increase with training (28).

mtDNA methylation

Early reports about the extent of mtDNA methylation disagreed on the exact percentage of the 5mC content in mtDNA vs. ncDNA (4–6). Subsequent studies (10, 11) concluded that, in mtDNA, 5mC occurred predominantly at the dinucleotide sequence CpG. Compared with ncDNA, mtDNA has fewer CpG dinucleotides (mouse, 287 CpGs in 16,299 nucleotides; human, 432 CpGs in 16,569 nucleotides; Cambridge Reference Sequence) and also lacks the typical CpG islands, which in ncDNA are considered to be the primary targets for 5mC-mediated gene regulation. It appears that the epigenetic mechanism of mtDNA methylation (a process of DNMT-mediated transfer of a methyl group from S-adenosyl-L-methionine to cytosine) depends on an isoform of DNMT1, the mtDNMT1, which binds to the mtDNA in a manner proportional to the density of CpG dinucleotides. This mtDNMT1 is the only known DNMT shown to possess a mitochondrial targeting sequence, which is presumably responsible for the mitochondrial import of this nuclear-encoded enzyme (11). Nevertheless, another DNMT, DNMT3A also was found in mitochondria, particularly under the pathological neurodegenerative conditions (29). Furthermore, a recent pilot
study suggested that mitochondria may contain DNMT3B as well (30). It is possible that all three enzymes play a role in determining the mtDNA 5mC levels. On the one hand, mtDNMT1 and DNMT3A/DNMT3B may catalyze the synthesis of 5mC from cytosine. On the other hand, DNMT3A and DNMT3B may have an additional role in regulating the levels and the location of cytosines available for methylation. Namely, the mammalian DNMT3A and DNMT3B, but not DNMT1, were shown to be a redox-dependent DNA dehydroxymethylases capable of converting 5hmC to cytosine (31). The possibility of a direct action of DNMT3A/DNMT3B on 5hmC is of interest with respect to the recently reported high abundance and a wide distribution of 5hmC in mtDNA (16).

It was proposed that the regulation of mtDNMT1 expression at the nuclear level, e.g., via the oxidative stress-susceptible transcription factors NRF1 and PGC1α and by the tumor suppressor p53, may be a mechanism for mitochondria to influence and epigenetically modify their own genome (11). If various signaling pathways that differentially regulate the expression of mtDNMT1 and the expression of other DNMT1 transcripts exist, DNA methylation would emerge as a critical mechanism for asynchronous regulation of nuclear and mitochondrial epigenomes.

The possible functional implications of mtDNA methylation have been discussed by Shock et al. (11). They include an altered mtDNMT1 expression followed by changes in mtDNA methylation, and ultimately, by alterations in the levels of mtDNA-encoded RNAs. Specifically, it was noted that altered mtDNMT1 expression asymmetrically affects the expression of transcripts from the heavy and light strands of mtDNA. Hence, mtDNMT1 overexpression was associated with increased transcription of NADH dehydrogenase subunit 1 from the heavy mtDNA strand (which has two promoters), whereas the levels of NADH dehydrogenase subunit 6 (ND6) mRNA (on the light strand) were decreased. A possible explanation for these differences is that cytosine methylation in mtDNA is capable of both repressing gene expression by mechanisms similar to the 5mC-mediated promoter suppression in ncDNA and increasing gene expression by an alternative mechanism. The latter could involve the mtDNMT1-mediated modifications of CpG dinucleotides and/or the interactions of mtDNMT1 protein with other putative regulatory proteins (11). For example, recent findings demonstrated that the transcription from the second heavy-strand promoter is regulated (repressed) by mitochondrial transcription factor A (TFAM), and it was hypothesized that epigenetic marks on mtDNA could influence the sites to which TFAM binds and the ensuing transcriptional response (32).

**mtDNA hydroxymethylation**

The initial identification of 5hmC in mtDNA (11) has been confirmed in several subsequent studies (15, 16, 33) and preliminary reports (30). Recently, a new method was developed for a high-resolution mapping of genomic 5hmC (16). The method is based on a DNA-modification-dependent restriction endonuclease AβISI coupled with sequencing (Aba-seq). Using Aba-seq and bioinformatics to analyze the results obtained from mouse mtDNA, these authors found the highest 5hmC site density in the mitochondrial genome in both CG and CH (H=A/C/T) context. In other words, in mtDNA, normalized CH 5hmC site density was as high as the normalized CG 5hmC site density (in ncDNA, the CH 5hmC site density was <1% of the CG 5hmC site density) (16). These results not only point to a new methodology for studying mitochondrial epigenetics but also suggest the existence of physiological mechanisms responsible for significant differences between mtDNA and ncDNA epigenomes.

In addition to mtDNMT1, whose presence within the mitochondria has been unequivocally demonstrated (11), a number of other proteins involved in epigenetic process have been reportedly found in mitochondrial fractions, e.g., DNMT3A (29), DNMT3B (30), histones (25), and also TET enzymes (15, 30, 33). Hence, it is possible that 5hmC found in mtDNA is a result of enzymatic (e.g., TET-mediated) hydroxymethylation. It is worth mentioning that before the discovery of TET-mediated 5hmC formation in the mammalian genome, the early findings of 5hmC in mammalian ncDNA (e.g., in the brain) (12) were assumed to be the result of oxidative DNA damage (34). Thus, it was shown that oxidative damage in both ncDNA and mtDNA may account for the majority of oxidized bases such as 5-hydroxycytosine (5hmC was not measured in these studies) (35, 36). Along these lines, it was reported that 5hmC can be produced experimentally by an action of free radicals on 5mC (37). However, this occurred in artificial conditions, and a similar effect has not been demonstrated in a biological system. Alternatively, it was suggested (11) that mtDNA hydroxymethylation may occur through a covalent addition of 5-hydroxymethyl group directly to DNA cytosine residues by mtDNMT1 (38) using formaldehyde generated from mitochondrial mixed-function oxidases. Furthermore, if, as suggested (29, 30), mitochondria contain DNMT3A and DNMT3B, these enzymes could contribute to the pattern of mtDNA hydroxymethylation via their 5hmC dehydroxymethylase activity (31). This activity would impact on the content and distribution of 5hmC in mtDNA by converting 5hmC to cytosine (Figure 3). Current advances in methodologies...
for proteomic mapping of mitochondria in living cells (39) could be used to further elucidate the machinery involved in mitochondrial epigenetics including the enzymatic formation of mitochondrial 5hmC.

Compared with 5mC, the functional significance of 5hmC modifications in ncDNA is less understood. Thus, no clear inferences can be made about the functional consequences of mtDNA hydroxymethylation yet. Considering the abundance and the peculiar distribution of 5hmC in mtDNA, it would appear unlikely that in mitochondria this epigenetic mark is only a transient intermediate of mtDNA demethylation (40, 41).

**Physiological and pathological modifications of mitochondrial epigenetics**

Aging was among the first physiological processes implicated in mitochondrial epigenetics. As early as the 1980s, it was shown that aging plays a role in modifying the methylation status of mitochondrial genome (9). In these experiments, human fibroblasts were collected from young (11–36 years) and old (67–76 years) subjects. Cells were grown *in vitro*. At late passages, their mtDNA methylation decreased but only in fibroblasts from young subjects. More recently, mtDNA methylation and hydroxymethylation were analyzed in different brain regions of young (4 months) and old (24 months) mice (15). The mtDNA content of 5hmC, rather than the content of 5mC, was significantly altered during aging. The direction of these changes, i.e., decrease or increase, was brain region specific. Also altered during aging was the brain expression of mtDNMT1 mRNA and TET mRNAs and proteins. Several preliminary reports confirmed the aging-associated alterations in human mtDNA methylation (42) and possibly hydroxymethylation (30, 43). It appears that, in human blood mtDNA, the methylation status of mitochondrial 12S rRNA gene decreased during aging. Collectively, these findings show evidence for the presence and susceptibility to aging of mammalian mitochondrial epigenetic mechanisms. It is plausible that future research will uncover functional and modifiable associations between the aging-altered mitochondrial epigenetics and aging-associated pathologies.

A particularly dynamic DNA methylation has been observed throughout mammalian gametogenesis. In addition, it was noted that mtDNA is typically unmethylated in blastocysts and embryonic stem cells but is partially methylated in germ cells (44). In oocytes, mtDNA methylation appears to require the presence of a DNMT family member protein called DNMT3L. Hence, mtDNA was hypomethylated in the oocytes lacking this protein (44). Compared with oocytes, the sperm mitochondrial genome appears to exist in a heavily methylated state (45).

In humans, mtDNA methylation in the D-loop, ND6, and cytochrome C oxidase (COⅠ) regions was studied in the liver biopsy samples (46). In these subjects, the methylated/unmethylated ratio of ND6 region of mtDNA inversely correlated with the subjects’ level of physical activity. Furthermore, methylation of ND6 was higher in the liver of subjects with nonalcoholic steatohepatitis compared with subjects with simple steatosis. In addition, the ND6 transcription and ND6 protein levels were decreased in samples with increased ND6 mtDNA methylation. These authors concluded that epigenetic changes of mtDNA are potentially reversible by interventional programs, as shown by the effects of physical activity on ND6 methylation (46).

The pathologies most frequently associated with epigenetic mechanisms and susceptible to epigenetic pharmacology are the cancers. The methylation status of the mtDNA D-loop was investigated and correlated with the expression of mitochondrial NADH dehydrogenase subunit 2 (ND2) gene in the tumor and the corresponding noncancerous tissues surgically resected from colorectal cancer patients (47). These authors found that the mtDNA D-loop of most noncancerous tissues was significantly more methylated than the D-loop in corresponding tumor tissues. Moreover, they suggested that demethylation of the D-loop plays a role in increasing ND2 expression, which in turn may be involved in the initiation and/or progression of colorectal cancer. Recently, the methylation
status of mitochondrial genome was characterized in a clinical study aimed at examining the association of epigenetic changes with the occurrence of cervix precancer and cancer in women (48). Although this study, in which three small regions of mtDNA containing CpG sites were analyzed for their 5mC status, concluded that methylation at CpG sites is low in mtDNA, it nevertheless shows differences in relation to disease state.

Whether only the enzymatic, e.g., mtDNMT1-mediated, mtDNA methylation or also the free radical-mediated cytosine C-5 methylation (49) are involved in epigenetic pathobiology of carcinogenesis remains to be explored.

In the pathologies of the central nervous system, alterations of mtDNA methylation have been linked to the pathobiology of amyotrophic lateral sclerosis (ALS) (29). In this work, the ALS-associated motor neuron cell death was linked to increased DNA methylation; experimental neuroprotection was achieved with a DNMT inhibitor RG108. These authors observed the motor neuron pathology-associated increase in 5mC levels both in ncDNA and mtDNA, and they also documented the pathology-associated increase of DNMT3A (and to a lesser extent DNMT1) immunoreactivity in the mitochondria. Another study utilized samples (immortalized lymphoblastoid cells) obtained from subjects with Down syndrome (autosomal trisomy associated with neurodevelopmental impairment) and suggested a possible involvement of mitochondrial epigenetics (50). These authors found the hypomethylation of mtDNA in Down syndrome patients compared with the corresponding age-matched controls.

The above-reviewed data on mammalian mitochondrial epigenetics including in humans indicate that the mitochondrial genome may participate in physiological and pathological processes beyond the typically considered mtDNA mutations and haplotypes. Some aspects of the research strategies previously used in studies of mtDNA mutations would need to be considered in mitochondrial epigenetics.

For example, heteroplasmy of mtDNA (the presence of more than one type of mitochondrial genome, e.g., with and without mutations, within a cell or organism) may play a role in making certain mtDNA variants differentially susceptible to epigenetic modifications. Furthermore, it is unclear whether heteroplasmy exists with respect to the actual mtDNA epigenetic modifications. Another important issue is a possible tissue- and cell-specific type of mitochondrial epigenetics. For example, even within the same tissue/organ (e.g., the brain), significant epigenetic differences were found between different cell types, e.g., neurons and glia (51). It has been proposed that, with respect to CpG vs. non CpG 5hmC content, the epigenetic modifications of mtDNA differ significantly from the modifications in ncDNA (16). Development of better methodologies for the characterization of mtDNA methylome and hydroxymethylome at single-nucleotide resolution would help us to elucidate the putative functional implications of such peculiar mitochondrial epigenetics. Finally, considering the high abundance of free radicals within mitochondria, it remains to be evaluated whether in this organelle the free radical-mediated 5mC and 5hmC formation (37, 49) plays any role in addition to the proposed enzymatic pathways for mtDNA methylation and hydroxymethylation.

Mitochondrial epigenome as a biomarker and a putative therapeutic target

The mitochondrial genome has been used in studies of molecular evolution and, based on mtDNA mutations, as a biomarker. From the above literature review, it appears that the epigenetic modifications of mtDNA occur in a dynamic fashion and possibly are reversible. Furthermore, they are susceptible to pharmacological modulations. For example, treatment of cells in vitro with an antiepileptic drug, valproic acid, significantly altered their mtDNA 5hmC content (33). Hence, it is likely that with future advancements in research on mitochondrial epigenetics, the mitochondrial epigenome would emerge as a useful biomarker and a putative therapeutic target.

A recent preliminary study (52) used samples from human subjects exposed to various airborne pollutants and measured the methylation levels in the D-loop and 12S rRNA regions of mtDNA as a biomarker. Exposure to metal-rich particulate matter (samples obtained from steel workers) was found to lead to increased mtDNA methylation in the 12S rRNA but not the D-loop region. In another preliminary study, mtDNA methylation was investigated as a possible biomarker in the placenta (53). It appeared that a particular pattern of CpG hypermethylation was found in mtDNA from the intrauterine growth-restricted placentas.

Based on the findings of pharmacologically altered mitochondrial epigenetics (33), it was proposed that the monitoring of mitochondrial epigenome could be used to evaluate the side effects and the therapeutic effects of psychiatric drugs (54). Meanwhile, the above-noted efficacy of a DNMT inhibitor, RG108, to reverse the pathological effects associated with elevated ncDNA and mtDNA methylation (29) demonstrated the feasibility of
References

Hari Manev graduated from the Zagreb Medical School in Croatia (MD and PhD), and completed his postdoctoral studies in neuroscience and neuropharmacology at Georgetown University in Washington, DC. He is currently a tenured Professor of Pharmacology in Psychiatry at the University of Illinois at Chicago. His previous appointments include research institutes (Institute Ruđer Bošković, Zagreb, Croatia; FIDIA-Georgetown Institute for the Neurosciences, Washington, DC; and the Allegheny-Singer Research Institute, Pittsburgh, PA), he has worked in the pharmaceutical industry (FIDIA SpA, Abano Terme, Italy), and in academia (Georgetown University, Washington, DC, and the Medical College of Pennsylvania and Hahnemann University – later named Allegheny University of the Health Sciences, Pittsburgh, PA). His research interests include brain aging, neurotoxicity and neuroprotection, circadian mechanisms, mechanisms of action of psychiatric treatments and addiction, and epigenetic mechanisms in the central nervous system.

Svetlana Dzitoeva (Dzitoyeva) graduated from North Ossetian State University (MS) and the Koltsov Institute for Developmental Biology, Russian Academy of Sciences, Moscow, Russia (PhD). She completed postdoctoral studies in molecular biology at the University of Illinois at Chicago (UIC), Chicago, IL. Currently, she is a Senior Research Specialist in Health Sciences in The Psychiatric Institute (UIC). In recent years, she has developed Drosophila models and techniques for neuropharmacological studies. Her current research interest includes epigenetic mechanisms in mammalian brain and mechanisms of action of neuropharmacological treatments.