The 18 kDa translocator protein, non-coding RNA, and homeostasis

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Abstract: Against the challenges and perturbations in their environment and physiology, biological systems are characterized by active maintenance of their homeostasis. The 18 kDa mitochondrial translocator proteins (TSPO) as well as non-coding RNAs (ncRNAs) play roles in homeostatic functions. The molecular responses to maintain health and counteract diseases, including insulting conditions such as injury and pathogen infection, involve coordinated modulation of gene expression programs. Studies have shown that TSPO knockdown and its ligands can regulate expression of numerous genes for proteins as well as ncRNAs. ncRNAs function directly as structural, catalytic, or regulatory molecules and thereby present a complexity as diverse as proteins and their various functions. This includes a diverse and interrelated range of regulatory and functional roles in transcriptional, post transcriptional, epigenetic, and nuclear processes. In this review, we give an overview of the diverse and potential interactions of ncRNAs and TSPO that may contribute to homeostasis of the organism. In this context, TSPO upregulation has been connected to several diseases, including cancer, neuronal damage, neurodegeneration, and inflammation. Moreover, TSPO ligands can serve to counteract such diseases. The same is true for ncRNAs, as targets as well curative agents. It is tempting to suggest that interactions between TSPO and ncRNAs may contribute to homeostasis of the organism.

Keywords: 18 kDa mitochondrial translocator protein (TSPO); gene expression modulation; non-coding RNA (ncRNA); homeostasis

18 kDa mitochondrial translocator protein (TSPO)

In previous studies we found that the 18 kDa mitochondrial TSPO may be at least partly involved in regulation of gene expression of non-coding RNAs (ncRNAs) (1,2). Importantly, modulation of gene expression is not a secondary effect of TSPO activation, but one of its primary functions (3). TSPO is a receptor molecule able to regulate various cellular and organismal functions, in order to maintain health and counteract diseases (4-7). These are functions that can be considered part of the overall homeostatic function of TSPO (4,8). Homeostasis, in this context, stands for any biological system's activities to maintain a dynamic equilibrium for health and survival (9).

A previous common name for TSPO was peripheral

benzodiazepine receptor (PBR), based on its capability to bind benzodiazepines in peripheral tissues (10). Classical TSPO ligands are the benzodiazepine Ro5-4864 (4'-chlorodiazepam) and the isoquinoline carboxamide derivative PK 11195 (11). The primary intracellular location of TSPO typically is the outer mitochondrial membrane (12,13). Numerous reports have demonstrated that TSPO serves various essential functions, including modulation of cell growth and proliferation, ATP production, regulation of the mitochondrial membrane potential (ΔΨm), heme synthesis, mitochondrial cholesterol import associated with steroid synthesis, adaptation to oxidative stress, generation of reactive oxygen species (ROS), modulation of gene expression, and initiation of programmed cell death. The regulatory role of the TSPO in programmed cell death as initiated by ΔΨm collapse is thought to present one mechanism whereby TSPO is involved in cancer and neurodegeneration (14). On occasion, apart from the mitochondria, TSPO can also be found in association with other cell organelles such as the cell nucleus and even the outer cell membrane (4,15,16). The association of the TSPO with the mitochondria-to-cell nucleus signaling pathway is thought to take part in regulation of cell nuclear gene expression (1-3). TSPO knockdown with siRNA as well as application of TSPO ligands indicated that TSPO is important for regulation of gene expression (1-3). In addition, pathway analysis suggested that this gene expression regulation serves various functions including programmed cell death, inflammation, immune response, cell migration, adhesion, cell differentiation, neurite outgrowth, proliferation, tumorigenesis, cell cycle, etc. (3). It can be suggested that modulation of cell nuclear gene expression and regulation of initiation of the mitochondrial apoptosis cascade can be considered main functions of TSPO and its ligands (3,17). This information gave further insights how TSPO could perform its homeostatic functions. In this context, TSPO upregulation has been connected to several diseases, including cancer, neuronal damage, neurodegeneration, and inflammation (16,18,19). Moreover, TSPO ligands can serve to counteract such diseases (7,20).

Generation of transgenic mice with TSPO knockout also suggested homeostatic functions of TSPO (21). For example, two distinct types of TSPO knockout mice to induce gonadal and steroidogenic cell-specific TSPO deletion indicated a role for TSPO in cellular cholesterol and lipid homeostasis (22). TSPO expression also appears to be essential for healthy adipocyte functions. In particular,

activation of TSPO in adipocytes improves regulation of glucose homeostasis (23). While discussed for mammals, the role of TSPO in homeostasis is well recognized in prokaryotes. In this context it should be noted that TSPO is a protein whose typical trans-membrane helix structure as well as functions have been remarkable preserved along the evolutionary record from Archaea and Bacteria to Eukaryotes (24,25). Studies on prokaryotes suggest that TSPO might be involved in iron homeostasis, synthesis of steroids that regulate membrane fluidity due to its localization, as well as to drive responses to stressors (26). Interestingly, a direct role of TSPO in expression of ncRNAs has been suggested (1,2) (*Figure 1*). In particular, TSPO appeared to be involved in modulation of nuclear gene expression including small nucleolar (sno) RNAs. Of the 610 genes affected by 24 hours of the TSPO classical ligand PK 11195 exposure, 6 were for small nucleolar RNAs. Of the 359 genes affected by 48 hours of PK 11195 exposure, 12 were for small nucleolar RNAs. Of the 1,249 genes affected by stable TSPO knockdown 65 were for small nucleolar RNAs (1,2).

ncRNAs

ncRNAs are more and more considered as participants in maintaining homeostasis of the host (27,28). While ncRNAs are not translated to proteins, they can modulate protein synthesis in the cell via various post transcriptional modulations, for example, translational repression. The number of ncRNAs within the human genome is known to be higher than RNA coding for proteins. Important functional ncRNAs include: small RNA such as microRNA (miRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), short interfering RNA (siRNA), PIWI-interacting RNA (piRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), extracellular RNA (exRNA), small Cajal body-specific RNA (scaRNA), and long ncRNA (lncRNA). Functions of all of these ncRNAs are summarized briefly below.

miRNAs, which are the most examined members of this family of snRNAs, are small non coding molecules synthesized from the double stranded region of hairpin RNA (29). They are associated with regulation of gene expression via mRNAs translation interference by activating the RNA induced silencing complex (RISC) (30). It has been proven that changes in the level of expression of different types of miRNAs influence the expression of genes responsible for a number of disorders and diseases, including cancer, non-alcoholic fatty liver disease (NAFLD),

Small nucleolar RNA gene expression changes in U11MG glioblastoma cells

After 24 hours of PK 11195 exposure	After 48 hours of PK 11195 exposure	After TSPO knockdown			
SNORD30	SNORD30	SNORD49B	SNORD42A	SNORA75	SNORA62
SNORA20	SNORA20	SNORD30	SNORD14C	SNORA4	SNORD76
SNORA43	LOC85391	SNORD25	SNORD43	SNORD14E	SNORD116-20
SNORD22	SNORD49A	SNORD49A	SNORD75	SNORD4B	SNORD109A
SNORD28	NUSAP1	SNORD27	SNORD47	SNORA27	RNU105B
NOC3L	SNORD49B	SNORD77	SNORD74	NOL11	SNORD116-14
SNORA73A	SNORD28	SNORD12C	SNORD79	NOP2	SNORD13
	SNORD4A	SNORD80	SNORD82	SNORD28	SNORD116-15
	LOC85389	SNORD78	SNORD20	SNORA3	SNORD116-8
	SNORA51	SNORD4A	SNORA44	SNORD29	SNORD116-1
	SNORD52	SNORA61	SNHG12	NOC3L	SNORA22
	SNORA73A	SNORD44	SNORD15A	SNORA1	SNORD116-3
		SNORD31	SNORD1B	SNORD1C	SNORD116-5
		SNORA74A	NOL9	SNORD102	SNORD116-24
		SNORA16A	NOLC1	SNORD6	
		SNORD26	SNORD42B	SNORD45B	
		SNORD22	SNORD83A	SNORD45C	

Summary:
Of the 610 genes affected by 24 hours of PK 11195 exposure 6 were for small nucleolar RNAs (2)
Of the 359 genes affected by 48 hours of PK 11195 exposure 12 were for small nucleolar RNAs (2)
Of the 1,249 genes affected by stable TSPO knockdown 65 were for small nucleolar RNAs (1)

Figure 1 Gene expression of snoRNA changed by TSPO ligand PK 11195 and TSPO knockdown.

cardiovascular disease, etc. (31-33).

As TSPO, specific miRNAs appear to play important roles in neurodegenerative diseases and brain injury. Microarray analyses have demonstrated that during mammalian brain development the expression levels of many miRNAs are dynamically controlled, suggesting a role in regulating brain structure and function (34). These same miRNAs can be differentially expressed in the brains of people suffering from CNS-related disorders. For example, various studies have shown significantly increases of miR-9 and miR-128, and a decrease of miR-107 in brains of Alzheimer Disease (AD) patients (35,36). In another study it was found that 15 miRNAs were dysregulated in sporadic AD, in particular increases of miR-197 and miR-511; and decreases of: miR-7i, miR-9, miR-15a, miR-19b, miR-22, miR-26b, miR-29b-1, miR-93, miR-101, miR-106b, miR-181c, miR-210, and miR-363 were found (37). Furthermore, already early in the pathogenesis of AD, miRNA levels can be altered, suggesting that miRNAs take part in the development of the disease (38). Regarding Huntington Disease (HD), miRNAs were found to be differentially expressed in post-mortem HD brains, for example decreases of miR-9 mir-29a, mir-124a,

mir-132, and mir-135b expression (39-41). Previous studies have shown that regulation of several miRNAs, including miR-9, miR-29a, and miR132/212, may be directly controlled through proximal binding sites for the REST protein (RE1-silencing transcription factor), potentially presenting a factor for aberrant transcriptional and post-transcriptional control in HD patients (39-42). Regarding Parkinson Disease (PD), from a panel of 224 miRNAs precursors from samples of midbrain, cerebellum, and cerebral cortex samples of PD patients and normal controls, 8 appeared to be enriched in midbrain relative to cerebral cortex or cerebellum, as determined with rtPCR (42). Expression of one of these eight precursor miRNAs, miR-133b was specifically deficient in the context of PD patient samples (42). Numerous studies have shown that brain injury affects expression of coding and ncRNAs, for example, the chronic condition of traumatic brain injury (TBI) can be accompanied by changes in gene expression of over 7,000 genes (involved in metabolism, receptor-mediated cell signaling, neuronal plasticity, immune cell recruitment, immune cell infiltration, and neurodegenerative disease) in the areas of secondary brain injury surrounding the primary injury (43). It can be

suggested that miRNAs can be used as biomarkers for these various conditions and diseases.

Regarding the well-known tRNAs and rRNAs, apart from their canonical translational functions, tRNAs can also regulate gene expression (44). Furthermore, amino-acylated tRNAs have been implicated as substrates for non-ribosomal peptide bond formation, post-translational protein labeling, modification of phospholipids in the cell membrane, and antibiotic biosynthesis. tRNA fragments (tRFs) have been recognized to play regulatory roles in translation and gene expression (45,46). Thus far, rRNA is only known as the RNA component of the ribosome (47).

siRNAs are small duplexes that consist of 19–23 paired nucleotides synthesized from double stranded DNA precursors (48,49). These molecules provide similar interference mechanism for silencing a specific gene via RISC as miRNAs. It is reported that siRNAs silencing effect is accomplished via the cooperation with members of the conserved Argonaute (AGO) protein family which enable targeting of complementary RNAs for degradation, translational repression, and transcriptional sequencing (50,51). siRNAs may be used for gene therapy (52).

Compared to miRNAs and siRNAs, piRNAs are somewhat longer molecules consisting of 24–31 nucleotides. They are derived from single stranded precursors (53). The function of piRNAs is enabled via cooperation with specific proteins known as PIWI, for example as expressed in gonads that produce RISCs with a number of RNAs (54). It has been shown that this interaction between PIWI proteins and piRNAs plays a key role in silencing transposable elements (TEs), whose mobility otherwise threatens genome integrity (55).

snRNAs are present in the nucleoplasm and the nucleolus of eukaryote cells. Research by Will and Luhrmann (56) has indicated that snRNAs are involved in the process of splicing of mRNA as elements of the spliceosome making them key players in removing introns and mRNA maturation (56).

As mentioned, we have found in two separate studies that apart from protein coding genes, expression of numerous genes for snoRNAs are affected by TSPO knockdown, and also by the TSPO ligand PK 11195 (1,2). These snoRNA distilled from more than thousand genes affected by TSPO and its ligands are compiled in *Figure 1*.

snoRNAs derive their name from their location in the nucleolus. snoRNAs primarily guide chemical modifications of other RNAs, mainly ribosomal RNAs, transfer RNAs and small nuclear RNAs (57,58). These post-transcriptional modifications are important for the production of efficient and accurate ribosomes (59). However, snoRNAs can also participate in modifications of snRNAs that mediate mRNA splicing (60). Similar to the splicing snRNAs, snoRNAs are complexed with specific proteins and exist as discrete ribonucleoprotein particles (snoRNPs) (61,62). ScaRNAs are snoRNAs that are localized in Cajal Bodies (CB) which guide the 2-O methylation and pseudouridylation of several snRNAs (63,64). ScaRNAs level of expression is crucial for regular mRNA splicing. Furthermore, snoRNA transcripts serve as the precursors of miRNA-like small RNAs and as regulators of alternative splicing (65,66).

In vitro studies showed that snoRNAs can act either as oncogenes or as tumor suppressors (67). Apart from cancer, snoRNAs may also play a role in neurodegeneration. For example, Snord 3A, a molecular marker and modulator of prion disease progression, was found to be elevated several times in Creutzfeldt Jacobson Disease patients as well as in animal models for the disease (68). Interestingly, SNORDA3 was also found to be affected by TSPO knockdown (*Figure 1*).

Thus, snoRNAs can participate at several stages of protein formation, including: (I) folding of pre-rRNA as RNA chaperones; (II) protein folding; (III) formation of rRNP substrates; (IV) RNA processing and base modification reactions; (V) assembly of ribosomal subunits; and (VI) export of assembled subunits. Hence it can be considered that optimal expression of these molecules is directly responsible for regular protein synthesis.

In addition to the aforementioned small ncRNAs which are highly abundant molecules, long non coding (lnc)RNA are somewhat larger, having more than 200 nucleotides (69,70). lncRNAs act as blockers of transcriptional and splicing factors, and as modifiers of chromatin protein, thereby regulating the processes of transcription and splicing. It is reported that some antisense lncRNAs can also participate in mRNA stabilization by preventing miRNA binding which makes them potential regulators of their functions as gene silencers (71). In addition, it is also suggested that some lncRNAs regulate Dicer endonuclease activity therefore interfering with siRNA expression (72). Furthermore, lncRNAs have a number of important roles in several biological processes such as, translation, apoptosis, pluripotency of stem cells, etc. (73-76). Studies have also reported the significance of the lncRNA *MALAT 1* (full name: 'metastasis associated lung adenocarcinoma transcript 1') in reducing inflammation in endothelial cells in diabetic

rats (77). Moreover, *MALAT 1* silencing also contributed in reducing glucose induced upregulation of inflammatory cytokines such as IL 6 and TNFα (78).

With studies on ncRNA such as discussed above it is becoming well understood that ncRNAs can dramatically affect the execution of myriad cellular programs (79). This study also states that ncRNAs present a complexity as diverse as mRNAs, including a diverse and interrelated range of regulatory and functional roles in transcriptional, post-transcriptional, epigenetic, and nuclear processes. This adds to the cell type-, developmental stage-, and stimulus-specific profiles of protein-coding mRNA expression, post-transcriptional modifications, localization, and translation. Thus, it can be safely concluded that ncRNAs present an intricate frame work that can well serve to maintain homeostasis of biological organisms.

ncRNA, TSPO, and homeostasis

Biological systems are characterized by active maintenance of their homeostasis under broad ranges of environmental and physiological conditions (9). At molecular biological levels, this includes responses to insulting conditions such as injuries, pathogenic infections, and diseases (80-82). Such responses involve coordinated modulation of gene expression programs (83). In this context of homeostasis, long and short ncRNAs regulate development and cell physiology; and are also involved in several human diseases, such as cancer, neurodegenerative disorders; and in a variety of stress responses, including host pathogen interactions (9). Here we want to pay a bit more attention to potential commonalities between TSPO and ncRNA in regulating homeostatic functions.

Various miRNAs play important roles in regulating stress by optimizing the levels of key proteins involved in stress response (84). Several miRNAs, for example miR-9, miR-146, and miR-155 present increased expression in acute stress, acting via negative feedback to alleviate inflammatory reactions (85). Other studies have shown miR-21 to be overexpressed in glioblastoma tumors, described as anti-apoptotic factor predicted to down regulate genes associated with advanced apoptosis (86). In the section of miRNAs it was discussed that miRNAs are participants in mechanisms related to brain injury and brain disease.

The use of aberrant miRNAs offers opportunities to screen, diagnose, and predict patients' outcome with high accuracy by simple blood testing for different types of cancer (87). In this context, miRNAs have been linked to the regulation of differentiation, proliferation, apoptosis, and exocytosis. These are functions that are also known to be under the control of TSPO, as discussed at the beginning of this review.

Here we want to pay attention to some more functions that imply regulation of homeostasis by TSPO as well as miRNAs. Since TSPO is abundantly expressed in various metabolically active tissues, interest has been directed toward its regulatory role in several important metabolic disorders. Because one of its endogenous ligands is cholesterol, TSPO expression was measured in high fat/high cholesterol fed mice that present an inverse correlation between TSPO expression and obesity related inflammation (88,89). Similarly, a significant decrease in mitochondrial TSPO expression was observed in obese individuals (90). In the same study, *in vitro* incubation of trophoblast cells with long chain saturated fatty acids, showed inhibited TSPO mRNA expression. Taking this into account, special interest has been shown in TSPO's role in atherosclerosis and fatty liver disease introducing it as a biomarker for oxidative stress (91). In addition, several studies have revealed that TSPO is highly expressed in white and brown adipose tissue (WAT and BAT), thus implying TSPO's involvement in adipocytes' metabolism making TSPO an important factor considering regulation of obesity (92). lncRNAs involvement in cholesterol and triglyceride homeostasis was also shown (93,94). miRNA relation to inflammation as a result of obesity was also observed. For example, Ortega *et al.* (95) reported significant increases in expression of miR-221, miR-222, and miR-155 under conditions of obesity and their consequent decrease in post weight loss patients (95). Also an association between miR-155 and inflammation has been made by Karkeni *et al.* (96) who affirmed up-regulation of this miR-155 by TNFα in adipose tissue (96). Jiang *et al.* (97) reported significant increase of miR-378 in mature adipocytes as a result of IL-6, TNFα, and leptin treatment thus confirming miR-378's connection to obesity related inflammation (97). Further research exploring the outcome of therapeutic treatment associated with different miRNA profiles could provide valuable data to advance drug regime selection.

It has been postulated that TSPO is involved in cardiovascular diseases as well as obesity (90,98). Thus, we also wanted to follow research regarding the potential involvement of miRNAs in cardiovascular diseases. Indeed, also lncRNA and miRNA appear to play crucial roles in cardiovascular diseases (99,100). In particular, it has been

shown that the cardiac apoptosis related lncRNA (*CARL*) interaction with miR-539 prevents myocyte fission and apoptosis, thereby obstructing cardiac remodeling otherwise typically following myocardial infarction (101). Studies have also reported the significance of *MALAT 1* expression in endothelial cells for their proliferation during a state of hypoxia (102).

Conclusions

Various studies are suggesting that TSPO as well as ncRNAs play roles in homeostatic functions. As studies have also shown that TSPO and its ligands can regulate expression of ncRNAs, it is tempting to suggest that interactions between TSPO and ncRNAs may contribute to homeostasis of the organism. This implies that such interactions may be targeted to treat particular disorders, ranging from cancer, cardiovascular disorders, inflammatory disorders, the chronic condition of brain injury, and neurodegenerative disease.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri.2017.12.02). JDS serves as an unpaid editorial board member of *Non-coding RNA Investigation* from August 2017 to July 2019. The other authors have no conflicts of interest to declare.

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