Published Online on 7 May 2018

Proc Indian Natn Sci Acad **84** No. 2 June 2018 pp. 513-520

DOI: 10.16943/ptinsa/2018/49333

Review Article

Roles of Long non-coding RNAs in Cellular Stress Response

ANSHIKA GOENKA[1] and SUBRAMANIAM GANESH*

Department of Biological Sciences and Bioengineering, Indian Institute of Technology, Kanpur 208 016, India

[1]Current address: Syngene International Ltd., Biocon Park, Bengaluru 560 099, India

(Received on 20 December 2017; Revised on 22 February 2018; Accepted on 08 March 2018)

Cellular systems are often exposed to variations in their environment and, as a consequence, the cell systems have evolved a variety of pathways to promote cell survival during such challenges. Such "pro-survival" cellular pathways, often referred to as cellular stress response pathways, involve intricate cellular signalling networks, some of which are evolutionarily conserved. Given that such response mechanisms have cascading effects on the cellular physiology, it is not unexpected that regulatory forms of long non-coding RNAs (lncRNAs) play critical roles in these processes as well. This short review focuses on the regulatory roles of lncRNAs in transcriptional control during cellular stress response in higher vertebrates. Here, we elaborate on a few recent examples from the mammalian systems on the role of lncRNAs in the heat shock response process.

Keywords: Long Non-coding RNAs (lncRNAs); Cellular Stress Response; Heat Shock Response; Transcriptional Regulation

The mRNA-centric paradigm of the human transcriptome had undergone a fundamental change with the advent of new generation of DNA and RNA sequencing technologies. With the "rediscovery" that the genome is pervasively transcribed (Kapranov *et al*., 2002; Rinn *et al*., 2003), it is now evident that RNA does not simply act just as a messenger molecule but directly regulates almost all the cellular processes (Lakhotia, 2017; Beckmann *et al*., 2016, Roundtree *et al*., 2017). Moreover, it is widely acknowledged now that the organismal complexity correlates to the non-coding content of the genome and not to its coding portion (Huttenhofer *et al*., 2005; Kung *et al*., 2013; Brosius, 2014; Lakhotia, 2017), thus signifying the non-coding component of the genome. The domain of non-coding RNA (ncRNA) biology was revolutionized with the sequencing of the human genome, which identified that the human genome encodes thousands of regulatory non-coding RNA, both small (<200 bp) and long (>200 bp) forms. The small regulatory ncRNAs consists of the microRNAs (miRNA) and the Piwi-interacting RNAs (piRNA), whereas those greater than 200bp are termed long non-coding RNA on the basis of a convenient practical cut-off in RNA purification protocols that excludes short RNAs (Kapranov *et al*., 2007). While miRNAs are mainly involved in post-transcriptional gene regulation events, piRNAs protect the integrity of the genome from invasion by genomic parasites such as transposable elements by silencing them. The long non-coding RNAs (LncRNAs), on the other hand, have crucial roles in the regulation of gene expression both in development and differentiation. Intriguingly, the number of lncRNAs in a species shows a positive correlation with genome complexity, indicating the RNA-based control in the evolution of multicellular organisms (Fatica and Bozzoni, 2014). The lncRNAs are greater than 200 nucleotides in length; these are often poly-adenylated and are devoid of an open reading frame (ORF) (Derrien *et al*., 2012). Further, they have the dual ability to function as a ligand for proteins involved in gene regulation processes as well as to mediate base pairing interactions which guide lncRNA containing complexes to specific RNA or DNA target sites. Another remarkable virtue of lncRNAs is their unique ability to fold into complex

**Author for Correspondence: E-mail: sganesh@iitk.ac.in*

secondary and higher order structures that provides higher accessibility to both proteins and target recognition sites (Batista and Chang, 2013; Guttman and Rinn, 2012; Rinn and Chang, 2012). The flexible (Zappulla and Cech, 2004) and modular (Tsai *et al*., 2010; Wutz *et al*., 2002) nature of lncRNAs enable them to tether proteins together, which otherwise would not have been able to interact. Thus lncRNAs regulate both transcriptional and post-transcriptional events. Such regulation is observed both in normal physiological conditions as well as during cellular stress response. This short review, as the title suggests, would mainly focus on some of the recent discoveries on the role of lncRNAs in cellular stress response in species that show homeostasis, such as mammals.

The cellular system is constantly subjected to stress in response to a variety of conditions such as a transient exposure to hot or cold temperatures, heavy metals, exogenous chemicals, oxidative stress, salt, and pH shifts among others (Morimoto, 1998; Fulda *et al*., 2010). The cellular systems have evolved remarkable combat processes to cope up with such transient stressors by mounting "cellular stress responses" which are essentially pro-survival mechanisms. Activation of the stress responses results in a reorganization of cellular physiology to support survival (Fulda *et al*., 2010). Such a response generally involves repression of the basal physiological processes of the cell, including the transcription, translation and splicing processes, and diversion of the energy saved to initiate the stress response pathways. For example, during a heat shock exposure, the general transcription and translation processes in the cell are repressed but there is an enhanced synthesis of the heat shock family of proteins, called heat shock proteins (HSPs), to prevent misfolding of proteins during the stress (Morimoto, 1998; Panniers, 1994). Intriguingly, lncRNAs are known to regulate heat shock response pathways at multiple levels. In this review, we would cover the recent discoveries on four such lncRNAs, namely the *HSR1* (Heat Shock RNA 1), *NEAT1* (nuclear paraspeckle assembly transcript 1), *Alu* RNA and the Satellite III RNA.

The Heat Shock RNA 1 (HSR1) lncRNA

Heat Shock Factor 1 (HSF1) – a highly conserved transcription factor – is the master regulator of the heat shock response pathway (Morimoto, 1998; Akerfelt *et al*., 2010). Under physiological conditions, the HSF1 protein is rendered inactive through an interaction with HSPs (Voellmy, 2004). Upon heat shock, the HSF1 monomers are released from the complex, and they trimerize and translocate to the nucleus to bind to sequence motifs termed as heat shock elements (HSEs) in the promoter regions of genes upregulated in response to heat shock (Kugel and Goodrich, 2006). Most often, such genes code for the HSPs. Intriguingly, in mammalian cells, the heat shock is known to induce the activation of HSF1 by forming a complex with a lncRNA and the translation elongation factor eEF1A (Shamovsky *et al*., 2006). The lncRNA, named *HSR1* (for Heat Shock RNA 1), is polyadenylated, constitutively expressed, and its expression level is altered during the heat shock (Shamovsky *et al*., 2006). The presence of *HSR1* is essential for the cells to mount effective heat shock response. Since the translation elongation factor eEF1A is involved in the *HSR1*-mediated activation of HSF1 during a heat shock, it could be argued that the heat shock-induced translation arrest may well be regulated by the *HSR1* (Kugel and Goodrich, 2006). More recent studies suggest that the *HSR1* sequences are evolutionarily conserved (Choi *et al*., 2015), and that the mammalian counterpart of the *HSR1* could have a bacterial origin, possibly via the horizontal gene transfer or through an infection process (Kim *et al*., 2010; Lakhotia, 2012; Choi *et al*., 2015).

The Alu and B2 SINE lncRNAs

The short interspersed elements (SINEs) represent a type of abundant repetitive sequences actively transcribed by the RNA polymerase III in the mammalian genome (Borodulina *et al*., 1999). The resulting ncRNAs, spanning about 200 bases, are known to have a 5' end sequence similar to tRNA-like sequence (Daniels and Deininger, 1985; Wilusz *et al*., 2008). Intriguingly, the SINE elements show species-specific repeat motifs, though the SINEs *per se* are retrotransposons (Kazazian, 2004). For example, in mouse, the SINEs code for two distinct types of ncRNAs– the *B1* and *B2* class while in humans SINE code for only one type that is the *Alu*ncRNA (Kassube *et al*., 2013). Exposure to a heat shock is known to increase the expression levels of *Alu* transcripts in human and the *B2* transcripts in mouse (Liu *et al*., 1995; Kim *et al*., 2001; Fornace *et*

al., 1989). Other stressors, such as infection and UV exposure are also shown to have similar effects suggesting their possible role in the cellular stress response (Walters *et al*., 2009). Subsequent studies have shown that, during heat shock, the *B2* and *Alu* transcripts bind directly to RNA Pol II to block the formation of transcription initiation complexes. The RNA binds to the catalytic cleft of RNA Pol II and is recruited into complexes with the polymerase which are assembled at the promoters, thereby keeping the polymerase from properly engaging with the DNA (Allen *et al*., 2004; Mariner *et al*., 2008) resulting in the heat-induced transcription repression. Further, presence of HSF1 binding sites in the *Alu* enriched regions of the heat shock responsive genes suggests HSF1 mediated regulation of these transcripts during heat shock (Pandey *et al*., 2011). *Alu* transcripts have also been implicated in other cellular processes regulating gene expression, such as alternative splicing, RNA editing, translation, and miRNA expression and function (Chen and Yang 2017), suggesting *B2*/*Alu* transcripts may regulate gene expression at multiple steps.

The Satellite III lncRNAs

One of the intriguing observations regarding HSF1 is the formation of nuclear stress granules in human cells. Exposure of human fibroblasts to heat shock results in the recruitment of HSF1 to discrete foci in the nucleus, which are referred to as the nuclear stress bodies (nSBs) (Jolly *et al*., 1997). Subsequent studies have shown that the recruitment of HSF1 into the nSBs is to induces the expression of a lncRNA, called the Satellite III transcripts (*Sat3*). These transcripts, ranging in length from 2 to 6 kb are detected only when the cells are exposed to stress such as heat shock and are induced by HSF1 (Metz *et al*., 2004; Rizzi *et al*., 2004; Sengupta *et al*., 2009). The *Sat3* transcripts are characterized by the presence of a consensus GGAAT repeat motif, and such repeat tracts in the DNA are often associated with the pericentromeric regions of the human chromosomes (Jolly *et al*., 2002; Valgardsdottir *et al*., 2005). Studies have shown that the heat shock-induced *Sat3* transcripts accumulate at the site of their synthesis to form the nSBs (Metz *et al*., 2004; Rizzi *et al*., 2004). While the 9q12 locus appears to be the primary locus for the *Sat3*-positive nSBs (Metz *et al*., 2004; Rizzi *et al*., 2004), studies did indicate that *Sat3* could be induced at several other chromosomal loci, and their expression could be dependent upon the extent or the type of stressors (Sengupta *et al*., 2009; Eymery *et al*., 2010). Besides HSF1, the nSB were found to recruit CREB binding protein (CBP), RNA polymerase II, splicing factors/RNA binding proteins (SF2/ASF or SRSF1) and several heterogeneous nuclear ribonucleoproteins (hnRNPs) (Chiodi *et al*., 2004; Denegri *et al*., 2001; Jolly *et al*., 2004; Weighardt *et al*., 1999). Recent studies have also shown that except for the HSF1, the other known components of the nSBs require the presence of *Sat3* transcript for the association with the nSBs, suggesting a scaffold-like function for the *Sat3* transcripts in the formation of nSBs (Metz *et al*., 2004; Goenka *et al*., 2016).

A number of possible functions have been ascribed to the *Sat3* transcripts in heat shock response (Jolly and Lakhotia, 2006). These include chromatin remodeling, alternative splicing and transcriptional regulation (Jolly *et al*., 2004; Jolly and Lakhotia 2006; Biamonti and Vourc'h, 2010; Zong *et al*., 2011; Morimoto and Boerkoel, 2013; Kawaguchi and Hirose, 2015; Goenka *et al*., 2016). One of the recent studies has shown that the Sat3 transcripts could mediate heat shock-induced transcriptional arrest (Goenka *et al*., 2016). The study demonstrates that *Sat3* transcripts sequester transcriptional factors, such as CBP, on the nSBs thus making them unavailable for the transcriptional activity. The splicing factor SRSF1 appears to be the critical protein that helps CBP to be sequestered on the *Sat3* positive nSBs. Intriguingly, ectopic overexpression of *Sat3* repeat-bearing transcripts mimicked heat shock response in human cells even when not exposed to a heat shock. The overexpressed *Sat3* formed nSBs, recruited SRSF1 and CBP onto the nSBs, and reduced the expression levels of genes that are normally down regulated during the heat shock exposure, suggesting that the *Sat3* transcript is a key player in the heat shock-induced transcriptional suppression of a few of the genes in the human cells (Goenka *et al*., 2016). The mechanism proposed for the *Sat3* transcripts during the heat shock response is very similar to the observations made for the hsr omega lncRNAs in *Drosophila*, a proposed functional homologue of *Sat3* in flies (Jolly and Lakhotia, 2006; Mallik and Lakhotia, 2009; Mallik and Lakhotia, 2010), suggesting a parallel evolution for these two transcripts in diverse species such as

humans and flies. Given that these lncRNAs negatively regulate gene expression, and that loss of hsr omega ameliorates Huntington disease phenotype in a *Drosophila* model, the possible roles of *Sat3* transcripts in the etiology of neurodegenerative disorders needs to be thoroughly investigated. Emerging evidence suggests that inclusions formed in degenerating neurons sequester transcription factors, and thus may bring about transcriptional dysregulation in the neuron. For example, the TAR DNA-binding protein of 43 kDa (TDP-43) was shown to recruit RNA polymerase and other transcription factors in neurons of patients with amyotrophic lateral sclerosis (ALS) contributing to transcriptional dysregulation (Yamashita *et al*., 2014). A similar mechanism could operate for the *Sat3* transcripts, wherein the sequestration of CBP to the nSBs is responsible for the transcriptional repression of genes during the oxidative stress and in the transcription dysregulation observed in neurodegeneration (Goenka *et al*., 2016). Our ongoing investigations in the laboratory indicate that the *Sat3* transcripts are induced in the neurons exposed to oxidative stress and that these transcripts are expressed in the degenerating neurons of patients with Alzheimer's disease (AD) or Parkinson disease (PD) (Goenka *et al.*, unpublished observations). Thus, the prolonged expression of *Sat3* due to the chronic physiological stress experienced by the neurons might mimic chronic heat stress and might contribute to neurodegeneration. Thus, it is tempting to speculate that suppression of *Sat3* might delay the neurodegenerative process in AD and PD, analogous to the observations that were made for the hsr omega transcript in the *Drosophila* model of HD (Mallik and Lakhotia, 2009; Mallik and Lakhotia, 2010).

The Nuclear Paraspeckle Assembly Transcript 1 (NEAT1) lncRNA

The *NEAT1* lncRNA is an essential structural element of the nuclear body paraspeckle and was originally shown to be transcribed from the chromosomal locus associated with the familial endocrine neoplasia (Guru *et al*., 1997). Intriguingly *NEAT1* lncRNA is induced in response to hypoxia conditions (Choudhry *et al*., 2015). Studies have shown that the *NEAT1* expression is regulated by the hypoxia-inducible factor, HIF-2α transcription factor activated by the hypoxic condition (Choudhry *et al*., 2015). Analogous to the functions of HSF1 in the heat shock response, the HIF2 regulates the expression of a number of genes during a hypoxic condition both to improve oxygen delivery and to reduce oxygen demand – a specific stress response mechanism (Majmundar *et al*., 2010). The HIF2-induced *NEAT1* expression results in increased number of paraspeckles in the cells during a hypoxia (Choudhry *et al*., 2015). Though the specific cellular functions of paraspeckles are not fully understood, emerging reports suggest that paraspeckles might regulate transcriptional and post-transcriptional processes (Hata *et al*., 2008; Torres *et al*., 2017). The increased *NEAT1* expression is associated with enhanced cell survival and proliferation and conversely, breast cancer patients with increased *NEAT1* expression show poor survival (Choudhry *et al*., 2015), suggesting a pro-cell survival function for the *NEAT1* mediated paraspeckles (Choudhry and Mole, 2016). Moreover, silencing *NEAT1* in mice sensitized preneoplastic cells to DNA-damage-induced cell death and impaired skin tumorigenesis (Adriaens *et al*., 2016).

Stress-induced lncRNAs: A Field on the Horizon

With the advent of functional high-throughput screening and sequencing systems, several novel lncRNAs have recently been found and a few more have been shown to be involved in the cellular stress response pathways. One such novel example is the p53-regulated lncRNA named *TRINGS* (Tp53-regulated inhibitor of necrosis under glucose starvation) which is found to protect tumor cells from cell death as opposed to the classical function of p53 to prevent malignant transformation. Upon glucose starvation, *TRINGS* lncRNA is upregulated in human tumor cells and inhibits the STRAP-GSK3β-NF-κB necrotic signaling to protect tumor cells from cell death (Khan *et al*., 2017). Another lncRNA *TERRA* (TElomeric Repeat containing RNA) is found to be involved in the protection of telomere DNA during stress. *TERRA* is upregulated during heat stress upon binding of HSF1 to the subtelomeric DNA. Notably, the knockdown of HSF1 impairs telomere integrity and enhances the telomeric DNA changes as *TERRA* does not get activated during heat stress in HSF1 deficient cells (Koskas *et al*., 2017). Similarly, a few more hypoxia-induced lncRNAs have been discovered in cancer since hypoxic regions are common in solid tumors. Some of these examples include *NEAT1* (up-

regulated in breast cancer), *H19* (up-regulated in p53 null mouse) and *UCA1* (upregulated in bladder cancer), and all of them are regulated by hypoxia (Chang *et al*., 2016). Intriguing, cellular senescence, a complex cellular process experience multiple adverse stimuli such as replicative stress, DNA damage, oxidative stress or oncogene, is known to associate with the expression of a few lncRNAs. For example, *ANRIL* lncRNA which is decreased during replicative senescence leading to transcription repression of the CDKN2A/CDKN2B gene locus involved in the regulation of the cell cycle (Abdelmohsen *et al*., 2013). The expression of *HOTAIR* lncRNA is known to increase during the replicative and irradiation-induced senescence to act as a scaffold for ubiquitin ligases thereby facilitating the ubiquitination of a few targets proteins to prevent premature senescence (Montes *et al*., 2016). Accumulation of senescent cells eventually lead to age related disorders, thus it would be of importance to study the role of lncRNAs in the aging process.

Stress response pathways involve a variety of regulatory networks in the cellular systems, and therefore it is not unexpected that lncRNAs are found to be involved in these processes. Given that such response mechanisms have cascading effects, the ncRNAs appear to have been selected for a diverse set of functions (Lakhotia, 2012). With the "rediscovery" that the "junk DNA" do have functional roles, and that "junk DNA" do get transcribed to form non-coding transcripts with critical regulatory roles (reviewed in Lakhotia, 2017), the coming decade is expected to uncover hitherto unknown functions for lncRNAs in the normal and in the abnormal cellular physiology.

Acknowledgments

The authors wish to thank Professor S C Lakhotia and Dr Rashmi Parihar for their critical inputs on the manuscript. We also wish to thank the anonymous referees for the constructive comments on an earlier version of the manuscript. The work on non-coding RNA and stress response pathways in the author's laboratory was supported by a research grant from the Department of Biotechnology (BT/HRD/35/01/01/2017) to SG.

Conflict of interest: None to declare.

References

Adriaens C, Standaert L, Barra J, Latil M, Verfaillie A, Kalev P, Boeckx B, Wijnhoven P W, Radaelli E, Vermi W, Leucci E, Lapouge G, Beck B, van den Oord J, Nakagawa S, Hirose T, Sablina A A, Lambrechts D, Aerts S, Blanpain C and Marine J C (2016) p53 induces formation of NEAT1 lncRNA-containing paraspeckles that modulatereplication stress response and chemosensitivity *Nat Med* **22** 861-868

Akerfelt M, Morimoto R I and Sistonen L (2010) Heat shock factors: integrators of cell stress, development and lifespan *Nat Rev Mol Cell Biol* **11** 545-555

Abdelmohsen K, Panda A, Kang M J, Xu J, Selimyan R, Yoon J H, Martindale J L, De S, Wood W H 3rd, Becker K G and Gorospe M (2013) Senescence-associated lncRNAs: senescence-associated long noncoding RNAs *Aging Cell* **12** 890-900

Allen T A, Von Kaenel S, Goodrich J A and Kugel J F (2004) The SINE-encoded mouse B2 RNA represses mRNA transcription in response to heat shock *Nat Struct Mol Biol* **11** 816-821

Batista P J and Chang H Y (2013) Long noncoding RNAs: Cellular address codes in development and disease *Cell* **152** 1298-1307

Beckmann B M, Castello A and Medenbach J (2016) The expanding universe of ribonucleoproteins: of novel RNA-binding proteins and unconventional interactions *Pflugers Arch* **468** 1029-1040

Biamonti G and Vourc'h C (2010) Nuclear stress bodies *Cold Spring Harb Perspect Biol* **2** a000695

Borodulina O R and Kramerov D A (1999) Wide distribution of short interspersed elements among eukaryotic genomes *FEBS Lett* **457** 409-413

Brosius J (2014) The persistent contributions of RNA to eukaryotic genome architecture and cellular function *Cold Spring Harb Perspect Biol* **6** a016089

Chang Y N, Zhang K, Hu Z M, Qi H X, Shi Z M, Han X H, Han Y W and Hong W (2016) Hypoxia-regulated lncRNAs in cancer *Gene* **575** 1-8

Chen L L and Yang L (2017) ALUternative Regulation for Gene Expression *Trends Cell Biol* **27** 480-490

Chiodi I, Corioni M, Giordano M, Valgardsdottir R, Ghigna C, Cobianchi F, Xu R M, Riva S and Biamonti G (2004) RNA recognition motif 2 directs the recruitment of SF2/ASF to nuclear stress bodies *Nucleic Acids Res* **32** 4127-4136

Choi D, Oh H J, Goh C J, Lee K and Hahn Y (2015) Heat Shock RNA 1, Known as a Eukaryotic Temperature-Sensing Noncoding RNA, Is of Bacterial Origin *J Microbiol Biotechnol* **25** 1234-1240

Choudhry H, Albukhari A, Morotti M, Haider S, Moralli D, Smythies J, Schödel J, Green C M, Camps C, Buffa F, Ratcliffe P, Ragoussis J, Harris A L and Mole D R (2015) Tumor hypoxia induces nuclear paraspeckle formation through HIF-2α dependent transcriptional activation of NEAT1 leading to cancer cell survival *Oncogene* **34** 4482-4490

Choudhry H and Mole D R (2016) Hypoxic regulation of the noncoding genome and NEAT1.Brief Funct *Genomics* **15** 174-185

Daniels G R and Deininger P L (1985) Repeat sequence families derived from mammalian tRNA genes *Nature* **317** 819-822

Denegri M, Chiodi I, Corioni M, Cobianchi F, Riva S and Biamonti G (2001) Stress-induced nuclear bodies are sites of accumulation of pre-mRNA processing factors *Mol Biol Cell* **12** 3502-3514

Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles D G, Lagarde J, Veeravalli L, Ruan X, Ruan Y, LassmannT, Carninci P, Brown J B, Lipovich L, Gonzalez J M, Thomas M, Davis C A, Shiekhattar R, Gingeras T R, Hubbard T J, Notredame C, Harrow J and Guigó R (2012) The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression *Genome Res* **22** 1775-1789

Eymery A, Souchier C, Vourc'h C and Jolly C (2010) Heat shock factor 1 binds to and transcribes satellite II and III sequences at several pericentromeric regions in heat-shocked cells *Exp Cell Res* **316** 1845-1855

Fatica A and Bozzoni I (2014) Long non-coding RNAs: new players in cell differentiation and development *Nat Rev Genet* **15** 7-21

Fulda S, Gorman A M, Hori O and Samali A (2010) Cellular stress responses: cell survival and cell death *Int J Cell Biol* **2** 14074

Fornace A J Jr, Alamo I Jr, Hollander M C and Lamoreaux E (1989) Induction of heat shock protein transcripts and B2 transcripts by various stresses in Chinese hamster cells *Exp Cell Res* **182** 61-74

Goenka A, Sengupta S, Pandey R, Parihar R, Mohanta G C, Mukerji M and Ganesh S (2016) Human satellite-III non-coding RNAs modulate heat-shock-induced transcriptional repression *J Cell Sci* **129** 3541-3552

Guru S C, Agarwal S K, Manickam P, Olufemi S E, Crabtree J S, Weisemann J M, Kester M B, Kim Y S, Wang Y, Emmert-Buck M R, Liotta L A, Spiegel A M, Boguski M S, Roe B A, Collins F S, Marx S J, Burns L and Chandrasekharappa S C (1997) A transcript map for the 2.8-Mb region containing the multiple endocrine neoplasia type 1 locus *Genome Res* **7** 725-735

Guttman M and Rinn J L (2012) Modular regulatory principles of large non-coding RNAs *Nature* **482** 339-346

Hata K, Nishimura R, Muramatsu S, Matsuda A, Matsubara T, Amano K, Ikeda F, Harley V R and Yoneda T (2008) Paraspeckle protein p54nrb links Sox9-mediated transcription with RNA processing during chondrogenesis in mice *J Clin Invest* **118** 3098-3108

Huttenhofer A, Schattner P and Polacek N (2005) Non-coding RNAs: hope or hype? *Trends Genet* **21** 289-297

Jolly C and Lakhotia S C (2006) Human sat III and Drosophila hsr omega transcripts: a common paradigm for regulation of nuclear RNA processing in stressed cells *Nucleic Acids Res* **34** 5508-5514

Jolly C, Konecny L, Grady D L, Kutskova Y A, Cotto J J, Morimoto R I and Vourc'h C (2002) In vivo binding of active heat shock transcription factor 1 to human chromosome 9 heterochromatin during stress *J Cell Biol* **156** 775-781

Jolly C, Metz A, Govin J, Vigneron M, Turner B M, Khochbin S and Vourc'h C (2004) Stress-induced transcription of satellite III repeats *J Cell Biol* **164** 25-33

Jolly C, Morimoto R, Robert-Nicoud M and Vourc'h C (1997) HSF1 transcription factor concentrates in nuclear foci during heat shock: relationship with transcription sites *J Cell Sci* **110** 2935-2941

Kapranov P, Cawley S E, Drenkow J, Bekiranov S, Strausberg R L, Fodor S P, Gingeras T R (2002) Large-scale transcriptional activity in chromosomes 21 and 22. *Science* May **296** 916-919

Kapranov P, Cheng J, Dike S, Nix D A, Duttagupta R, Willingham A T, Stadler P F, Hertel J, Hackermüller J, Hofacker I L, Bell I, Cheung E, Drenkow J, Dumais E, Patel S, Helt G, Ganesh M, Ghosh S, Piccolboni A, Sementchenko V, Tammana H and Gingeras T R (2007) RNA maps reveal new RNA classes and a possible function for pervasive transcription *Science* **316** 1484-1488

Kassube S A, Fang J, Grob P, Yakovchuk P, Goodrich J A and Nogales E (2013) Structural insights into transcriptional

repression by noncoding RNAs that bind to human Pol II *J MolBiol* **425** 3639-48

Kawaguchi T and Hirose T (2015) Chromatin remodeling complexes in the assembly of long noncoding RNA-dependent nuclear bodies *Nucleus* **6** 462-467

Kazazian H H Jr (2004) Mobile elements: drivers of genome evolution *Science* **303** 1626-1632

Khan M R, Xiang S, Song Z and Wu M (2017) The p53-inducible long noncoding RNA TRINGS protects cancer cells from necrosis under glucose starvation *EMBO J* **36** 3483-3500

Kim C, Rubin C M and Schmid C W (2001) Genome-wide chromatin remodeling modulates the Alu heat shock response *Gene* **276** 127-133

Kim D S, Lee Y and Hahn Y (2010) Evidence for bacterial origin of heat shock RNA-1 *RNA* **16** 274-279

Kim C, Rubin CM, Schmid C W (2001) Genome-wide chromatin remodeling modulates the Aluheat shock response *Gene* **276** 127-33

Koskas S, Decottignies A, Dufour S, Pezet M, Verdel A, Vourc'h C and Faure V (2017) Heat shock factor 1 promotes TERRA transcription and telomere protection uponheat stress *Nucleic Acids Res* **45** 6321-6333

Kugel J F and Goodrich J A (2006) Beating the heat: A translation factor and an RNA mobilize the heat shock transcription factor HSF1 *Mol Cell* **22** 153-154

Kung J T, Colognori D and Lee J T (2013) Long noncoding RNAs: Past, present, and future *Genetics* **193** 651-669

Lakhotia S C (2012) Long non-coding RNAs coordinate cellular responses to stress Wiley *Interdiscip Rev RNA* **3** 779-796

Lakhotia S C (2017) Fromheterochromatin to long noncoding RNAs in *Drosophila*: expanding the arena of gene function and regulation *Adv Exp Med Biol* **1008** 75-118

Liu W M, Chu W M, Choudary P V and Schmid C W (1995) Cell stress and translational inhibitors transiently increase the abundance of mammalian SINE transcripts *Nucleic Acids Res* **23** 1758-1765

Majmundar A J, Wong W J and Simon M C (2010) Hypoxia-inducible factors and the response to hypoxic stress *Mol Cell* **40** 294-309

Mallik M, Lakhotia S C (2009) RNAi for the large non-coding hsromega transcripts suppresses polyglutamine pathogenesis in Drosophila models *RNA Biol* **4** 464-478

Mallik M and Lakhotia S C (2010) Improved activities of CREB binding protein, heterogeneous nuclear ribonucleo proteins and proteasome following down regulation of noncoding hsromega transcripts help suppress poly(Q) pathogenesis in fly models. *Genetics* **184** 927-945

Mariner P D, Walters R D, Espinoza C A, Drullinger L F, Wagner S D, Kugel J F and Goodrich J A (2008) Human Alu RNA is a modular transacting repressor of mRNA transcription during heat shock *Mol Cell* **29** 499-509

Metz A, Soret J, Vourc'h C, Tazi J and Jolly C (2004) A key role for stress-induced satellite III transcripts in the relocalization of splicing factors into nuclear stress granules *J Cell Sci* **117** 4551-4558

Montes M and Lund A H (2016) Emerging roles of lncRNAs in senescence *FEBS J* **283** 2414-2426

Morimoto M and Boerkoel C F (2013) The role of nuclear bodies in gene expression and disease *Biology (Basel)* **2** 976-1033

Morimoto R I (1998) Regulation of the heat shock transcriptional response: cross talk between a family of heat shock factors, molecular chaperones, and negative regulators *Genes Dev* **12** 3788-3796

Pandey R, Mandal A K, Jha V and Mukerji M (2011) Heat shock factor binding in Alu repeats expands its involvement in stress through an antisense mechanism *Genome Biol* **12** R117

Panniers R (1994) Translational control during heat shock *Biochimie* **76** 737-747

Rinn J L, Euskirchen G, Bertone P, Martone R, Luscombe N M, Hartman S, Harrison P M, Nelson F K, Miller P, Gerstein M, Weissman S and Snyder M (2003) The transcriptional activity of human Chromosome 22 *Genes Dev* **17** 529-540

Rinn J L and Chang H Y (2012) Genome regulation by long noncoding RNAs *Annu Rev Biochem* **81** 145-166

Rizzi N, Denegri M, Chiodi I, Corioni M, Valgardsdottir R, Cobianchi F, Riva S and Biamonti G (2004) Transcriptional activation of a constitutive heterochromatic domain of the human genome in response to heat shock *Mol Biol Cell* **15** 543-551

Roundtree I A, Evans M E, Pan T and He C (2017) Dynamic RNA Modifications in Gene Expression Regulation *Cell* **169** 1187-1200

Sengupta S, Parihar R and Ganesh S (2009) Satellite III non-coding RNAs show distinct and stress-specific patterns of induction *Biochem Biophys Res Commun* **382** 102-107

Shamovsky I, Ivannikov M, Kandel E S, Gershon D and Nudler E (2006) RNA-mediated response to heat shock in mammalian cells *Nature* **440** 556-560

Torres M, Becquet D, Blanchard M P, Guillen S, Boyer B, Moreno M, Franc J L and François-Bellan A M (2017) Paraspeckles as rhythmic nuclear mRNA anchorages responsible for

circadian gene expression *Nucleus* **8** 249-254

Tsai M C, Manor O, Wan Y, Mosammaparast N, Wang J K, Lan F, Shi Y, Segal E and Chang H Y (2010) Long noncoding RNA as modular scaffold of histone modification complexes *Science* **329** 689-693

Valgardsdottir R, Chiodi I, Giordano M, Cobianchi F, Riva S and Biamonti G (2005) Structural and functional characterization of noncoding repetitive RNAs transcribed in stressed human cells *Mol Biol Cell* **16** 2597-2604

Voellmy R (2004) On mechanisms that control heat shock transcription factor activity in metazoan cells *Cell Stress Chaperones* **9** 122-133

Walters R D, Kugel J F and Goodrich J A (2009) InvAluable junk: the cellular impact and function of Alu and B2 RNAs *IUBMB Life* **61** 831-837

Weighardt F, Cobianchi F, Cartegni L, Chiodi I, Villa A, Riva S and Biamonti G (1999) A novel hnRNP protein (HAP/SAF-B) enters a subset of hnRNP complexes and relocates in nuclear granules in response to heat shock *J Cell Sci* **112** 1465-1476

Wilusz J E, Freier S M and Spector D L (2008) 3' end processing of a long nuclear-retained noncoding RNA yields a tRNA-like cytoplasmic RNA *Cell* **135** 919-932

Wutz A, Rasmussen T P and Jaenisch R (2002) Chromosomal silencing and localization are mediated by different domains of Xist RNA *Nat Genet* **30** 167-174

Yamashita M, Nonaka T, Hirai S, Miwa A, Okado H, Arai T, Hosokawa M, Akiyama H and Hasegawa M (2014) Distinct pathways leading to TDP-43-induced cellular dysfunctions *Hum Mol Genet* **23** 4345-4356

Zappulla D C and Cech T R (2004) Yeast telomerase RNA: a flexible scaffold for protein subunits *Proc Natl Acad Sci U S A* **101** 10024-10029

Zong X, Tripathi V and Prasanth K V (2011) RNA splicing control: yet another gene regulatory role for long nuclear noncoding RNAs *RNA Biol* **8** 968-977.