REVIEW

Widening HSF1 horizon: the microRNA connection

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Heat shock factor 1 (HSF1) is an evolutionary conserved transcription factor which acts as protector of cellular proteome against adverse environmental conditions including increased temperature in eukaryotes. HSF1 positively regulates expression of a set of cytoprotective proteins popularly called as heat shock proteins (HSPs) as part of an adaptive mechanism of cells known as heat shock response (HSR). It has also been shown that apart from cellular stress response, HSF1 has the ability to regulate many other biological processes including aging, metabolism, development etc. This is primarily achieved by the ability of HSF1 to regulate expression of myriad of genes other than those coding for classical HSPs in presence and/or absence of stress. MicroRNAs (miRNAs) are short endogenous RNA molecules which can regulate many biological processes by acting as post-transcriptional regulators of gene expression. Altered expression of miRNAs in response to thermal stress has been reported in different species; however, the underlying mechanism remained elusive. We recently showed that HSF1 has the ability to regulate expression of miRNAs by binding to their upstream sequences and our result established hsa-miR-432 as the first HSF1-regulated miRNA.We therefore speculate that the landscape of HSF1 transcripts is much broader than it was earlier thought and includes HSF1-regulated miRNAs, the recently identified non-coding arm of HSF1 transcripts. The HSF1-regulated miRNAs have the potential to regulate many cellular events by acting as important downstream molecules of HSF1.Our finding thus uncovers a novel functional aspect of HSF1 with the emergence of hsa-miR-432 as a novel transcriptional target of HSF1.

Keywords: Heat shock response; Heat shock factor 1; microRNA

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Heat Shock Factor 1 (HSF1) is a prime integrator of transcriptional responses during stress [1]. Although the role of HSF1 in cellular stress response received much attention throughout the years, HSF1 also directs many physiological processes even in absence of stress including development, metabolism, aging etc. [2]. The widespread functional activity of HSF1 in cellular milieu is supposedly mediated by its downstream protein coding genes. Initially HSF1 was thought to regulate the expression of only stress-responsive genes coding for heat shock proteins (HSP). However, genome-wide studies reveal that in addition to classical heat shock genes, HSF1 could also induce transcription of large numbers of non-classical cytoprotective heat shock genes under basal and/or stressed condition [3, 4].

MicroRNAs (miRNAs) are short (20-23 nucleotide), endogenous, single stranded RNA molecules that act as post-transcriptional regulators of gene expression [5]. MiRNAs are now recognized as major regulators of many biological processes including cell proliferation, apoptosis, differentiation etc. [6, 7]. Over the years, active involvement of miRNAs in response to different stress stimuli including hyperthermia [8], hypoxia [9], ER stress [10] etc. has been reported.

Thermal stress has been shown to alter miRNA expression in human [8; 11], mice [12; 13] and rat [14]. However, the significance or functional relevance of such alteration is known only in few cases. For example, mice subjected to cytoprotective heat shock treatment showed significant increase in miR-21 expression which could reduce myocardial infarction after ischemia-reperfusion injury [12]. In an attempt to identify thermally altered expression of miRNAs in HeLa cells, we measured expression of a set of miRNAs in unstressed and stressed HeLa cells. We subsequently identified 8 thermally altered miRNAs, of which 7 miRNAs viz. hsa-miR-34a, hsa-miR-125b, hsa-miR-128, hsa-miR-146a, hsa-miR-205, hsa-miR-221 and hsa-miR-432 were thermally upregulated whereas one miRNA (hsa-miR-154) was thermally downregulated[15]. Interestingly, hsa-miR-34a and hsa-miR-125b were earlier reported to be induced by heat shock in human dermal fibroblast [8]. The same study also reported heat shock-driven decreased hsa-miR-154 expression [8], as also observed by us. Our finding further recapitulated an earlier observation that miR-34a expression could be induced by hyperthermia in rat [14]. Despite many reports revealing heat shock-driven altered expression of miRNAs in many species including human, the underlying mechanism of such alteration remained obscure. We hypothesized that altered expression of miRNAs by thermal stress could be direct transcriptional effect of HSF1, the major effector of heat shock response in mammalian cells. HSF1 induces transcription of its downstream genes by directly binding to specific DNA elements present in their promoter. These elements, popularly known as heat shock elements (HSEs) are composed of two or more pentameric units arranged as inverted adjacent arrays of the sequence 5'-nGAAn-3' [16; 17].

Reports of thermally altered miRNAs in higher eukaryotes known so far has been summarized in **Table 1**. Very recently, Li *et al.*, [18] reported that expression of miR-135b is directly regulated by HSF1 and it promotes tumor invasion and metastasis by targeting RECK and EVI5 in hepatocellular carcinoma. It was, however, not shown whether expression of miR-135b could be induced by thermal stress. This is perhaps the second report depicting regulation of miRNA transcription by HSF1.

It is noteworthy that promoter region of miRNAs are poorly defined in many cases. This is partly due to the lack of knowledge regarding the exact length and genomic location of primary transcripts (pri-miRNAs) and partly due to the heterogeneity of the miRNA biogenesis pathway. Intronic miRNAs are often co-expressed with host genes and some of them share the same promoter [19, 20]. In some cases, however, independent promoters for intronic miRNAs, independent of host genes have also been identified [21]. The role of intronic miRNA promoters is largely unknown and this adds another layer of complexity to the transcriptional regulation of miRNAs. Transcription start site (TSS), especially for the intergenic miRNA is not known for most of the miRNAs. It has been observed that promoters of several miRNA genes could be located several thousand bases away and share the same general features as those of protein-coding genes [22, 23]. MiRNA genes located within 50 kb of each other can be processed from polycistronic primary transcripts [24]. Like protein-coding genes, miRNA genes are usually transcribed by RNA polymerase II [25]. However, several miRNAs have also been observed to be transcribed by RNA polymerase III [26]. Many intronic miRNAs can be transcribed by both RNA polymerase II and RNA polymerase III [21].

To test the possibility that HSF1 regulates expression of thermally altered miRNAs by directly binding to the upstream sequences, we searched upstream sequences of all thermally altered miRNAs for presence of any putative HSE by a search tool described earlier [27]. Our search revealed that all thermally altered miRNAs, except hsa-miR-146a, contained one or more putative HSEs within 20kb upstream region. Out of the 8 thermally altered miRNAs, hsa-miR-154 was found to have maximum number of (6) putative HSEs in its upstream region. Intriguingly, hsa-miR-154 was the only miRNA whose expression was significantly repressed by elevated temperature in HeLa cells [15]. Although HSF1 has been best characterized as transcriptional activator, it can also repress gene expression through transcriptional regulation [28]. Therefore, we speculate that heat shock-driven downregulation of hsa-miR-154 could also be mediated by HSF1 through putative HSF1-binding sites present in hsa-miR-154 upstream sequence.

We noticed that the minimum distance between a thermally altered miRNA (pre-miRNA) and a putative HSE was 392 bp that separated hsa-miR-432 (pre-miR-432) and a putative HSE present in its upstream. We attempted to determine whether HSF1 could regulate hsa-miR-432 expression through this HSE. By reporter assay and chromatin immunoprecipitation, we showed that the putative HSE present in -392 to -378 region of hsa-miR-432 is responsive to both heat stress and ectopic HSF1. Moreover, occupancy of HSF1 at this site increased significantly in response to heat shock in HeLa cells, revealing the fact that the putative HSE is functionally active and has the potential to become transcriptionally competent upon heat stress. We further demonstrated that ectopic HSF1, upon heat shock, could induce hsa-miR-432 expression whereas knocking down HSF1 by siRNA inhibited the ability of cells to boost hsa-miR-432 expression in response to hyperthermia [15].

Table 1. Summary of thermally altered (upregulated and downregulated) miRNAs in higher eukaryotes

Organism	Tissue / Cell type	Altered miRNAs	References
Thermally upregulated miRNAs			
Human	Adult human dermal fibroblasts (HDF)	miR-22, miR-101, miR-125b, miR-133b, miR-192, miR-378, miR-382, miR-424, miR-452	[8]
Human	HeLa and JAR cell lines	miR-125b, miR-154, miR-382	[11]
Human	HeLa cells	miR-34a, miR-125b, miR-128b, miR-146a, miR-205, miR-221, miR-432	[15]
ICR mice	Heart tissue	miR-1, miR-21, miR-24	[12]
Mouse	Gastrocnemius muscle tissue	miR-9-3, miR-10a*, miR-27a, miR-29b-1, miR-30b, miR-30c-2, miR-30e, miR-136, miR-138, miR-153, miR-199a-3p, miR-211, miR-344, miR-363, miR-369-3p, miR-375, miR-376a*, miR-376b*, miR-377, miR-466b-2, miR-466k, miR-494, miR-669l, miR-673-3p, miR-692, miR-708*, miR-1190, miR-1939, miR-1944, miR-1945, miR-1962, miR-1964, miR-2136, miR-let-7a-2	[13]
Sprague-Dawley rats	Small intestine tissue	miR-7a, miR-27b, miR-30a*, miR-34a, miR-34b, miR-125a-5p, miR-137, miR-140*, miR-154, miR-185, miR-200a, miR-203, miR-210, miR-219-5p, miR-375, miR-500, miR-672, miR-let-7d	[14]
Thermally downregulated miRNAs			
Human	Adult human dermal fibroblasts (HDF)	miR-7, miR-18a, miR-29b, miR-31, miR-33a, miR-138, miR-154, miR-196a, miR-196b, miR-204, miR-218, miR-222, miR-376a, miR-487b, miR-606, miR-1298, miR-let-7c, miR-let-7d	[8]
Human	HeLa cells	miR-154	[15]
Mouse	Gastrocnemius muscle tissue	miR-7f-2, miR-23a, miR-23b, miR-34a-5p, miR-151, miR-293, miR-300, miR-302a, miR-329, miR-331-5p, miR-351, miR-467a, miR-467a-1*, miR-467d*, miR-467f, miR-483, miR-669f, miR-669m-2, miR-669o, miR-671-5p, miR-698, miR-702, miR-879*, miR-874, miR-1937c, miR-1950, miR-1954	[13]
Sprague-Dawley rats	Small intestine tissue	miR-23a, miR-31, miR-142-3p, miR-142-5p, miR-148b-3p, miR-150, miR-193, miR-204, miR-223, miR-322, miR-434	[14]

Human miR-432 is poorly characterized as yet. A recent report from our laboratory showed that hsa-miR-432 can induce neuronal differentiation in human neuroblastoma cells [29]. However, how hsa-miR-432 expression is regulated remained unknown. It was earlier reported that expression of hsa-miR-432 and its host gene has no correlation, suggesting that hsa-miR-432 is possibly regulated through regulatory sites independent of its host gene promoter [30]. This hsa-miR-432 is member of a cluster which also includes hsa-miR-136, hsa-miR-127, hsa-miR-431 and hsa-miR-433. Of these, expression of hsa-miR-127 was reported to be induced in a urinary bladder carcinoma cell line and in fibroblasts; independent of the other members of the same cluster via a transcription start site located a few hundred base pairs upstream of the pre-miRNA [31]. Notably, we found hsa-miR-127 unaltered by heat shock treatment whereas the same treatment was able to induce hsa-miR-432 expression [15]. Thus, it seems likely that although present in same cluster, miRNAs of this cluster might be regulated independently through distinct regulatory sites and factors depending on cell type and condition.

To understand the possible function(s) of thermally altered miRNAs identified from our study, we performed functional enrichment analysis with the validated targets of 8 thermally altered miRNAs. Altogether these 8 miRNAs are known to target 1059 unique genes, as shown in miRTarBase database [32, 33]. These genes were analyzed by online software GeneCodis[34, 35, 36] for enrichment of specific Gene Ontology (GO) descriptors for biological processes (BP), molecular functions (MF) and KEGG pathways. Our analysis revealed significant enrichment of 702 GO biological processes, 154 different GO molecular function classes and 103 different KEGG pathways [15].

We observed that significantly enriched GO terms were largely associated with cellular processes like transcription, apoptosis, cellular stress response, development etc. For example, GO terms like regulation of gene expression (GO:0010468), regulation of sequence-specific DNA binding transcription factor activity (GO:0051090) etc. clearly indicated that proteins associated with these terms are involved in **transcription**. Similarly, many GO terms related to **apoptosis** (e.g. regulation of apoptotic process (GO:0042981), induction of apoptosis (GO:0006917), anti-apoptosis (GO:0006916) etc.), **development** (e.g. (regulation of developmental process (GO:0050793), multicellular organismal development (GO:0007275), neuron development (GO:0048666) etc.) and **stress response** (e.g. response to ethanol (GO:0045471), response to oxidative stress (GO:0006979), response to hydrogen peroxide (GO:0042542), cellular response to reactive oxygen species

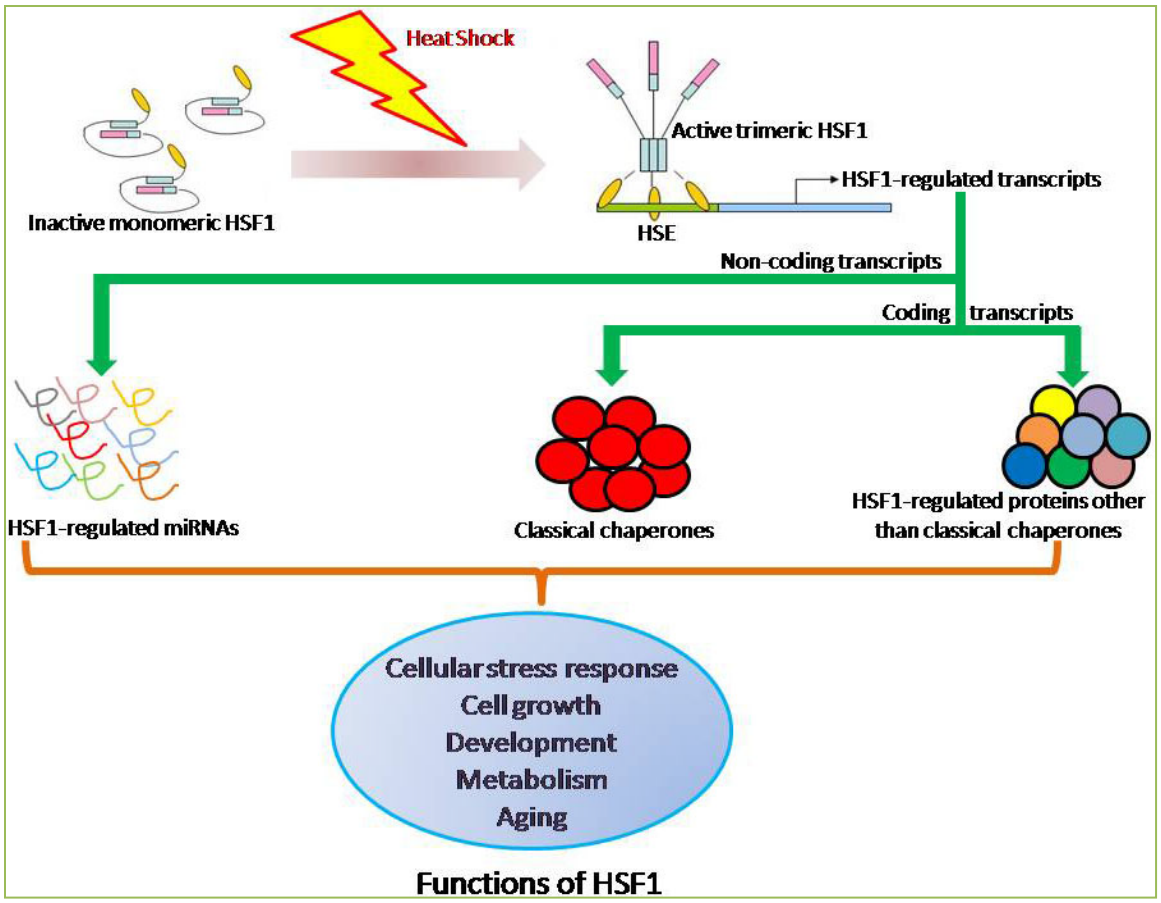

Figure 1.A proposed model depicting involvement of HSF1-regulated miRNAs in many biological processes regulated by HSF1. Upon heat shock, inactive HSF1 monomers undergo various changes and modifications to become transcriptionally active HSF1 trimer. The active HSF1 trimers recognize specific DNA elements (HSE) and thus regulate expression of its downstream targets which apart from classical chaperones and other non-classical heat shock proteins; also include HSF1-regulated miRNAs, the newly found arm of HSF1 targets. All these three types of HSF1 targets contribute to the ability of HSF1 to regulate various biological processes.

(GO:0034614) etc.) were also found over-represented within targets of thermally altered miRNAs. Interestingly, direct involvement of HSF1 in all these biological processes is already established. Therefore it appears that HSF1 and thermally altered miRNAs are functionally implicated in similar biological events. We further noticed that many cancer pathways including Prostate cancer (Kegg:05215), Pancreatic cancer (Kegg:05212), Colorectal cancer (Kegg:05210) etc. and pathways associated with protein folding diseases like Huntington's disease (Kegg:05016), Alzheimer's disease (Kegg:05010), Parkinson's disease (Kegg:05012) etc. were significantly enriched within validated targets of thermally altered miRNAs [15]. This result indicates that thermally altered miRNAs in response to heat shock regulate these processes and likely to participate in these diseases.

The link between HSF1 and cancer is manifold. Altered HSF1 expression is associated with many types of cancer [37, 38]. Furthermore HSF1 has been shown to promote tumorigenesis[39, 40]. A recent report revealed that HSF1 regulates a transcriptional program different from that of heat shock to support highly malignant human cancers [41].Therefore several attempts have been made to inhibit HSF1 as part of anticancer strategy [42, 43]. We speculate that thermally altered miRNAs might play crucial role in tumorigenesis by targeting genes involved in cancer pathogenesis. Intriguingly, three thermally induced miRNAs viz. hsa-miR-34a, hsa-miR-125b and hsa-miR-221 are known to target tumor suppressor protein TP53.

The beneficial effect of HSF1 in the context of pathogenesis associated with many protein folding diseases including Huntington's Disease[44], Alzheimer's Disease [45] and Parkinson's Disease [46] is evident. This is primarily due to the ability of HSF1 to simultaneously induce multiple heat shock proteins which act as molecular chaperones and facilitates disassembly of toxic inclusion bodies and/or its clearance by ubiquitin-proteasome system or autophagy. Significant enrichment of these pathways with the targets of thermally altered miRNAs strongly showed functional

overlapping of HSF1 and thermally altered miRNAs. Earlier report from our laboratory revealed that Huntingtin, the protein mutated in Huntington's Disease, is a target of miR-125b and miR-146a [47], both of which were later identified as thermally induced miRNAs [15]. Thus, we hypothesize that thermally altered miRNAs might contribute to the ameliorative activity of HSF1 by targeting key genes associated with these proteopathies.

In summary, our study uncovered a novel function of HSF1; its ability to regulate expression of miRNAs. Our findings also established hsa-miR-432 as the first miRNA identified as a downstream transcriptional target of HSF1. It is interesting to note that thermally altered miRNAs identified from our study are known to regulate many cellular events by targeting multiple genes. The functional overlapping between HSF1 and thermally altered miRNAs at the cellular and molecular levels indicates that thermally altered miRNAs might act as important downstream players of HSF1 and regulate biological processes like cellular stress response, development etc. It remains to be found out the common target genes of HSF1 and the miRNAs regulated by HSF1.

With the recent reports revealing ability of HSF1 to regulate expression of miRNAs [15, 18], it is gradually becoming apparent that HSF1-regulated miRNAs have great potential to act as key players of many cellular processes. The overlapping of functional role(s) of HSF1 and thermally induced miRNAs further strengthens the hypothesis that HSF1-regulated miRNAs might influence various biological events regulated by HSF1.

It was traditionally thought that transcriptional targets of HSF1 comprise of only coding genes, which code either classical chaperones or other non-classical heat shock proteins. However our present knowledge suggests the existence of another wing of HSF1 targets, the HSF1-regulated miRNAs, which together with other HSF1 targets regulate various biological processes under basal and/or stressed condition **(Figure 1)**. Our knowledge of HSF1-regulated miRNAs is still very rudimentary with a lot of unanswered questions. We hope that identification of other HSF1-regulated miRNAs will throw light on their precise role as downstream HSF1 targets in regulating different biological processes.

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