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Insight into the roles of long non-coding RNAs in ultraviolet-induced skin diseases

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Long non-coding RNAs (LncRNAs) comprise different types of RNA polymerase II-transcripted molecules, exhibit nucleotide lengths of greater than 200 nucleotides and do not undergo protein translation. Due to their characteristic feature of open reading frame, they have often been labelled as the "noise" of genomic transcription. Even though lncRNAs are widely transcribed genes, their expression level is lower than that of the protein-coding genes. Depending on their position relative to the protein-coding genes in the genome, lncRNAs are categorized as sense, antisense, bidirectional, intronic, and intergenic. Recently it has been shown that lncRNAs played important roles in both regulating cellular processes (cell differentiation and ontogeny) and disease development (pathogenic infection, immune destruction). Further, they have been implicated to be the hallmark of all cancers, the specific expression of lncRNA in tumor can be used to predict the prognosis and their stability in circulating body fluid (plasma and urine) provide a new basis for the development of cancer diagnosis and treatment. As lncRNAs act as a signal, decoy, guide, and scaffold molecule to regulate gene expression both transcriptionally and post-transcriptionally, elucidation of its function and the underlying regulatory mechanisms is of great significance for the advancement of life science research [Figure 1A].

lnc-CD1D-2:1 mediated the ultraviolet (UV) B-induced melanogenesis in primary melanocytes through the reactive oxygen species (ROS) pathway.[1] LncRNAs GS1-600G8.5 and RP13-631K18.2 up-regulation was induced by only UVA exposure[2] even after being irradiated with both UVA and UVB for three consecutive days. Knockdown of GS1-600G8.5, a crucial regulator of interleukin (IL)-8 resulted in decrease of the IL-8 mRNA expression and secretion. LincRNA-p21 is the major mediator of the UVB-induced, p53-dependent apoptosis in keratinocytes (KCs).[3] Further, expression of the lncRNA AC005779.1 had significantly increased in the UVB-irradiated KCs.[4] LncRNA HULC up-regulated BNIP3 to activate the Janus kinase/signal transducer and activator of transcription (1/3) pathway enhancing the UV-induced damage in HaCaT cells. These results provide promising targets for medical treatment.[5]

Metastasis-associated lung adenocarcinoma transcript 1 *(MALAT1)*, an important member of the lncRNAs family, is also known as the nuclear enriched autosomal transcript 2. UVB radiation showed increased expression of *MALAT1* lncRNAs in dermal fibroblasts leading to photoaging and senescence. However, as the UVB radiation did not change the expression level of *MALAT1* in KCs, it was concluded that *MALAT1* expression was dependent on the cell type undergoing UVB radiation. Further, *MALAT1* regulated the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway elements in a ROS independent manner to induce the UVB rays associated. Its role in cell migration was established by another group who showed that knockdown of *MALAT1* contributed to the reduction of cell migration in A375 cell lines (human melanoma cells).[6] Remarkably, *MALAT1* also interacted with the SP1 protein to promote the SP1-mediated transcriptional regulation of SP1 target genes in the lung adenocarcinoma cells.[7]

HOTAIR is the first lncRNA found to have a trans-acting effect. *HOTAIR* is widely involved in the regulation of malignant process such as proliferation, apoptosis, angiogenesis, invasion, and metastasis.[8]*HOTAIR* monitored epigenetic modification by the histone H3K27me3 and regulated Wnt inhibitory factor 1 and phosphatase and tensin homolog (PTEN), thereby affecting the Wnt, Akt signaling pathways. Another study showed that

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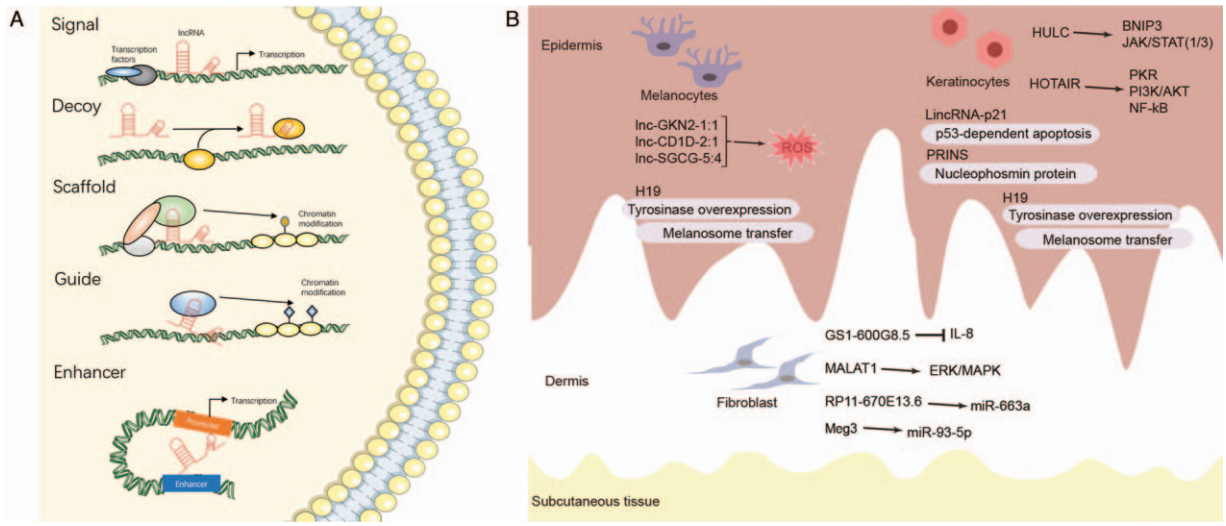

Figure 1: (A) Schematic diagram of the five archetypes of LncRNA mechanism. (B) Emerging roles for lncRNAs in UV-induced diseases. BNIP3: BCL2-interacting protein 3; ERK/MAPK: Extracellular signal-regulated kinase/mitogen-activated protein kinase; IL-8: Interleukin-8; JAK/STAT (1/3): Janus kinase/signal transducer and activator of transcription (1/3); LncRNA: Long non-coding RNA; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; NF-κB: Nuclear factor kappa-B; PI3K: Phosphatidylinositol 3-kinase; PKR: Protein kinase R; PRINS: Psoriasis associated RNA induced by stress.

HOTAIR (HOX transcript antisense RNA) knockdown inhibited the motility and invasiveness of A375 cells and reduced the degradation of the extracellular matrix.[9] Meanwhile, overexpression of *HOTAIR* upregulated the protein kinase R (PKR) expression to activate phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) and nuclear factor kappa-B (NF-κB) pathways in KCs (HaCaT cells). This promoted the UVB-induced apoptosis and inflammatory injury.[10] It has been shown that *HOTAIR* had higher expression levels in melanomas than those in non-tumor tissues.[11]

TINCR gene deficient epidermis lacks the terminal differentiation ultrastructure and exhibits keratohyalin granules intact lamellar bodies absence of normal keratin hyaluronan granule formation and 81.4% decrease in the epidermal tissue layer granules. Caspase, which maintains the function of the epidermal barrier by hydrolyzing proteins to promote apoptosis exhibits a decrease in its activity by 83.7% in the absence of *TINCR*. *TINCR* also played a key role in the suppression of tumor formation in squamous cell carcinoma.[12]

A balance between the anti-differentiation lncRNAs *(lncRNA-ANCR)* and *TINCR* levels is essential *in vivo* for the differentiation of epidermal cells. *ANCR* maintains progenitor cells in their original state, whereas *TINCR* does the opposite via up-regulation of the musculoaponeurotic fibrosarcoma (MAF): MAF oncogene homolog B factors to induce cell cycle arrest and terminal differentiation, respectively. Previously, it has been shown that the proliferation of melanocytes is strictly regulated by KCs. Up-regulation of *ANCR* and down-regulation of TINCR keeps the KCs undifferentiated. A balance between the levels of *ANCR* and *TINCR* can ensure the regulation of KC on melanocytes [Figure 1B].

Growth-arrested DNA damage-inducible gene 7 *(GADD7)*, a DNA damage-inducible lncRNA, has been shown to be involved in the cell-cycle regulation of the G1/S checkpoint via modulation of mRNA expression post-transcriptionally by altering mRNA stability. These results are in accordance with the previous study showing that overexpression of *GADD7* alone did not raise the level of cellular ROS or induce ER stress. Psoriasis associated RNA induced by stress linked to the nucleophosmin protein, played an important role in the cellular stress response in the skin. Further RP11-670E13.6 delayed cellular senescence in the UVB damaged human dermal fibroblasts through the p16-pRB pathway[13] and RP11-670E13.6 bound directly to miR663a to modulate the derepression of Cdk4 and Cdk6 via ceRNA mechanism.[14]

H19 is the first lncRNA discovered to be located in the human chromosome 11p15.5. It forms the H19/insulin-like growth factor 2 (IGF-2) imprinted gene group composed of IGF-2 and *H19*. Though, previously it has been shown that the *H19* knockdown in melanocytes did not contribute to tyrosinase overexpression, however, a recent study utilizing a mixed system involving *H19* siRNA transfected normal human KCs and non-transfected normal human melanocytes, showed overexpression of tyrosinase and promoted melanosome transfer. Furthermore, though, UV irradiation did not, estrogen treatment reversed this effect. Thus, *H19* might be related with the pathogenesis of melasma. Another study showed that in endothelial cells, an mtDNA-transcribed long-non-coding-RNA (ASncmtRNA-2) contributed to the establishment of replicative senescence via the cell cycle arrest in the G2/M phase. This mechanism may be related with hsa-miR-4485 and hsa-miR-1973.[15] Interestingly, the UV irradiation associated *TUG-1* promoted apoptosis acted through down-regulation of miR-421 expression via the caspase-3 axis in cataract to regulate lens epithelial cell apoptosis.[16]

In conclusion, lncRNAs have been shown to be superior disease biomarkers having important transcriptional and post-transcriptional regulatory role, vital to the

quasi-personalized treatment selection and improvement of outcome prediction process. They played an important role in regulation of different cellular processes and the development of diseases, such as cell differentiation, ontogeny, pathogenic infection, and immune destruction. They acted as a signal, decoy, guide, and scaffold molecule to regulate gene expression on transcriptional level and post-transcriptional level. Thus, elucidation of their function and regulatory mechanisms is of great significance to the life science research. However, the pathway, target, and regulatory mechanism of lncRNAs in UV-induced diseases have not yet been fully studied. Some, like the *lnc-CD1D-2:1* acted through the ROS pathway to induce melanogenesis in the primary melanocytes, while *MALAT1* contributed to the photo-aging process through the regulation of the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathway, in a ROS-independent manner. In addition, overexpression of the *HOTAIR* up-regulated the expression of PKR to activate the PI3K/AKT and NF-κB pathways in KCs, while *RP11-670E13.6* delayed cellular senescence in UVB damaged human dermal fibroblasts through the p16-pRB pathway. Further research to study the expression and regulation of lncRNAs will help us design better targeted therapies for the prevention and treatment of skin diseases. Moreover, as most of these studies have been conducted *in vitro*, they need to be verified *in vivo* both in mice and humans for clinical development of therapeutics. Perhaps the technology of lncRNA transfection *in vivo* is not mature or efficient in the field of skin. It is believed that in the near future, there will be more *in vivo* experimental verification, even clinical experimental verification.

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Conflicts of interest

None.

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