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LncRNAs in CONDBITs Perspectives, From Genetics towards Theranostics
(LncRNAs dalam Perspektif CONDBITs, Dari Genetik ke Theranostik)

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ABSTRACT

LncRNAs (Long noncoding RNAs) are novel group of ncRNAs and has been discovered to be pervasively transcripted in the genome, characterized as endogenous cellular RNAs consist of more than 200 nucleotides. They are ordered in view of function, transcript length, relation with protein-coding genes and other functional DNA elements, and subcellular localization. Theranostics is a novel study in medicine that combines specific targeted biomolecules based upon molecular-based test. As novel finding in the field of molecular medicine, lncRNA is indispensable tools in theranostics based medicine that allows specific targeting of molecular pathway for diagnostics and therapeutics. LncRNAs may execute as signals, decoys, guides, and scaffolds in their natural capacities. LncRNA expression is controlled by transcriptional and epigenetic factors and processes. LncRNAs also relate detracting biological programs. Here we reviewed lncRNAs in disorders/diseasest horoughly based on CONDBITs perspectives, i.e.: cardiology, oncology, neurology and neuroscience, dermatology, the biology of molecular and bioinformatics, immunology, and technologies (related with "-omics"; transcriptomics and "nano"; nanotechnology). It was narrated the lncRNA biomarkers that abundant in cardiovascular, neurodegenerative, dermatology, and immunology perspective. However, as cancer is the most widely studied disease, more biomarkers are available for this particular case. There are abundant cancer-associated lncRNAs. The most frequent learned lncRNA molecules in cancer are HOTAIR, MALAT1, LincRNA-p21, H19, GAS5, ANRIL, MEG3, XIST, HULC. LncRNAs in cancer diagnosis and monitoring, e.g.: H19 and AA174084 (gastric), HULC (hepatocellular), PCA3 (prostate). Prognostic lncRNAs, e.g.: HOTAIR and NKILA (breast), MEG3 (meningioma), NBAT-1 (neuroblastoma), SCHLAP1 (prostate). LncRNAs predicting therapeutic responsiveness, e.g.: CCAT1 (colorectal), HOTAIR (ovarian). Thus, it is concluded that the CONDBIT perspective is useful to describe the encouraging outlook of this transcriptomics-based medicinal approach.

Keywords: LncRNAs; CONDBITs perspectives; disease hallmarks; bioinformatics; theranostics

ABSTRAK

LncRNAs (Long noncoding RNAs) ialah kumpulan ncRNA yang novel dan banyak ditranskripsikan daripada genom serta dicirikan sebagai RNA endogen yang mengandungi lebih daripada 200 nukleotida dalam sel. Spesies RNA tersebut adalah terkawal dari segi fungsi, panjang transkrip, hubungan dengan gen yang mengekodkan protein dan unsur DNA lain yang berfungsi serta lokasi dalam bahagian subsel. Theranostik pula merupakan bidang kajian yang novel dalam perubatan yang menggabungkan biomolekul sasaran khusus berdasarkan ujian molekul. Sebagai penemuan baru dalam bidang perubatan molekul, lncRNA merupakan molekul sasaran dalam bidang perubatan theranostik yang membolehkan penemuan tapak jalan molekul yang spesifik untuk tujuan diagnostik dan terapeutik. LncRNAs dapat bertindak sebagai molekul isyarat, umpan, pandu dan perancah secara semula jadi. Pengekspresan LncRNA adalah di bawah kawalan tranksripsi dan faktor serta proses epigenetik. LncRNAs juga menghubungkaitkan program biologi. Di sini, kami mengulas kefungsian lncRNAs dalam penyakit kegagalan secara terperinci dari perspektif CONDBITs iaitu kardiologi, onkologi, neurologi and neurosains, dermatologi, biologi molekul and bioinformasi, imunologi, dan teknologi (berkenaan dengan "-omik"; transkriptomik dan "nano"; nanoteknologi). Penanda biologi lncRNA dilaporkan banyak terdapat dalam perspektif kardiovaskular, neurodegeneratif, dermatologi, and imunologi. Kanser sebagai penyakit yang telah banyak dikaji, semakin banyak penanda biologi telah ditemukan untuk penyakit ini. Terdapat banyak lncRNAs yang berkait rapat dengan kanser. Antara yang kerap dikaji adalah HOTAIR, MALAT1, LincRNA-p21, H19, GAS5, ANRIL, MEG3, XIST, HULC. LncRNAs yang banyak digunakan untuk diagnosis dan pengawasan kanser adalah seperti H19 and AA174084 (gastrik), HULC (hepatoselular), PCA3 (prostat). LncRNAs prognostik pula termasuk HOTAIR and NKILA (payu dara), MEG3 (meningioma), NBAT-1 (neuroblastoma), SCHLAP1 (prostat). LncRNAs yang digunakan untuk menjangka tindak balas terhadap rawatan adalah seperti CCAT1 (colorectal), HOTAIR (ovarian). Oleh itu, perspektif CONDBIT adalah sangat berguna untuk memerihalkan pendekatan yang berdasarkan transkriptomik.

Kata kunci: LncRNAs; perspektif CONDBITs; penanda penyakit; bioinformasi; theranostik

INTRODUCTION

LNCRNA ANNOTATION

LncRNAs (Long noncoding RNAs) are novel group of ncRNAs and has been discovered to be pervasively transcribed in the genome, characterized as endogenous cellular RNAs consist of more than 200 nucleotides (Mattick & Rinn 2015; Amaral & Mattick 2008). They have several general basic attributes, such as elective splicing, polyadenylation, low abundance, deficiency of protein product, and low sequence identity. They constitute a very heterogeneous group of RNA molecules that permits them to cover an expansive range of molecular-cellular functions by actualizing different modes of activity. They are ordered in view of function, transcript length, relation with protein-coding genes and other functional DNA elements, and subcellular localization.

LncRNAs may execute as signals, decoys, guides, and scaffolds in their natural capacities (Iwakiri, Hamada & Asai 2016). LncRNAs assume an imperative part in controlling gene expression at diversified levels, including chromatin alteration, transcriptional and posttranscriptional regulation, through multiple pathways that involve interplay with RNA binding proteins, subduing a major promoter of their aim gene, or performing as a co-activator of transcription factors (Sun et al. 2015). LncRNA expression is controlled by transcriptional and epigenetic factors and processes. LncRNAs also relate detracting biological programs (growth and development, the formation of cell identity, distribution of stress responses). There are 32,183 human annotated lncRNAs based on LNCipedia 2.0. Another study distinguished 6,736 lncRNA genes in the human genome (Devaux et al. 2015). In this end, lncRNA could be found on every manifestation of maladies in human. Moreover, the importance of lncRNA studies should be stated on every discussion on the molecular mechanism of the diseases. LncRNA is an indispensable aspect of theranostics-based therapy and diagnostics because it is only targeting specific molecular mechanism in the cell, in particular the transcriptomics pathway.

CARDIOVASCULAR PERSPECTIVE

LncRNAs have risen as critical regulators of cardiovascular development. LncRNAs control the differentiation of pluripotent stem cells and cardiac precursors into functional adult cardiac cells in the early phase of life. Afterward, they regulate cellular senescence and many pathways required in cardiovascular disorders (Devaux et al. 2015).

LncRNAs KCNQ1OT1 (class antisense, species human, chromosome 11) has important roles in arrhythmia and cardiac development(Korostowski, Sedlak, and Engel 2012; Bokil et al. 2010). LncRNAs Ak011347, Bvht, Fendrr (class intergenic, species mouse) have also the important role in cardiac development (Klattenhoff et al. 2013; J. G. Zhu et al. 2014; Grote et al. 2013).

Additionally, lncRNAs have an imperative part of heart development. A novel lncRNA Braveheart (AK143260) required for specification of the cardiac lineage in vitro. Depletion of lncRNA (AK143260) causes loss of beating cardiomyocytes during embryonic stem cell differentiation and an inability to initiate a network of genes specifying key cardiac transcription factors and myofibril assembly components. This lncRNA is needed for interceding the transition from mesoderm to multipotent cardiac progenitors (Schonrock, Harvey & Mattick 2012).

Another class of lncRNAs, i.e. SRA transcripts, have a critical capacity as coactivators of nuclear receptor signaling, muscle differentiation, and components of gene insulator complexes. It is also connected with dilated cardiomyopathy (Friedrichs et al. 2009). One of lncRNA, namely ALC-1 antisense, from class NAT (natural antisense transcript) has a vital role in the regulation of ALC-1. It has a noteworthy association while induced in hypertrophic ventricles (Ritter et al. 1999). Inhibition of MALAT1 in vivo by oligonucleotides diminished vascularization, indicating MALAT1 as an intriguing target to control angiogenic processes (Michalik et al. 2014).

Myocardial infarction associated transcript (MIAT) was identified as lncRNA which before 2006 also known as GOMAFU, AK028326, RNCR2. It is a non-coding RNA that has a pathobiological role in the cardiovascular system. MIAT dysregulation has a critical impact on the pathogenesis of MI and atherosclerosis, as well as another microvascular dysfunction, via enigmatic pathways (Yan et al. 2015; Liao et al. 2016; Vausort, Wagner & Devaux 2014).

HEART FAILURE

Long non-coding RNAs (lncRNAs) also play an important role in heart failure (El Azzouzi, Doevendans & Sluijter 2016). Some lncRNAs have been observed to be changed in the developing or diseased heart, several single nucleotide polymorphisms (SNP) in lncRNAs have appeared to be emphatically correlated with cardiovascular disease. For instance, SNPs in myocardial infarction associated transcript (MIAT) and antisense non-coding RNA in the INK4 locus (ANRIL) will forecast the increased risk of cardiovascular disease (Carlock et al. 1985; Ishii et al. 2006). In addition, lncRNA H19 was fundamentally upregulated in fizzling murine hearts, indicating a role for hypoxia-regulated lncRNA expression in heart failure (Lee et al. 2011; Yang et al. 2014). LncRNA MT-LIPCAR (human species, chromosome M) can predict survival in patients with heart failure (Kumarswamy et al. 2014).

Actually, lncRNA levels not only responded more sensitively to LVAD (left ventricular assist device) support but their expression profile permitted to recognize left ventricular samples from patients with ischemic and nonischemic heart failure before and after LVAD support (Consortium et al. 2013; Samani et al. 2007).

There are some LncRNAs with potential biomarker applications. CDKN2BAS1 (ANRIL) can be utilized as a risk factor biomarker for coronary artery disease and myocardial infarction. MIAT can be used as a risk factor biomarker for myocardial infarction (Ishii et al. 2006).

ONCOLOGY PERSPECTIVE

There are abundant lncRNAs associated with cancer, such as APL or acute promyelocytic leukemia (NEAT1), bladder cancer (GHET1, Linc-UBC1, H19, MALAT1, MEG3, SNHG16, TUG1, UCA1), breast cancer (ANRIL, BC040587, BCAR4, BCYRN1, DSCAM-AS1, GAS5, H19, HOTAIR, HOTAIRM1, IRAIN, LincRNA-BC4, LincRNA-BC5, Loc554202, LSINCT5, MALAT1, MEG3, MIR31HG, PINC, PVT1, SRA1, XIST, ZNFX1-AS1), cervical cancer (HOTAIR, GAS5), colorectal cancer (CASC2, CCAT1, CRNDE, GAS5, HULC, HOTAIR, KCNQ1OT, lncRNA-422, LincRNA-p21, Lnc-LET, MALAT1, NR_015441, NR_033374, R05532, SNGH16), endometrial carcinoma (CASC2, HOTAIR, MALAT1), epithelial squamous cell carcinoma or ESCC (Taurine-upregulated gene 1 or TUG1, lincPOU3F3), gallbladder cancer (lncRNA-LET), gastric cancer (LINC00152, GAPLINC, PVT1, HOTAIR, FENDRR, AC138128.1, BRAF-activated non-coding RNA or BANCR), glioma (HOTAIR, uc.283plus, lincPOU3F3), hepatocellular carcinoma (UFC1, MT1DP, lncRNA-LET), leukemia (ANRIL, DLEU1, DLEU2, MEG3, MIR155HG, TCL6, WT1-AS), melanoma (ANRIL, BANCR, C9orf14, SPRY4-IT1), multiple myeloma (MALAT1), non-Hodgkin lymphoma (BIC), NSCLC or non-small cell lung carcinoma (RP11385J1.2, TUBA4B, PVT1, HOTAIR, MALAT1, CARLo5), osteosarcoma (MALAT1, BC040587), ovarian cancer (HOST2), pancreatic cancer (BC008363, DAPK, HOTAIR, HULC, MALAT1, MAP3K14, PPP3CB, PVT1), prostate cancer (C20orf166AS1, CBR3-AS1, CTBP1-AS, ENSG00000261777, GAS5, H19, MALAT1, NEAT1, PCA3, PCAT1, PCGEM1, PRNCR1, PTENP1, RP11-267A15.1, ucRNAs, XIST), thyroid carcinoma/cancer (AK023948, BANCR, NAMA, PTCSC3) (Eis et al. 2005; Isin & Dalay 2015; R. Zhang et al. 2016).

There are a lot of new lncRNA transcripts dysregulated in ccRCC (clear cell renal cell carcinoma) that is benefit for novel diagnostic biomarkers. The expression of lncRNAs was successfully validated for upregulated or highly overexpressed in ccRCC (lnc-BMP2-2, lnc-CPN2-1, lnc-FZD1-2, lnc-ITPR2-3, lnc-SLC30A4-1, lnc-SPAM1-6), downregulated (lnc-ACACA-1, lnc-FOXG1-2, lnc-LCP2-2, lnc-RP3-368B9, lnc-TTC34-3), and unregulated (lnc-ERCC5-1, lnc-RP11-480I12.4.1-1) transcripts using qPCR. Another lncRNAs in ccRCC are MALAT1, SPRY4-IT1 (Gutschner & Diederichs 2012; Zhang et al. 2016; Blondeau et al. 2015).

Some lncRNAs are overexpressed or decreased in multiple human cancer. ANRIL (antisense non-coding RNA in the INK4 locus) is positively correlated with poor prognosis and considered as a risk factor in various types of human cancers, such as breast cancer, esophageal squamous cell carcinoma, gastric cancer, hepatocellular carcinoma, lung cancer, and ovarian cancer (Hua et al. 2015). BANCR (BRAF-activated non-coding RNA) is abundant in some types of human cancer, i.e. colorectal cancer, papillary thyroid carcinoma, malignant melanoma (Li et al. 2015). HOTAIR (HOX antisense intergenic RNA) is a key regulator of chromatin dynamics and gene regulation (Bhan & Mandal 2015). It appears to be disrupted in some cancers and diseases. It was downregulated in ependymomas and aortic valve calcification. It was upregulated in various carcinomas i.e. ATRTs (atypical teratoid rhabdoid tumors) such as medulloblastomas, and juvenile pilocytic astrocytomas. Breast cancer, cervical tumors/cancers, colorectal carcinomas, endometrial tumors/carcinomas, esophageal squamous cell carcinoma (ESCC), gall bladder cancers, gastric cancers, gastrointestinal stromal tumors/cancers, gliomas, hepatocellular carcinoma, laryngeal squamous cell cancer, melanoma, nasopharyngeal carcinoma, nonfunctional pituitary adenoma, non-small cell lung cancer, prostate cancer, ovarian cancers, pancreatic tumors/cancers, renal carcinomas, sarcoma, small cell lung cancer, Ta/T1 bladder cancer, urothelial carcinoma, also upregulated in osteoarthritis and pre-eclampsia (Hua et al. 2015; Qiu et al. 2015; Bhan & Mandal 2015; Hajjari & Salavaty 2015; Huang et al. 2014; Li et al. 2015). Some of lncRNAs are elucidated in Table 1 below.

NEURODEGENERATIVE PERSPECTIVE

There are a lot of long ncRNAs involved in neurological disorders. They are ANRIL, BDNF-AS, ncRNA-a, Evf-2, HTTAS_v1, SCAANT1, 116HG, ATXN8OS, 17A, Gomafu, BACE1-AS, BC200, Antisense Uchl1, HAR1F, HAR1R, etc. ANRIL which do regulate transcription has INK4b/ARF/INK4a locus as a target and associated with neural system tumors. Long ncRNAs that regulating transcription are BDNF-AS, ncRNA-a, Evf-2, HTTAS_v1, SCAANT1, 116HG. Long ncRNAs that regulating mRNA processing are ATXN8OS, 17A, Gomafu. Long ncRNAs that regulating translation are BC200 and antisense Uchl1. BACE1-AS regulates mRNA stability and has an important role in pathophysiologic of Alzheimer's disease (AD). The other lncRNAs that involved in AD are 17A and BC200. ncRNA-a involved in Opitz–Kaveggia syndrome. Evf-2 that has Dlx5/6 as its target may have roles in many neurological disorders, such as autism, epilepsy, Rett-syndrome, schizophrenia, etc. SCAANT1 has Ataxin 7 as a target and involved in Spinocerebellar ataxia 7. ATXN8OS has MBLN1 as the target and involved in Spinocerebellar ataxia 8. 116HG upregulates many genes as the target and involved in Prader–Willi syndrome. Gomafu has DISC1 and ERBB4 as targets and involved in schizophrenia, mainly associated with behavioral abnormalities. Antisense

TABLE 1. Some cancer associated LncRNAs

No.	LncRNA	Type of Cancer	References
1.	ANRIL (antisense non-coding RNA in the INK4 locus) DD3/PCA3	basal cell carcinoma, bladder cancer, melanomas, neurofibromas	(Cunnington et al. 2010; Zhu et al. 2015; Stacey et al. 2009; Pasmant et al. 2011)
2.	DD3/PCA3	Prostate cancer	(Bussemakers et al. 1999; Durand et al. 2012; Ploussard et al. 2011)
3.	GAS5 (growth arrest-specific transcript 5)	Renal cell carcinoma (RCC)	(Qiao et al. 2013)
4.	H19	Kidney cancer	(Frevel et al. 1999)
5.	HIF-1alpha-AS1 and AS2	Kidney cancer	(Thrash-Bingham & Tartof 1999; Bertozzi et al. 2011)
6.	HOTAIR	Several cancer; i.e.: breast, colon, liver, and pancreas	(Gupta et al. 2010; Kogo et al. 2011; Geng et al. 2011; Kim et al. 2013)
7.	HULC (highly upregulated in liver cancer)	Hepatocellular carcinoma	(Panzitt et al. 2007)
8.	LncTCF7	Liver CSCs (Cancer Stem Cells)	(Wang et al. 2015)
9.	MALAT-1	Small cell lung cancer	(Gutschner et al. 2013)
10.	MEG3 (GTL1)	Renal cell carcinoma (RCC)	(Kawakami et al. 2006)

Uchl1 has UCHL1 as its target and involved in Parkinson's disease (PD). There are minimally eight known lncRNAs that were observed to change significantly in the brains of Huntington's disease (HD) patients: TUG1 and NEAT1 are upregulated, MEG3 and DGCR5 are downregulated, while HTTAS_v1 and BDNF-AS are transcriptionally regulated.

Another lncRNAs involved in Person with HD are HAR1F and HAR1R (Vučićević, Schrewe & Orom 2014; Pollard et al. 2006).

Herein the Table 2 some of specific long ncRNAs as hallmarks in many neurological problems and neurodegenerative diseases and disorders.

TABLE 2. Specific lncRNA in neurological problem

No.	Diseases / disorders	LncRNA	References
1.	Alzheimer's disease (AD)	beta-site amyloid precursor protein cleaving enzyme-1 antisense transcript (BACE1-AS)	(Luo & Chen 2016; Decourt & Sabbagh 2011; Evin & Hince 2013; Faghihi et al. 2008)
2.	Alzheimer's disease (AD)	51A	(Ciarlo et al. 2013; Ma et al. 2009)
3.	Alzheimer's disease (AD)	17A	(Wan, Su & Zhuo 2017; Massone et al. 2011)
4.	Alzheimer's disease (AD)	neuroblastoma differentiation marker 29 (NDM29)	(Massone et al. 2012)
5.	Alzheimer's disease (AD)	BC200 (brain cytoplasmic 200 RNA)	(Mus, Hof & Tiedge 2007)
6.	Alzheimer's disease (AD)	brain cytoplasmic (BC) RNA BCYRN1	(Mus, Hof & Tiedge 2007; Lukiw et al. 1992)
7.	Alzheimer's disease (AD)	NAT-Rad18	(Zlatanou et al. 2016; Parenti et al. 2007)
8.	Amyotrophic lateral sclerosis (ALS)	AS C9ORF72 (chromosome 9 ORF 72)	(Renton et al. 2011; Zu et al. 2013; Lagier-Tourenne et al. 2013)
9.	Autistic spectrum disorder (ASD)	MSNP1AS (moesin pseudogene 1, antisense)	(Wilkinson & Campbell 2013; Kerin et al. 2012)
10.	Glioblastoma (GBM)	There are 104 matched lncRNA-mRNA pairs for 91 differentially expressed lncRNAs In the GBM group, 654 lncRNAs were downregulated and 654 were upregulated	(Han et al. 2012)
11.	Huntington's disease (HD)	MEG3	(Zhao et al. 2010)
12.	Huntington's disease (HD)	TUG1	(Khalil et al. 2009)
13.	Huntington's disease (HD)	NEAT1 (Nuclear enriched abundant transcript)	(Johnson 2012)
14.	Parkinson's disease (PD)	PINK1-AS (phosphatase and tensin homologue–induced kinase 1)	(Scheele et al. 2007)
15.	Parkinson's disease (PD)	AS Uchl1	(Carrieri et al. 2015)
16.	Spinocerebellar Ataxia	ATXN8OS	(Chen et al. 2008)
17.	Spinocerebellar Ataxia	ATXN7L3B	(Munhoz et al. 2009)

DERMATOLOGY PERSPECTIVES

Long noncoding RNA has promising impacts and roles in dermatology problems, including melanoma, psoriasis, keratinization, and Cutaneous Squamous Cell Carcinoma (cSCC). Herein we decipher them concisely.

MELANOMA

The lncRNA SPRIGHTLY (also known as SPRY4-IT1) is upregulated in human melanoma cells. It lies within the intronic region of SPRY4 gene. SPRIGHTLY is transcribed from the first intron of SPRY4 (Sprouty 4 gene). In human melanoma cells, it is highly upregulated. In normal human melanocytes, it is ectopically expressed at low levels. It contributes to the regulation of DNA damage response, chromosome organization, cell proliferation, cell cycle, and apoptosis in melanocytes. It also regulates proliferation, motility, and apoptosis that constitute cancer hallmarks. Together with its target genes, SPRIGHTLY has an impact in melanocyte dedifferentiation and their transformation into melanomas. It has a lot of important roles in multiple regulatory pathways in melanomas. Its dysfunction in melanoma cells prohibits cell growth, differentiation, and induced apoptosis (Khaitan et al. 2011; Zhao et al. 2016; Mazar et al. 2010, 2014).

Long noncoding RNAs involved in the synthesis of melanin. LncRNA-H19 has an important role in the formation of melasma. Irradiation of melanocytes with 20 mJ/cm^2 UVB changed expression 807 lncRNAs more than two-fold using Agilent lncRNA chip expression profile detection technology. LncRNAs involve in the UVB-induced stress response. Some lncRNAs expression alterations triggered by UVB are dependent on ROS generation. ROS-mediated production of lnc-CD1D-2:1 participated in the UVB-induced melanogenesis. MAPK signaling pathway was engaged in the melanogenesis, therefore p38, ERK, and JNK phosphorylation levels were observed. The UVB-induced alterations in lncRNAs involve in the etiopathogenesis of melanoma. LncRNAUCA1 was engaged in H2O2-induced cell apoptosis, signifying relationship between ROS and lncRNAs (Kim, Lee & Lee 2010; Kim et al. 2014; Peng et al. 2014; Liu et al. 2015; Zeng et al. 2016).

Targeting a lncRNA in vivo is a potentially putative therapeutic choice, such as SAMMSON (previously known as LINC01212). SAMMSON lncRNA plays important roles in melanoma development. It is arranged by an alternative SOX factor such as SOX9, understood as a key antagonistic role to SOX10 in melanoma. It is detectable in melanocytes or non-invasive vertical growth phase melanomas, in invasive vertical growth phase melanoma, and in migratory melanoblasts (Shakhova et al. 2015; Goding 2016; Leucci et al. 2016; Hoek & Goding 2010).

SAMMSON confers a growth advantage on melanoma cells. Targeting SAMMSON for degradation reduced clonogenicity, irrespective of BRAF, NRAS, or p53 status, including in cell lines exhibiting BRAF inhibitor resistance, but did not affect melanocytes, highlighting the ''addiction'' of melanomas to SAMMSON expression. It also reduced viability/growth of invasive melanoma cells, known to exhibit increased resistance to MAPK therapeutics. Importantly, ectopic expression of SAMMSON in melanoma cells conferred a growth advantage, indicating that SAMMSON acts in trans, an observation consistent with the lack of effect on MITF expression following SAMMSON knockdown (Shakhova et al. 2015; Goding 2016; Leucci et al. 2016; Hoek & Goding 2010) .

Deciphering SAMMSON lncRNA biogenesis, we can understand how the MITF amplicon impacts melanoma proliferation. MITF (microphthalmia-associated transcription factor) is a microenvironmental hallmark of melanoma. It is required for melanoblast survival while development, melanocyte differentiation, suppresses invasion, promotes proliferation, and drives "phenotype switching" which props melanoma development (Shakhova et al. 2015; Goding 2016; Leucci et al. 2016; Hoek & Goding 2010).

The SAMMSON lncRNA gene is co-amplified with MITF in melanoma. SAMMSON-p32 complex is needed for correct mitochondrial biogenesis. Depletion of SAMMSON leads to stress connected accumulation of mitochondrial peptide precursors, mitochondrial import defects, and p53-independent apoptosis. BRAF inhibitors (BRAFi) boost dependency on mitochondrial oxidative phosphorylation and collaborate with SAMMSON inhibition (Shakhova et al. 2015; Goding 2016; Leucci et al. 2016; Hoek & Goding 2010).

PSORIASIS

There are 971 lncRNAs were statistically significant expressed in psoriasis patients, which whom 399 were underexpressed whereas 572 were overexpressed. Some of them show decreased expression in psoriasis person, such as LOC285194, Car Intergenic 10, ST7OT. Of overexpressed 572 lncRNAs, CARD14 lncRNA was significantly overexpressed. Mutations in CARD14 genes are related to susceptibility to psoriasis (Gupta et al. 2016).

KERATINIZATION

Long ncRNAs was performed by transcriptome sequencing of keratinocytes. The keratinocytes sampled were derived from palmar and forearm skin. This research had been identified 125 candidate lncRNAs which is involved in keratinization (Nomura 2016).

CUTANEOUS SQUAMOUS CELL CARCINOMA

PICSAR is lncRNA that has an important role in Cutaneous Squamous Cell Carcinoma (cSCC) progression. LncRNA PICSAR is overexpressed in cSCC cells, both in vivo and in culture. It regulates both proliferation and migration of cSCC cells and growth of cSCCs cells in vivo. It increases the activity of ERK1/2 pathway through inhibition of MAPK phosphatase DUSP6. PICSAR is a putative biomarker and futuristic therapeutic target in cSCC management (Piipponen et al. 2016).

IMMUNOLOGY PERSPECTIVE

Long noncoding RNAs (lncRNAs) have been appeared to assume imperative parts in immune cells responses and developments via various mechanisms. They have been observed to control transcriptional or post-transcriptional regulation of innate and adaptive immune responses through novel methods for blending with RNA and DNA or protein-protein interactions (Zhang & Cao 2016).

Some lncRNAs are involved in immune cell development processes, such as immune cell activation, differentiation, proliferation. They are NRON, lnc-DC, NTT, GAS5, HOTAIRM1, etc (Zhang & Cao 2016).

LncRNAs control the innate immune responses. Numerous lncRNAs that have been connected to innate immunity have been found by RNA-Seq studies and microarray, i.e.: Lethe, NEAT1, NKILA, PACER, and THRIL (Table 3), that represent the magnificent patterns of lncRNAs that are ensnared in regulating immune cells functions and immune genes expressions (Guttman et al. 2009; Carpenter & Fitzgerald 2015; Imamura & Akimitsu 2014; Li & Rana 2014).

TABLE 3. The roles of lncRNAs in innate immune responses

No.	lncRNA	References
1.	Lethe	(Zgheib et al. 2017; Rapicavoli et al. 2013)
2.	NEAT1	(Imamura et al. 2014; Hirose et al. 2014)
3.	NKILA (NF-KappaB interacting lncRNA)	(Huang et al. 2016)
4.	PACER (p50-associated COX-2 extragenic RNA)	(Krawczyk & Emerson 2014; Cui et al. 2014; Qian et al. 2016)
5.	THRIL (linc1992)	(Szmyrka-Kaczmarek et al. 2014; Li et al. 2014)

AUTOIMMUNE DISEASES AND LNCRNA

Autoimmune diseases are complicated and enigmatic diseases resulting from the interaction between genetics, epigenetics, and environmental factors (Wu et al. 2015). LncRNAs dysregulation regulate certain mechanisms in autoimmune diseases, including PRINS (10p12.1) arranges G1P3 to maintain the keratinocyte hyperproliferation in psoriasis (Szegedi et al. 2012, 2010). Dysregulation of lncRNAs influences various autoimmune diseases. For further explanation, we elucidate in the Table 4 herein.

TABLE 4. Autoimmune diseases and lncRNA Narration

No.	Diseases	References
1.	Psoriasis Vulgaris (PV)	(Szegedi et al. 2012, 2010; Sonkoly et al. 2005; Bari et al. 2011; Chang et al. 2006; Holm et al. 2005)
2.	Systemic lupus erythematosus (SLE)	(Cope & Feldmann 2004; Chatenoud 2006; Shi et al. 2014; Giles, Nycz & Boackle 2016)
3.	Rheumatoid arthritis (RA)	(Song et al. 2014; Messemaker et al. 2016; Lu et al. 2016)

TECHNOLOGY PERSPECTIVES

The genome annotation technology is necessary to provide database management for transcriptomics data (Parikesit et al. 2014). In this respect, the gene prediction pipeline is important to annotate the missing information in the genomes (Goel, Singh & Aseri 2013). This pipeline is especially crucial in annotating the transcriptomics data that still currently lacking information. Problem arises, as the generated data will be grown exponentially, in the scale of petabytes. Thus, the data mining method for big data storage is very feasible to be applied on daily basis in order to extract for definite transcriptomics pattern (Ranganathan et al. 2011). This hunt for information could only be

resolved with the complete mastery of bioinformatics science (Liew, Yan & Yang 2005). Herewith, as more sophisticated pattern recognition methods are in place, the jobs for extracting meaningful transcriptomics fingerprint will become more feasible (da Sacco, Baldassarre & Masotti 2012).

BIOINFORMATICS RESOURCES

Several websites-based bioinformatics resources are available to researchers for lncRNA research. They contain multiple repositories, databases, softwares, and other annotation tools. Bioinformatics databases that based on websites is revealed through this Table 5.

All databases that provide information about lncRNAs can identify human. Some of them include specific information towards rat (lncRNAdb, DIANA-lncBase, Functional lncRNA Database, Noncode v3.0, CHIPBase), also specific towards another model organisms (lncRNAdb, CHIPBase, Functional lncRNA Database, and DIANA-lncBase). Especially, lncRNAdb and Noncode v3.0 databases include lncRNAs that express in some species, from yeasts to plants. This databases offer information about specific characterization of lncRNAs cells or tissues: lncRNAdb, lncRNome, CHIPBase, Noncode v3.0, and DIANALncBase. Only Noncode v3.0 and lncRNAdb localize lncRNAs cellular (Fritah, Niclou & Azuaje 2014).

There are different bioinformatics tools for predicting the functions and structures of RNA sequences, including some tools that concatenate other experimental data in the analysis. Moreover, remembering that the recent experimental exploratory methods are still restricted in their throughput and output, quick bioinformatics tools to recognize and characterize lncRNAs with reasonable preciseness are needed (Iwakiri, Hamada & Asai 2016).

Below we evince the available bioinformatics databases and tools which beneficial for discovering long non-coding RNAs and analyzing their secondary structures, conservation, interactions, co-expressions, and subcellular localization through Table 6.

SUMMARY

We have expounded multiperspectives of lncRNAs comprehensively based on CONDBITs perspectives, i.e.: cardiology, oncology, neurology and neuroscience, dermatology, the biology of molecular and bioinformatics, immunology, and technologies. The CONDBITs perspectives could be seen in the Table 7 below.

ACKNOWLEDGEMENT

TABLE 5. The database for lncRNA research (Based on our exploration)

No.	Database	Website
1.	CHIPBase	deepbase.sysu.edu.cn/chipbase
2.	DIANA-LncBase	diana.imis.athena-innovation.gr
3.	fRNAdb	www.Ncrna.org/frnadb
4.	Human Body Map lincRNAs	www.Broadinstitute.org/genome bio/human lincrnas
5.	LNCipedia	www.lncipedia.org
6.	lncRNAdb	www.lncrnadb.org
7.	lncRNAdb Expert Database	http://rnacentral.org/expert-database/lncrnadb
8.	lncRNADisease	cmbi.bjmu.edu.cn/lncrnadisease
9.	LncRNADisease database	http://www.cuilab.cn/lncrnadisease
10.	lncRNome	genome.igib.res.in/lncRNome
11.	lncRNAtor	http://lncrnator.ewha.ac.kr/index.htm
12.	Noncode v3.0	noncode.org/NONCODERv3
13.	the Functional lncRNA Database	www.valadkhanlab.org
14.	UCSC	genome.ucsc.edu

TABLE 6. The explanation on bioinformatics database

No.	Bioinformatics Databases/Tools	References
1.	NGS (next-generation sequencing) technologies or tiling microarrays	(Iwakiri, Hamada & Asai 2016)
2.	LAST, Tophat, STAR	(Kim et al. 2013; Kiełbasa et al. 2011; Dobin et al. 2013)
3.	BLASTX	(Gish & States 1993)
4.	PORTRAIT, CPC (Cording-Potential Calculator)	(Kong et al. 2007; Wang et al. 2013)
5.	RNAcode, PhyloCSF	(Washietl et al. 2011; Lin, Jungreis & Kellis 2011)
6.	QRNA, RNAz	(Rivas & Eddy 2001; Gruber et al. 2010)
7.	Expression Atlas	(Petryszak et al. 2014; Uhlén et al. 2015; Klijn et al. 2015)
8.	ROKU	(Kadota et al. 2006)
9.	ENCODE project	(Djebali et al. 2012)
10.	HITS-CLIP, PAR-CLIP, RAP-RNA, RIA-seq	(Licatalosi et al. 2008; Hafner et al. 2010; Engreitz et al. 2014; Kretz et al. 2013)
11.	IntaRNA	(Busch, Richter & Backofen 2008)
12.	CopraRNA	(Wright et al. 2013)
13.	A computational pipeline including multiple computational sequence analysis devices (IntaRNA, LAST, RactIP, Raccess, and TanTan)	(Frith, Hamada & Horton 2010; Kato et al. 2010; Kiryu et al. 2011; Frith 2011)
14.	RPI-Pred	(Suresh et al. 2015)
15.	catRAPID, RPI-seq, lncPRO	(Bellucci et al. 2011; Muppirala, Honavar & Dobbs 2011; Lu et al. 2013)
16.	Machine learning approaches, e.g.: support vector machine (SVM), Fisher's LDA (linear discriminant analysis), SVM (support vector machine), and RF (random forest)	(Pancaldi & Bähler 2011)
17.	Mfold, CentroidFold, RNAfold, and RNAstructure	(Sato et al. 2009; Hamada, Kiryu, et al. 2009; Zuker 2003; Lorenz et al. 2011; Mathews 2014b, 2014a)
18.	CentroidHomfold	(Hamada et al. 2011)
19.	DMS-seq, FragSeq, MAP-seq, Mod-seq, PARS, SHAPE-seq	(Rouskin et al. 2014; Ding et al. 2014; Underwood et al. 2010; Seetin et al. 2014; Talkish et al. 2014; Y. Wan et al. 2014; Loughrey et al. 2014)
20.	RNAalifold and Centroid Alifold	(Bernhart et al. 2008; Hamada, Sato & Asai 2011; Hamada 2015)
21.	ProbCons	(Do et al. 2005)
22.	CentroidAlign, LARA, LocARNA, MAFFT, MXSCARNA	(Hamada, Sato, et al. 2009; Bauer, Klau & Reinert 2007; Will et al. 2012; Katoh & Toh 2008; Tabei et al. 2008)
23.	PETcofold	(Seemann et al. 2011)
24.	Raccess	(Kiryu et al. 2011)
25.	Rchange	(Kiryu & Asai 2012)
26.	MEMERIS and RNAcontext	(Hiller et al. 2006; Kazan et al. 2010)
27.	PLEK (predictor of long non-coding RNAs and messenger RNAs based on an improved k-mer scheme)	(Zhang & Zhou 2014)

TABLE 7. The CONDBITs perspectives of lncRNAs

Abbreviation		Narration
C	:	KCNQ1OT1 has important roles in arrhythmia and cardiac development. MIAT dysregulation has a critical impact on the pathogenesis of myocardial infarction (MI) and atherosclerosis. MT-LIPCAR can predict survival in patients with heart failure. CDKN2B-AS1 (ANRIL) can be used as a risk factor biomarker for coronary artery disease and MI.
O	:	There are abundant lncRNAs associated with cancer, i.e.: breast cancer (ANRIL, BC040587, BCAR4, BCYRN1, DSCAM-AS1, GAS5, H19, HOTAIR, HOTAIRM1, IRAIN, LincRNA-BC4, LincRNA-BC5, Loc554202, LSINCT5, MALAT1, MEG3, MIR31HG, PINC, PVT1, SRA1, XIST, ZNFX1-AS1), cervical cancer (HOTAIR, GAS5), prostate cancer (C20orf166-AS1, CBR3-AS1, CTBP1-AS, ENSG00000261777, GAS5, H19, MALAT1, NEAT1, PCA3, PCAT1, PCGEM1, PRNCR1, PTENP1, RP11-267A15.1, ucRNAs, XIST). ANRIL correlated with poor prognosis and considered as a risk factor in various types of human cancers, such as breast cancer, esophageal squamous cell carcinoma, gastric cancer, hepatocellular carcinoma, lung cancer, ovarian cancer.
N	:	BACE1-AS concentrations were increased in patients with Alzheimer's disease.
D	:	SAMMSON lncRNA plays important roles in melanoma development. Some of LncRNAs show decreased expression in psoriasis person, such as LOC285194, Car Intergenic 10, ST7OT. Of overexpressed 572 lncRNAs, CARD14 lncRNA was significantly overexpressed.
B	:	NONCODE 2016 (www.noncode.org) contains 527,336 lncRNA transcripts from literature and public databases. NGS technologies or tiling microarrays to observe the fragments of the transcribed units of the lncRNA sequences.
I	:	NEAT1 has response to TLRs stimulus. Useful for formation of nuclear body paraspeckles. PRINS is overexpressed in PV. Several LncRNAs, i.e.: anti-NOS2A, Hotair, MEG9, LUST, TUG1, NEAT1 and SNHG4 were upregulated, whereas PRINS, PR antisense transcripts, mascRNA, and HOXA3as were downregulated in rheumatoid arthritis.
T	:	Synergy-omics based technologies in lncRNAs researches in the future potentially make them as powerful biomarker and theranostics on certain diseases and disorders.

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