DOWNLOAD PDF NON-CODING RNAS IN HUMAN DISEASE

Chapter 1 : Non-coding RNA Research - Journal - KeAi

The most well-studied sequences in the human genome are those of protein-coding genes. However, the coding exons of these genes account for only % of the.

Open in a separate window 3. From these studies, a large amount of disease-associated SNPs are found to be mapped to non-coding genomic regions. While some of these SNPs could be associated with enhancers, it would not be surprising that many others are associated with lncRNAs. The MIAT transcript is approximately 10 kb in length and has five exons. In contrast to the non-risk allele, the risk allele has more intense binding of nuclear protein s. Expression studies have confirmed that ANRIL is expressed in multiple atherosclerosis-related cell lines, including vascular endothelial cell, monocyte-derived macrophages and coronary smooth muscle cells [64 ,]. LncRNAs in Autoimmune Diseases Long non-coding RNAs may also function in the regulation of downstream protein-coding genes, thus forming a complicated mutual regulation network with both coding and non-coding genes [,]. Recent studies have shown that autoimmune diseases, which result from an inappropriate immune response of the body against substances and tissues normally present in the body, have a complex genetic context that involves multiple protein-coding and non-coding genes. For example, in association study of affected individuals and controls, Shirasawa et al. The RNA expression level of PRINS is decreased in the uninvolved psoriatic, but not healthy, epidermis with treatment of T-lymphokines that are known to precipitate psoriatic symptoms. Previous transcriptome studies have shown a number of lncRNAs in the mammalian brain, and most of them exhibit particular expression profiles within specific neuroanatomical regions, cell types, or subcellular compartments, implicating that lncRNAs probably have a significant impact on neurological regulation [ ]. In vitro studies of FMR4 have shown that it may function to prevent neurons or their progenitors from apoptosis during the progress of development in human. Dysregulation of these delicate interactions may result in various neurological disorders [69 , 79]. SCA8 is an autosomal dominant disorder caused by repeat expansion [ ]. Two bidirectionally transcribed genes are located within the SCA8 expansion region: AD is a form of dementia, which is believed to be caused by the formation of amyloid plaques in neurons [ ]. In AD patients, the level of BC becomes upregulated. The increased expression of BC was found to be correlated with the severity of AD [74]. In addition, studies of BC1, the mouse functional homolog of BC, have shown that BC1 knockout mice exhibit behavioral changes, thus demonstrating an important role for BC1 in brain function [ ]. All these results suggest that dysregulation of BC may contribute to AD susceptibility. LncRNAs in Cancers Cancer is a broad group of various diseases in which abnormal cells divide uncontrollably and tend to invade other tissues. Up to now, although hundreds of oncogenes and tumor suppressor genes have been identified, the exact cause of most cancers remains unknown or poorly understood. In recent years, researchers have increasingly come to recognize lncRNAs as major mediators in cancer pathogenesis [ ]. Thus far, no concrete evidence has surfaced to indicate any lncRNAs as causal factors in cancer. Here, we discuss some examples of such lncRNAs. Like protein-coding oncogenes, some lncRNAs can promote cell proliferation and induce tumorigenesis. Metastasis-associated lung adenocarcinoma transcript 1 MALAT-1 , which correlates with high metastasis and poor prognosis in non-small-cell lung cancer, is an abundant 8. MALAT-1 is broadly expressed in normal human tissues and is found to be upregulated in many solid tumors, such as lung, breast, prostate, liver, and colon tumors [91 , 92 ,]. MALAT-1 is believed to play a vital role in cell proliferation, migration, and invasion. By interacting with serine-arginine-rich splicing factor SR , which is responsible for alternative splicing AS in a concentration- and phosphorylation-dependent manner, studies have shown that MALAT-1 can modulate the phosphorylation of SR proteins and thus regulate AS of selective pre-mRNAs [ ]. MALAT1 is also involved in the regulation of cell mobility. RNAi-mediated silencing of MALAT1 impaired the in vitro migration of lung adenocarcinoma cells and reduced cell proliferation and invasive potential in a cervical cancer cell line [92]. Studies have shown that HOTAIR is overexpressed in breast tumors, hepatocellular carcinoma, and colorectal cancer [â€”]. Recent studies revealed that HOTAIR is likely to work as a molecular scaffold to bind two distinct histone modification complexes, the Polycomb repressor complex 2

PRC2 and the histone demethylase LSD1, facilitating their genome-wide retargeting to specific regions for coupled histone H3K27 methylation and H3K4 demethylation [ ]. These observations indicate that dysregulation of HOTAIR may reprogram the epigenetic information to promote tumor cell invasion and subsequent metastasis. Long non-coding RNAs can also act as tumor suppressor genes. One example is maternally expressed gene 3 MEG3 , a maternally imprinted RNA gene of approximately nucleotides [94]. Studies have revealed that MEG3 is expressed in many normal tissues, but not in the majority of human meningiomas or human meningioma cell lines [ ]. Moreover, ectopic expression of MEG3 was found to suppress the growth of several human cancer cell lines, further supporting the effect of MEG3 on tumor suppression [95]. MEG3 was found to be a positive regulator of p53, a tumor suppressor protein [ ]. In cells that are transfected with MEG3, p53 protein level increases significantly, which results in dramatically stimulating the transcription of pdependent genes from a presponsive promoter. Studies have shown that MEG3 is also capable of inhibiting cell proliferation in the absence of p53 [ ]. These data suggest that MEG3 can function as a tumor suppressor through both pdependent and pindependent pathways. MEG3 has a total of twelve isoforms from alternative splicing, all of which contain three distinct secondary folding motifs M1, M2, and M3. Deletion analysis indicates that motifs M2 and M3 are important for p53 activation. Furthermore, a hybrid MEG3 RNA, which contains a piece of unrelated sequence, but preserves the original secondary structure, retained the functions of both p53 activation and growth suppression [ ]. As a regulatory lncRNA, all of these experiments demonstrated that the proper conformation of MEG3 is critical to its biological functions. Conclusions Long non-coding RNAs are rapidly becoming a focal point for intensified research in the biological and medical sciences. Increasing evidence has indicated that lncRNAs play important roles in various critical biological processes and that they add a new layer of complexity to already complex human diseases. We believe that the further functional and mechanistic studies of these versatile macromolecules will expand our understanding of general principles in biological systems and provide new approaches to the diagnosis and treatment of complex human diseases. Conflicts of Interest The authors declare no conflict of interest. An integrated encyclopedia of DNA elements in the human genome. Initial sequencing and analysis of the human genome. An integrated knowledge database of non-coding RNAs. The transcriptional landscape of the mammalian genome. Characterization of the pirna complex from rat testes. Functional surprises from the RNA world. Large-scale prediction of long non-coding RNA functions in a coding-non-coding gene co-expression network. Integrative annotation of long noncoding RNAs. Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Structure and function of long noncoding RNAs in epigenetic regulation. Molecular mechanisms of long noncoding RNAs. Transcription of antisense RNA leading to gene silencing and methylation as a novel cause of human genetic disease. Long noncoding intronic RNAs are differentially expressed in primary and metastatic pancreatic cancer. X inactivation and the complexities of silencing a sex chromosome. Long non-coding RNA hotair reprograms chromatin state to promote cancer metastasis. Past, present, and future. Evolution and functions of long noncoding RNAs. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. LincRNAs act in the circuitry controlling pluripotency and differentiation. Long intronic noncoding RNA transcription: Expression noise or expression choice? A natural sense-antisense transcripts database. Antisense transcription in the mammalian transcriptome. Antisense transcripts in the human genome. RNA exosome depletion reveals transcription upstream of active human promoters. Cell stress and translational inhibitors transiently increase the abundance of mammalian sine transcripts. A coding-independent function of gene and pseudogene mRNAs regulates tumour biology. The rosetta stone of a hidden RNA language? Ultraconserved regions encoding ncRNAs are altered in human leukemias and carcinomas. Widespread transcription at neuronal activity-regulated enhancers. The functional RNA database 3. Databases to support mining and annotation of functional RNAs.

Chapter 2 : [Full text] Functions and mechanisms of long noncoding RNAs in lung cancer | OTT

tRNA-derived small non-coding RNAs in human disease In the last decade, numerous tsncRNAs have been found in different type of human cell lines, tissues or extracellular body fluids, and some of them are associated with diseases, such as cancer, metabolic disorder, pathological stress injuries, neurodegenerative diseases, and virus infection.

They were originally thought to represent errors in splicing and considered to be of low abundance, however, there is now an increased appreciation of their important function in gene regulation. Interestingly, they have been found to be abundant, evolutionally conserved and relatively stable in the cytoplasm. It has been proposed that circRNA regulate gene expression at the transcriptional or post-transcriptional level by interacting with miRNAs and that circRNAs may have a role in regulating miRNA function in cancer initiation and progression. In addition, though originally thought to be non-coding, there is now increasing evidence to suggest that select circRNAs can be translated into functional proteins. Although much remains to be elucidated about circRNA biology and mechanisms of gene regulation, these ncRNAs are quickly emerging as potential disease biomarkers and therapeutic targets in cancer. The first examples of circRNA transcripts were first identified over 30 years ago, however at that time they were thought to represent errors in RNA splicing, but are now appreciated to have important functions in gene regulation Sanger et al. This development has led to the identification of thousands of individual circRNAs that are endogenous to mammalian cells and are both highly stable and abundant in vivo compared to their linear counterparts Jeck and Sharpless, More recently, advances in high-throughput sequencing, novel bioinformatics approaches and corresponding experimental validation, have proven that circRNAs actually represent a distinct class of ncRNAs Jeck and Sharpless, This confers stability on circRNAs and makes them very abundant in the cytoplasm Jeck et al. It has been proposed that cellular levels of circRNAs may be regulated by either endonucleic activity or removal by exosomes Lasda and Parker, Their high abundance, stability and evolutionary conservation between species suggests that they may have an important regulatory role and indeed, recent evidence suggests circRNAs appear to act as miRNA sponges, in part due to the competitive endogenous RNA ceRNA network Hansen et al. Although their exact roles and mechanisms of gene regulation remain to be clarified, circRNAs may have potential as disease biomarkers and novel therapeutic targets. Inhibition of the canonical spliceosome using isoginkgetin, a pre-mRNA splicing inhibitor, reduces circRNA levels as well as the levels of the spliced linear transcript, providing evidence for a role for the spliceosome in circRNA biogenesis Starke et al. The expression of circRNA does not always correlate with the expression level of the linear transcript from which the circRNA is derived, indicating that expression of circRNA is regulated and that the spliceosome must be able to discriminate between forward splicing, i. In some cases, this happens with a single exon, whereas in others the start of an upstream exon splices to the end of a downstream exon, with the intervening RNA circularized, producing circRNAs from multiple exons. Alternatively, if the intron between the exons is retained, the resulting circular transcript is referred to as exonâ€”intron circRNA Li Z. Finally, intronic circRNAs can be produced from intron lariats that are resistant to degradation by de-branching enzymes Jeck et al. During the backsplicing process, the two segments bind into a circle first, the exonic and intronic sequences in the binding part are cut out by the spliceosome with the remaining introns brought together to form intronic circRNA. QKI mediates regulation of circRNA biogenesis by binding to each intron flanking a circRNA and facilitates dimerization to form a looped structure which promotes circularization. It has been implicated in decreasing circRNA production by weakening and editing RNA duplexes which decreases the likelihood of circularization Rybak-Wolf et al. Further evidence for translation of exonic circRNAs is from Wang et al. Similarly, Chen et al. Additionally, Legnini et al. The resultant protein has a functional role in muscle differentiation in Duchenne muscular dystrophy by regulating myoblast proliferation. This method was further developed by scanning for out-of-order paired end reads for specific genes which then allowed for quantitative PCR qPCR validation in cancer and non-cancer cell lines Salzman et al. The detection of circRNAs was further developed by Jeck et al. Using this strategy, thousands of circRNAs have been identified that can contain one or more coding exons from linear messenger RNAs

mRNA and can be hundreds to thousands of nucleotides in length Guo et al. The majority of circRNAs have been identified from advances in high throughput sequencing technology. However, there remains non-uniformity in RNA-Seq data sets as circRNA have relatively low abundance compared with their linear counterparts and some data sets were generated in the absence of RNase R enrichment Szabo and Salzman, Bioinformatic Pipelines A number of bioinformatic algorithms have been developed for identifying circRNAs. This was further improved by adding a false discovery rate FDR -controlled filtration based on statistics of alignment quality scores Salzman et al. Leading on from this, Memczak et al. Further algorithms for mapping low-divergent sequences against a large reference genome have also been used to identify circRNAs using BWA-MEM and Segemehl software, which can identify circular junctions Bassett et al. Circle Seq is an example of a bioinformatics pipeline that uses a biochemical approach for genome-wide identification of circRNAs and has led to the discovery of thousands of circRNA candidates Danan et al. High throughput sequencing was performed and the resulting reads were aligned to the human genome using a mapping algorithm, Mapsplice, which identifies back-splice junctions rather than identifying the exon order Wang et al. Back-splice reads were identified using a segmented mapping approach and reads were significantly enriched in the RNase R treated samples compared to the control samples no RNase R , thus allowing detection of circRNAs. Significantly, a large proportion of circRNA alternatively spliced exons cannot be detected in mRNAs and are enriched with binding sites of distinct splicing factors from those enriched in mRNA exons Gao et al. Online Databases A number of online resources exist, which provides investigators access to online circRNA databases. CircBase provides online merged and unified data sets of circRNAs and the evidence supporting their expression can be accessed and scripts are available to identify known and novel circRNAs in sequencing data Glazar et al. A similar database is Circ2Traits which provides a database of potential circRNAs associated with diseases in humans Ghosal et al. It allows the researcher to do several functions including i identify potential circRNAs which can act as RBP sponges and ii design junction-spanning primers for specific detection of circRNAs of interest. Ongoing research into the role and function of circRNA has initially focused on their potential regulatory role. One such role is the ceRNA network and further bioinformatic pipelines have been developed to search for miRNA sponge candidates Guo et al. An important function of miRNAs is the ability to regulate hundreds of targets, as well as to collectively function in networks in which a single target may have multiple MREs Felekkis et al. Pipelines have been created using algorithms for miRNA target prediction, which allows for the identification of candidates for experimental validation Glazar et al. It has been detected in a number of malignancies, where it has been demonstrated to function as both an oncogene and a tumor suppressor including breast Reddy et al. In diabetic mouse models, cirRS-7 overexpression has been shown to improve insulin secretion by inhibiting miR-7 function in pancreatic islet cells Memczak et al. In hepatocellular cancer HCC , ciRS-7 was over-expressed in cancer tissues with the corresponding miR-7 expression levels down-regulated when compared with adjacent non-tumor tissues Yu et al. Sry circRNA exists primarily as a circular product that is predominantly localized to the cytoplasm Koopman et al. In vitro studies showed that silencing circHIPK3 in cancer cell lines caused a significant decrease in cancer cell growth Zheng et al. It increases the level of ITCH, a protein coding gene, which provokes ubiquitin-mediated Dvl2 degradation and inhibits canonical Wnt signaling leading to an overall anti-tumor effect Li F. Exosomal circRNAs Due to their high degree of stability and their resistance to exonuclease degradation, circRNAs may accumulate in cells if their levels are not adequately controlled by cellular mechanisms Conn et al. EVs are membrane-bound vessels that are released from cells and can contain cellular components, including proteins, lipids, and RNA. Different EV types, including exosomes, have been characterized on the basis of their biogenesis or release pathways. The presence of circRNAs within exosomes was also confirmed in a panel of cancer cell lines, including colon, lung, stomach, breast and cervical cancer Li Y. Cardiovascular Disease Ischaemic heart disease IHD is a leading cause of morbidity and mortality in the developed world. Interestingly hypoxia, a known risk factor for atherosclerosis, is a key stimulus for angiogenesis and is associated with significant regulation of circRNAs Boeckel et al. This is supported by evidence from Boeckel et al. Further evidence for the role of circRNA in cardiovascular disease is supported by research from Jakobi et al. Some of these candidates coincide with disease-associated gene loci that have

been previously linked to cardiovascular disease. This is further supported by research from Lukiw et al. UBE2A a central effector in the ubiquitination cycle, that aids the clearance of amyloid peptides via phagocytosis. It is depleted in sporadic AD brain and contributes to amyloidogenesis. Further evidence for an association with aging comes from the detection of senescence-associated circRNAs Panda et al. Cellular senescence is a state of indefinite growth arrest triggered by the exposure of cells to stress-causing stimuli and has been associated with disease processes such as sarcopenia, arthritis, diabetes, neurodegeneration and cancer Campisi, Diabetes Diabetes is associated with significant long-term health consequences and earlier methods of detection and better treatments are required. The potential gene targets for miR-7 were identified from bioinformatics analyses and include Myrip regulates insulin granule secretion and Pax6 enhances insulin transcription. The expression of miRNA is dysregulated in human cancer through various mechanisms, including amplification or deletion of miRNA genes, abnormal transcriptional control of miRNAs, dysregulated epigenetic changes and defects in the miRNA biogenesis machinery Peng and Croce, Gastric Cancer Cancer of the stomach remains a common cause of cancer-related deaths in the world, despite a marked decline in the incidence in many developed nations. Interestingly, this circRNA was found to be downregulated in gastric tumor tissue compared to normal controls. It was also associated with clinical and pathological features such as stage, distant metastases, gender and age Li P. Colorectal Cancer CRC is the third most commonly diagnosed cancer and third leading cause of cancer death in both men and women. Five circRNAs were randomly selected for validation, with four of the five circRNAs showing reduced expression in cancer compared to normal colon mucosa tissues with only one significantly altered: Similarly, cirITCH, has also been found to be downregulated in colorectal tissues compared to normal tissue Huang et al. Bladder Cancer Bladder cancer arises from the epithelial lining of the urinary bladder and is the ninth most common cause of cancer globally. Using this method, Zhong el al. Hepatocellular Carcinoma HCC Hepatocellular carcinoma HCC is a primary malignancy of the liver and occurs predominantly in patients with underlying chronic liver disease and cirrhosis. In contrast to this, Shang et al. Similarly, Yu et al. As ciRs-7 is a known miR-7 sponge, further investigations, which included knockdown of ciRs-7 and overexpression of miR-7, found that ciRS-7 acts as an oncogene partly through targeting miR-7 in HCC. Other Cancers Other studies have identified reduced expression of circRNAs in oesophageal and lung cancer tissues compared to peritumoural and normal tissues Li F. Profiling for circRNA expression has also been performed in other upper gastrointestinal cancers including pancreatic cancer, showing significant dysregulation compared to normal tissue Qu et al. Furthermore, targeting circRNAs associated with known cancer related genes may identify novel methods to overcome therapy related resistance Li F. It has been proposed that circRNA regulate gene expression at the transcriptional or post-transcriptional level by interacting with miRNAs Hansen et al. An important function of miRNAs is the ability to regulate hundreds of targets Felekkis et al. Emerging evidence indicates that cirs-7 regulates miR-7 expression. It has also been demonstrated that RBPs may serve as regulatory activators or inhibitors in the formation of circRNAs in some conditions Conn et al. Oncogenic fusion proteins are formed by the joining together of two otherwise-separated genes, leading to the formation of a fusion gene and the generation of a mutated protein which can result in the onset and progression of cancer Meyerson et al. It has been proposed that f-circRNAs are formed by unrelated intronic sequences coming together, which leads to new events of backsplicing Barrett et al. These f-circRNAs were validated in the appropriate cell line models and were shown to exert both proto-oncogenic and pro-proliferative effects promoting cancer development. Furthermore, examining pathways involved with carcinogenesis could allow investigators identify circRNAs that could be used as biomarkers. Wnt signaling has been shown to contribute to human tumor progression Padala et al. If circRNAs are confirmed to regulate this pathway, circRNAs could also be targeted in order to interrupt this pathway and inhibit tumor growth and development. Other researchers have shown that overexpression of ciRS-7 in cancer tissues permitted inhibition of miR-7 and subsequent activation of EGFR and RAF1 oncogenes, again, strengthening the argument that circRNAs play a role in cancer initiation and development Weng et al. Future Directions Ongoing research is furthering our understanding of the complex circRNA network in non-cancer and cancer conditions, with early data suggesting roles in cancer initiation, progression and therapy resistance. The fact

that certain circRNAs appear to be specific to certain diseases, are stable and have a regulatory function has led to further research into the use of circRNAs as potential diagnostic, prognostic biomarkers and therapeutic targets. Reliable sensitive and specific biomarkers are needed to aid researchers and clinicians in the early diagnosis of disease, identification of high risk populations and to develop targeted therapies and assess response. These blood-based analyses may also allow researchers to monitor responses to treatment, to detect resistance to treatment or to detect early recurrence in real time. In the future it may be possible to use circRNA mimics in the same way to treat both non-cancer and cancer conditions.

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Long non-coding RNAs have also been reported to be dysregulated in different types of neurodegenerative diseases, such as spinocerebellar ataxia type 8 (SCA8) and Alzheimer's disease (AD). SCA8 is an autosomal dominant disorder caused by repeat expansion [ ].

Lung cancer is a heterogeneous disease, and there is a lack of adequate biomarkers for diagnosis. Long noncoding RNAs lncRNAs are emerging as an important set of molecules because of their roles in various key pathophysiological pathways, including cell growth, apoptosis, and metastasis. We review the current knowledge of the lncRNAs in lung cancer. In-depth analyses of lncRNAs in lung cancer have increased the number of potential effective biomarkers, thus providing options to increase the therapeutic benefit. In this review, we summarize the functions, mechanisms, and regulatory networks of lncRNAs in lung cancer, providing a basis for further research in this field. The 5-year survival rate of this heterogeneous disease is The regulated ncRNAs can be categorized by length as follows: Notably, ectopic expression of lncRNAs is associated with a great variety of diseases. Second, lncRNAs have fewer exons, although they harbor standard canonical splice sites. In addition, lncRNAs show strict tissue specificity. Certain transcription factors can bind to the promoter region of lncRNAs, such as c-myc, p53, and Sox2. Classification and functions of lncRNAs The most recent classification of lncRNAs is based on their location relative to that of target protein-coding genes. According to these criteria, lncRNAs can be classified as exonic, intronic, overlapping, or intergenic. Moreover, based on the transcriptional direction with respect to protein-coding genes, lncRNAs are divided into two groups, namely sense and antisense. Cis-acting lncRNAs mediate gene expression based on their position in the vicinity of the target gene transcriptional site. However, trans-acting lncRNAs can control the expression of genes at any loci based on the recruitment of proteins to the target sites to participate in transcriptional regulation. A lncRNAs act as decoys to attract transcription factors and influence protein activity. B In addition, the ability to aggregate different proteins has highlighted their usefulness as scaffolds. C lncRNAs also have a critical role in signal regulation. E lncRNAs play essential roles in guiding chromatin-remodeling enzymes to target sites. Decoys lncRNA decoys exert biological functions by binding to proteins indirectly and playing a role in multiple processes of life. Signal lncRNAs play critical roles in signal regulation and in the responses to various stimuli. Upon specific expression, they can modulate translation and integrate developmental cues. Consequently, E2F1 is released inappropriately and contributes to gastric cancer cell proliferation. Recent evidence highlights a classification of circRNAs as miRNA sponges that contribute to the downregulation of target genes. Guide Multiple studies indicate that nuclear-retained lncRNAs function in guiding chromatin modifiers to specific genomic loci. Xist gives rise to stable epigenetic silencing of large-scale genes in the X-chromosome by tethering PRC2 to the transcriptional site, inducing the formation of H3K27me3 to inactivate heterochromatin. Among lncRNAs in prostate cancer, two overexpressed lncRNAs bind to the androgen receptor, promoting androgen receptor binding to an enhancer. Accumulating evidence indicates that lncRNAs may regulate alternative splicing by cis-acting mechanisms or by recruiting regulatory splicing factors. These findings suggested that lncRNAs can regulate alternative splicing through the establishment of a splicing-specific chromatin signature. Here, we discuss recent discoveries that implicate aberrant lncRNAs in lung cancer Table 1. In addition, we provide a framework of systematically functionalized lncRNAs and integrate them with the protein-coding RNA dimension in complex networks Figure 2. Up, upregulated; down, downregulated. Figure 2 Overview of the regulatory network of lncRNAs in lung cancer. Blue frames represent onco-lncRNAs. Green frames represent tumor suppressor lncRNAs. Purple frames represent IFs pathway. MALAT1 generates a primary noncoding transcript that is enriched in the nucleus. MALAT1 has been shown to be a critical regulator of the metastasis phenotype in lung cancer cells. In addition, the secondary structure of HOTAIR contains four independently folding modules, two of which are evolutionarily conserved protein-binding domains. Reciprocally, the conserved lncRNA sequence does not always possess the same function in other species as expected. High HOTAIR levels are associated with invasion and metastases and linked to an advanced stage of disease and

poor survival in patients with lung cancer. One of these mechanisms is transcriptional repression of HOXA5 gene. HOXA5 is related to postnatal lung development. These sites have essential roles in the tumorigenesis process. Meanwhile, its expression level is significantly correlated with cell proliferation and colony formation ability in lung cancer cell lines. This gene family is associated with cutaneous malignant melanoma and neural system tumors. ANRIL includes several isoforms with tissue-specific expression because it consists of 19 exons. It is plausible that ANRIL modulates the expression of miRa, thereby inhibiting the proliferation of lung cancer cells during lung tumorigenesis. H19 Characteristics of H19 H19 is located on chromosome 11q H19 is a paternally imprinted gene that is spliced into five exons. The H19 gene locus is complex, harboring conserved miR and antisense protein-encoding transcript HOTS , which is a tumor suppressor. There is an imprinting control region ICR between them. As a result, the enhancer binds to H19 and induces its expression. Conversely, on paternal chromosomes, the ICR is methylated and binds to the enhancer, resulting in H19 downregulation. Knockdown of H19 expression in hypoxia has a suppressing effect on cancer cell proliferation, anchorage-independent growth, and colony formation. Notably, the upregulated H19 is loss of imprinting independent in the airway epithelia of smokers in comparison with nonsmokers. High levels of MVIH expression are prognostic indicators of poor survival. MMPs are involved in multiple biological processes, including remodeling of extracellular matrix, cell proliferation, differentiation, and metastasis. A study identified a p53 transcription factor-binding site in the PVT1 promote region. In addition, patients with high levels of PVT1 expression show poor survival. Previous evidence indicates that MEG3 is a tumor suppressor because of its role in modulating angiogenesis. Evidence to date indicates that GAS5 modulates the activity of glucocorticoid-responsive genes. In this process, GAS5 represents a clear example of a decoy lncRNA, which competitively binds to the glucocorticoid receptor and prevents it from binding to glucocorticoid response elements. In turn, GAS5 suppresses miR expression in a feedback loop between them. The TUG1 gene displays a high level of conservation in the human, mouse, rat, dog, and cow genomes. Moreover, patients with low level of TUG1 expression display a higher TNM stage, increased tumor size, and relatively poor overall survival. BANCR is upregulated in malignant melanoma, colorectal carcinoma, and papillary thyroid carcinoma tissues, suggesting a common oncogenic role. Furthermore, knockdown of BANCR expression leads to the promotion of cell migration and invasion but inhibition of metastasis. It is plausible that downregulated BANCR promotes cell proliferation by downregulating p21 expression. One of the main barriers to the success of lung cancer therapy is the lack of tumor biomarkers for early diagnosis. In the previous studies, evidences have mainly focused on elucidation of lncRNAs in cellular and mouse models. Indeed, to accurately and comprehensively understand the role of lncRNAs in human, large clinical cases of pathological characteristics as well as the prognosis are needed. Indeed, the clinical integration of lncRNAs with respect to prognostic and predictive biomarker signatures will increase the therapeutic benefit. Here, we summarize the recent research and regulatory networks of lncRNAs Figure 2 in lung cancer. Interestingly, the key role of PRC2 in modulating proliferation and cell cycle of lung cancer cells has been emerging. Several growth-related genes including p21 and p53 have been shown in the hinge of network. Generally, MMPs play a critical role in tumor cell growth and metastasis by altering the environments in which the cells grow. Additionally, miRNAs as high-potential biomarkers have critical position in regulatory network of lung cancer; for example, miRa represses HOX5 expression, thereby promoting metastasis. Although an impressive number of studies in the last decade focused on the characteristics and functions of ncRNAs, research is still in its infancy and presents great challenges. First, as the sequence and structure of lncRNAs are only poorly conserved, the canonical knockdown and knockout methods may have no effect. In addition, ectopic expression of lncRNAs may not show obvious phenotypes as with protein-coding transcripts. Second, reference value is not always high between different researches, owing to different and multiple functions of lncRNAs in different tissues and cells. Therefore, elucidating the biological functions of lncRNAs is not easy. Third, the limited bioinformatical resources are another reason. Similarly, bioinformatic tools, such as lncRNA secondary structure prediction, remain to be developed. Unraveling the functions and regulatory mechanisms of lncRNAs in lung cancer might be a future breakthrough to improve our understanding of this network. The integration of miRNA and lncRNA signature profiling in lung cancer may be a useful tool for

clinical applications. Conclusion lncRNAs are increasingly being recognized as critical molecules in various biological processes. In addition to the various types, there is a large number of lncRNAs, and they show numerous modes of interaction. Based on the location concerning the nearest protein-coding gene, lncRNAs can be classified into four subclasses, namely exonic, intronic, overlapping, and intergenic lncRNAs. According to their function, lncRNAs can be categorized as signal, decoy, sponge, guide, and scaffold molecules. It has become increasingly clear that lncRNAs are involved in tumorigenesis in many cancers. Acknowledgment This work was supported by grants from the National Natural Science Foundation of China Nos , , , , , and Disclosure The authors report no conflicts of interest in this work.

Chapter 4 : Non-coding RNA - Wikipedia

The Emerging Role of Long Noncoding RNAs in Human Disease Posted by: lncRNA Administrator in Review Paper February 12, 0 1, Views Only a small fraction of the human genome corresponds to protein-coding genes.

Abundance[edit] A recent study found only one-fifth of transcription across the human genome is associated with protein-coding genes, [3] indicating at least four times more long non-coding than coding RNA sequences. It has been suggested through multiple studies that testis , [6] and neural tissues express the greatest amount of long non-coding RNAs of any tissue type. The GENCODE consortium has collated and analysed a comprehensive set of human lncRNA annotations and their genomic organisation, modifications, cellular locations and tissue expression profiles. Several lncRNAs have been found to in fact encode for peptides with biologically significant function. However, further investigations into vertebrate lncRNAs revealed that while lncRNAs are conserved in sequence, they are not conserved in transcription. Some argue that these observations suggest non-functionality of the majority of lncRNAs, [29] [30] [31] while others argue that they may be indicative of rapid species-specific adaptive selection. There have been several attempts to delineate the different categories of selection signatures seen amongst lncRNAs including: However, despite accumulating evidence suggesting that the majority of these are likely to be functional, [37] [38] only a relatively small proportion has been demonstrated to be biologically relevant. As of June , a total of human lncRNAs that with experimental evidences have been community-curated in LncRNAWiki a wiki-based, publicly editable and open-content platform for community curation of human lncRNAs. NcRNAs modulate the function of transcription factors by several different mechanisms, including functioning themselves as co-regulators, modifying transcription factor activity, or regulating the association and activity of co-regulators. For example, the ncRNA Evf-2 functions as a co-activator for the homeobox transcription factor Dlx2 , which plays important roles in forebrain development and neurogenesis. The existence of other similar ultra- or highly conserved elements within the mammalian genome that are both transcribed and fulfil enhancer functions suggest Evf-2 may be illustrative of a generalised mechanism that tightly regulates important developmental genes with complex expression patterns during vertebrate growth. In the broad sense, this mechanism allows the cell to harness RNA-binding proteins, which make up one of the largest classes within the mammalian proteome, and integrate their function in transcriptional programs. These examples, which bypass specific modes of regulation at individual promoters to mediate changes directly at the level of initiation and elongation transcriptional machinery, provide a means of quickly affecting global changes in gene expression. The ability to quickly mediate global changes is also apparent in the rapid expression of non-coding repetitive sequences. It was argued that HSR-1 is present in mammalian cells in an inactive state, but upon stress is activated to induce the expression of heat shock genes. In post-transcriptional regulation[edit] In addition to regulating transcription, ncRNAs also control various aspects of post-transcriptional mRNA processing. The formation of RNA duplexes between complementary ncRNA and mRNA may mask key elements within the mRNA required to bind trans-acting factors, potentially affecting any step in post-transcriptional gene expression including pre-mRNA processing and splicing, transport, translation, and degradation. In splicing[edit] The splicing of mRNA can induce its translation and functionally diversify the repertoire of proteins it encodes. Likewise, the expression of an overlapping antisense Rev-ErbAa2 transcript controls the alternative splicing of the thyroid hormone receptor ErbAa2 mRNA to form two antagonistic isoforms. Also, long ncRNAs that form extended intramolecular hairpins may be processed into siRNAs, compellingly illustrated by the esi-1 and esi-2 transcripts. However, the generation of endo-siRNAs from antisense transcripts or pseudogenes may also silence the expression of their functional counterparts via RISC effector complexes, acting as an important node that integrates various modes of long and short RNA regulation, as exemplified by the Xist and Tsix see above. For example, the majority of protein-coding genes have antisense partners, including many tumour suppressor genes that are frequently silenced by epigenetic mechanisms in cancer. Imprinting[edit] Many emergent themes of ncRNA-directed chromatin modification were first apparent within the phenomenon of imprinting , whereby only one allele of a gene is expressed from

either the maternal or the paternal chromosome. In general, imprinted genes are clustered together on chromosomes, suggesting the imprinting mechanism acts upon local chromosome domains rather than individual genes. These clusters are also often associated with long ncRNAs whose expression is correlated with the repression of the linked protein-coding gene on the same allele. Xist expression is followed by irreversible layers of chromatin modifications that include the loss of the histone H3K9 acetylation and H3K4 methylation that are associated with active chromatin, and the induction of repressive chromatin modifications including H4 hypoacetylation, H3K27 trimethylation, [] H3K9 hypermethylation and H4K20 monomethylation as well as H2AK monoubiquitylation. These modifications coincide with the transcriptional silencing of the X-linked genes. Telomeric non-coding RNAs[edit] Telomeres form the terminal region of mammalian chromosomes and are essential for stability and aging and play central roles in diseases such as cancer. Their association with chromatin, which suggests an involvement in regulating telomere specific heterochromatin modifications, is repressed by SMG proteins that protect chromosome ends from telomere loss. In aging and disease[edit] Recent recognition that long ncRNAs function in various aspects of cell biology has focused increasing attention on their potential to contribute towards disease etiology. A handful of studies have implicated long ncRNAs in a variety of disease states and support an involvement and co-operation in neurological disease and cancer. The first published report of an alteration in lncRNA abundance in aging and human neurological disease was provided by Lukiw et al. Expression analyses that compare tumor cells and normal cells have revealed changes in the expression of ncRNAs in several forms of cancer. For example, in prostate tumours, PCGEM1 one of two overexpressed ncRNAs is correlated with increased proliferation and colony formation suggesting an involvement in regulating cell growth. Overexpression of PRINS is associated with psoriasis susceptibility, with PRINS expression being elevated in the uninvolved epidermis of psoriatic patients compared with both psoriatic lesions and healthy epidermis. Further analysis of one ultraconserved ncRNA suggested it behaved like an oncogene by mitigating apoptosis and subsequently expanding the number of malignant cells in colorectal cancers. It seems likely that the aberrant expression of these ultraconserved ncRNAs within malignant processes results from important functions they fulfil in normal human development. Recently, a number of association studies examining single nucleotide polymorphisms SNPs associated with disease states have been mapped to long ncRNAs. Many SNPs associated with certain disease conditions are found within non-coding regions and the complex networks of non-coding transcription within these regions make it particularly difficult to elucidate the functional effects of polymorphisms.

Chapter 5 : Non-Coding RNA | An Open Access Journal from MDPI

This volume focuses on the roles of long non-coding RNAs (lncRNAs) in contexts ranging from human cancers to cardiovascular disease and ageing.

Entities Foreign Institutions are eligible to apply Non-domestic non-U. Organizations are eligible to apply. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. The NIH Policy on Late Submission of Grant Applications states that failure to complete registrations in advance of a due date is not a valid reason for a late submission. The same DUNS number must be used for all registrations, as well as on the grant application. The renewal process may require as much time as the initial registration. Obtaining an eRA Commons account can take up to 2 weeks. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support. Additional Information on Eligibility Number of Applications Applicant organizations may submit more than one application, provided that each application is scientifically distinct. The NIH will not accept duplicate or highly overlapping applications under review at the same time. This means that the NIH will not accept: A new A0 application that is submitted before issuance of the summary statement from the review of an overlapping new A0 or resubmission A1 application. A resubmission A1 application that is submitted before issuance of the summary statement from the review of the previous new A0 application. Application and Submission Information 1. See your administrative office for instructions if you plan to use an institutional system-to-system solution. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review. Letter of Intent Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review. By the date listed in Part 1. Overview Information , prospective applicants are asked to submit a letter of intent that includes the following information: Since the goal of this program is to support exploratory and developmental research projects, extensive background material and preliminary data are not required. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or, when available, from investigator-generated data. The following modifications also apply: All applications, regardless of the amount of direct costs requested for any one year, should provide a Data Sharing Plan that details the rapid sharing, release, and access of data, tools, models, reagents, and other resources generated under this project to the broader scientific community in adherence to the requirements and timelines described in the NIAID Data and Reagents Sharing and Release Guidelines https: Only limited Appendix materials are allowed. Foreign Institutions Foreign non-U. Submission Dates and Times Part I. Overview Information contains information about Key Dates and times. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections that might be necessary for successful submission. When a submission date falls on a weekend or Federal holiday , the application deadline is automatically extended to the next business day. Organizations must submit applications to Grants. Applicants are responsible for viewing their application before the due date in the eRA Commons to ensure accurate and successful submission. Paper applications will not be accepted. Applicants must complete all required registrations before the application due date. Eligibility Information contains information about registration. For assistance with your electronic application or for more information on the electronic submission process, visit Applying Electronically. If you encounter a system issue beyond your control that threatens your ability to complete the submission process on-time, you must follow the Guidelines for Applicants Experiencing System Issues. See more tips for avoiding common errors. Upon receipt, applications will be evaluated for completeness and compliance with application instructions by the Center for Scientific Review and responsiveness by components of participating organizations , NIH. Post Submission Materials Applicants are required to follow the instructions for post-submission materials, as described in the policy. Any instructions provided here are in addition to the

instructions in the policy. Application Review Information 1. Criteria Only the review criteria described below will be considered in the review process. As part of the NIH mission , all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system. For this particular announcement, note the following: An R21 grant application need not have extensive background material or preliminary information. Accordingly, reviewers will emphasize the conceptual framework, the level of innovation, and the potential to significantly advance our knowledge or understanding. Preliminary data are not required for R21 applications; however, they may be included if available. Overall Impact Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field s involved, in consideration of the following review criteria and additional review criteria as applicable for the project proposed. Scored Review Criteria Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field. Significance Does the project address an important problem or a critical barrier to progress in the field? Is there a strong scientific premise for the project? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field s? Innovation Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed? Approach Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects? Environment Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements? Additional Review Criteria As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items. Protections for Human Subjects For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research. Vertebrate Animals The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

Chapter 6 : Long Non-Coding RNAs and Complex Human Diseases

Non-coding RNAs (ncRNAs) are involved in the regulation of numerous biological processes and pathways and therefore have been extensively studied in human diseases. Previous reports have shown that non-coding RNAs play a crucial role in the pathogenesis and aberrant regulation of respiratory diseases.

History of molecular biology Nucleic acids were first discovered in by Friedrich Miescher [10] and by RNA had been implicated in protein synthesis. Biological roles[edit] Noncoding RNAs belong to several groups and are involved in many cellular processes. These range from ncRNAs of central importance that are conserved across all or most cellular life through to more transient ncRNAs specific to one or a few closely related species. The more conserved ncRNAs are thought to be molecular fossils or relics from the last universal common ancestor and the RNA world , and their current roles remain mostly in regulation of information flow from DNA to protein. Proteins are shown in blue and the two RNA strands in orange and yellow. Many of the conserved, essential and abundant ncRNAs are involved in translation. Ribosomal RNAs catalyse the translation of nucleotide sequences to protein. RNase MRP is restricted to eukaryotes. Another ubiquitous RNP called SRP recognizes and transports specific nascent proteins to the endoplasmic reticulum in eukaryotes and the plasma membrane in prokaryotes. Note the bulk of the complex is in fact ncRNA. In eukaryotes the spliceosome performs the splicing reactions essential for removing intron sequences, this process is required for the formation of mature mRNA. There are two different forms of the spliceosome, the major and minor forms. There are two main groups of self-splicing RNAs: This regulation can occur in trans or in cis. There is increasing evidence that a special type of ncRNAs called enhancer RNAs , transcribed from the enhancer region of a gene, act to promote gene expression. A single miRNA can reduce the expression levels of hundreds of genes. The main function of miRNAs is to down-regulate gene expression. This interaction represses expression from a sigmadependent promoter during stationary phase. Chromatin is progressively converted to an open configuration, as several species of ncRNAs are transcribed. These RNA elements form one of two possible structures in regions encoding very short peptide sequences that are rich in the end product amino acid of the operon. A terminator structure forms when there is an excess of the regulatory amino acid and ribosome movement over the leader transcript is not impeded. When there is a deficiency of the charged tRNA of the regulatory amino acid the ribosome translating the leader peptide stalls and the antiterminator structure forms. This allows RNA polymerase to transcribe the operon. These piRNA complexes piRCs have been linked to transcriptional gene silencing of retrotransposons and other genetic elements in germ line cells, particularly those in spermatogenesis. The repeats are separated by spacers of similar length. It has been demonstrated that these spacers can be derived from phage and subsequently help protect the cell from infection. The telomeres contain condensed DNA material, giving stability to the chromosomes. The enzyme is a reverse transcriptase that carries Telomerase RNA , which is used as a template when it elongates telomeres, which are shortened after each replication cycle. Xist X-inactive-specific transcript is a long ncRNA gene on the X chromosome of the placental mammals that acts as major effector of the X chromosome inactivation process forming Barr bodies. X chromosomes lacking Tsix expression and thus having high levels of Xist transcription are inactivated more frequently than normal chromosomes. However, a handful of other bifunctional RNAs are known to exist e. In Drosophila , hormones such as ecdysone and juvenile hormone can promote the expression of certain miRNAs. Furthermore, this regulation occurs at distinct temporal points within C.

Chapter 7 : The Emerging Role of Long Noncoding RNAs in Human Disease | lncRNA Blog

This volume focuses on the roles of long non-coding RNAs (lncRNAs) in contexts ranging from human cancers to cardiovascular disease and ageing. The role of lncRNAs in X-inactivation and those lncRNAs derived from pseudogenes, past retroelements integrated within the human genome, as well as the.

Find articles by Ballarino, M. Find articles by Morlando, M. Find articles by Fatica, A. Find articles by Bozzoni, I. Periodically, new non-canonical functions have been ascribed to RNA, such as the ability to act as a catalytic molecule or to work independently from its coding capacity. Recent annotations show that more than half of the transcriptome encodes for RNA molecules lacking coding activity. Here we illustrate how these transcripts affect skeletal muscle differentiation and related disorders. We discuss the most recent scientific discoveries that have led to the identification of the molecular circuitries that are controlled by RNA during the differentiation process and that, when deregulated, lead to pathogenic events. These findings will provide insights that can aid in the development of new therapeutic interventions for muscle diseases. The impact of these molecules in the control of cell development, differentiation, and growth has now been established, and it is clear that these molecules exert their functions in both nuclear and cytoplasmic compartments 1. Muscle differentiation has been one of the most exploited and studied processes due to the availability of suitable cellular systems that faithfully recapitulate in vivo differentiation and animal models for different muscle diseases 2 â€” 4. Alterations in myogenesis may underlie many muscle disorders, including sarcopenia, cachexia, and muscular dystrophies, where alterations in regenerative capacity play a crucial role in disease progression and outcome. Moreover, perturbation of regulatory circuits controlling muscle homeostasis are involved in structural and functional changes that occur during muscle atrophy and hypertrophy; therefore, the identification of new components controlling muscle differentiation and regeneration could clarify the molecular pathogenic mechanisms in different diseases and potentially allow the identification of new therapeutic targets. Additionally, the molecular circuits controlled by miRNAs have been largely characterized 5. During myogenesis an intricate relationship between miRNAs and myogenic factors is established, with miRNAs acting synergistically or antagonistically. Notably, the major myomiRs have an interesting evolutionary and genomic correlation: While mice lacking only one of the two miR-1 or miR copies displayed minor defects, mainly of cardiac type, deletion of both copies resulted in lethality 9 , Conversely, deletion of the regenerative miR in mice substantially delayed regeneration induced by cardiotoxin injury Figure 1 summarizes the most relevant circuits controlled by miRNAs in skeletal muscle cells. Conversely, these same transcription factors can directly control expression of these miRNAs through regulatory feedback loops 9 , 12 , Figure 1 miRNA-mediated regulatory networks in myogenesis and skeletal muscle diseases. Schematic representation of the differentiation stages leading from progenitor muscle cells to terminally differentiated fibers. The most relevant regulatory circuits between miRNAs and protein factors are shown. Deregulation of miRNA expression is a common feature of several skeletal muscle disorders, and rescue of their correct expression in mouse models ameliorates disease phenotypes 11 , 14 , Duchenne muscular dystrophy DMD , the most common and severe muscular disease characterized by mutations in the dystrophin gene, provides a relevant example of disease-linked miRNA activity that is involved in pathogenic circuits. Besides serving as a structural protein that protects muscle fibers from mechanical damage, dystrophin controls the switch from early to late phases of differentiation, acting as an epigenetic modulator of gene expression through a pathway involving neuronal NOS nNOS and histone deacetylase 2 HDAC2 22 , In normal muscle, dystrophin activates nNOS, which in turn nitrosylates HDAC2, leading to its release from the chromatin of specific target genes to drive transcriptional activation. Several miRNA genes were identified as targets of this pathway, including miRNAs involved in terminal differentiation of muscle, such as miR-1 and miR, and the more ubiquitous miR and miR In dystrophic muscles, the absence of dystrophin disrupts such circuitry, leading to reduced levels of specific miRNAs, which favors the onset of dystrophic pathogenic traits such as oxidative damage through upregulation of the miR-1 target glucosephosphate dehydrogenase G6PD and fibrosis through deregulation of the collagen mRNAs targeted by miR 17 , 24 , 25 Figure 1. Notably, both

miR-1 and miR, which are poorly expressed in murine and human dystrophic muscles, were recovered in exon skippingâ€”treated mdx mice a murine model of DMD and DMD myoblasts Genetic deletion of miR in mdx mice accelerated and worsened the dystrophic phenotype 11 , while sustained expression of miR promoted satellite cell differentiation and fusion, suggesting that the strong activation of miR in dystrophic muscles induces compensatory circuits to promote the formation of new myofibers in response to disease-induced injury. This activity is mediated at the molecular level through suppression of several negative regulators of myogenesis, including paired box proteinâ€”7 PAX7 , Notch3, and insulin-like growth factorâ€”binding proteinâ€”5 IGFBP5 11 , Expression of miR was dramatically increased in an ALS mouse model where pathological alterations are first detected in muscle, particularly at the neuromuscular junction NMJ prior to motor neuron loss Therefore, miR was suggested to slow ALS progression by sensing motor neuron injury and promoting the compensatory regeneration of neuromuscular synapses Two important downstream targets are likely involved in this pathway: HDAC4, which has been implicated in the control of neuromuscular gene expression 31 , and the FGF signaling pathway, which promotes presynaptic differentiation at the NMJ Remarkably, for both DMD and ALS, miR expression was upregulated at disease onset and had beneficial effects, suggesting an important role for miR as a stress-inducible suppressor of skeletal muscle disease. RMS is also characterized by the overexpression of early myogenic markers including desmin, myogenin, and myogenic differentiationâ€”1 MyoD 33 , which are trapped in a nonfunctional state, thereby inhibiting terminal differentiation of myogenic progenitor cells Even though the roles of miR-1 and miR in RMS are still not well defined, several studies suggest that they play an important role in the pathogenesis of this cancer. Additionally, the exogenous expression of miR in RMS cells blocks tumor growth and promotes terminal differentiation, suggesting that reconstitution of proper miRNA levels could have potential therapeutic applications Global gene expression analysis of RMS cells after miR overexpression led to the identification of two modulated genes: Notably, miR plays a dual role in dystrophic muscles. It controls satellite cell activation by repressing the synthesis of the myogenic determination factor MYF5 40 and regulates fiber maturation by targeting several terminal differentiation proteins, including dystrophin In exon skippingâ€”treated human DMD myoblasts, miR inhibition increased dystrophin rescue, indicating that interfering with miR activity can improve DMD therapies aimed at efficiently recovering dystrophin synthesis. Similarly, the atrial-specific upregulation of miR in human atrial fibrillation AF was recently shown to cause atrial loss of dystrophin and nNOS, leading to the electrical phenotype induced by AF Lnc and miR have similar expression profiles, with high expression in proliferating myoblasts and downregulation upon muscle differentiation. Like miR, lnc is also enriched in mdx muscles, and its downregulation is less pronounced upon differentiation of dystrophic myoblasts, reinforcing the hypothesis that lnc plays a crucial role in controlling myoblast proliferation and suggesting a synergistic activity of the overlapping miRNA and lncRNA transcripts Moreover, human MIR31HG sustained myoblast proliferation and counteracted differentiation, indicating that, despite the poor sequence conservation, lnc function is evolutionarily conserved More recently, other miRNAs miRb, , and a were found to target dystrophin mRNA and to increase in dystrophic myofibers, paralleling disease severity These miRNAs are also increased in a wide variety of muscle disorders, such as myositis, Miyoshi myopathy, and limb-girdle muscular dystrophy 16 , 17 , 46 , suggesting that inflammatory miRNAs can be a common signature of muscle diseases where chronic inflammation is present. Targeting of such miRNAs could be effectively combined with other therapeutic strategies, such as the exon skipping approach in DMD Moreover, such circulating miRNAs can be delivered to recipient cells, where they can control translation of target mRNAs 56 , Specific miRNA signatures have been described in a large collection of skeletal muscle diseases 58 â€” 62 and neuromuscular disorders such as ALS Measurements of the levels of these miRNAs revealed that they correlated with disease severity and decreased when correction of the phenotype and dystrophin rescue were achieved through exon skipping Therefore, circulating miRNAs may be potential diagnostic markers not only for monitoring disease progression, but also for evaluating the outcomes of different therapies. Moreover, the ability of exosomal and circulating miRNAs to be delivered to target cells opens new possibilities for the therapeutic regeneration of skeletal muscle Recently, lncRNAs have been found in body fluids; however, only a few studies have explored the potential use of these

molecules as biomarkers for muscle pathologies. To date, alteration of lncRNA levels in plasma has been reported only in heart failure in humans and mice 66 â€” These findings provided a number of candidates to be functionally tested in vivo. Moreover, several transcripts appeared to be dysregulated in dystrophic versus wild-type muscles, indicating their possible link with muscle disorders LncRNAs elicit vastly different effects depending on their subcellular compartmentalization, as discussed below see Table 1. Recognition of the target regions by lncRNAs can occur through different mechanisms, such as bridging proteins and RNA-DNA hybrids, including triple helix formation 73 â€” The ability of lncRNAs to act as scaffolds for different protein factors allows them to mediate different functions 76 â€” In most cases, lncRNAs recruit chromatin remodeling and modifying complexes to activate or repress transcription Figure 2 , iii ; however, they can also have indirect effects on their targets by acting as decoys for transcription factors Figure 2 , ii , modulating regulatory proteins, and controlling long-range, three-dimensional chromosomal structures Figure 2 , iv 74 , Figure 2 Models of lncRNA function in myogenesis. Nuclear lncRNAs may act as: Activating green or repressing red histone modifications together with the sites of DNA methylation black are indicated. DBE-T is one of the first examples of a nuclear lncRNA that functions in gene expression control and is involved in a severe skeletal pathology In patients with facioscapulohumeral muscular dystrophy FSHD , the presence of a reduced number of D4Z4 repeats leads to decreased polycomb complex binding to this region and consequent activation of DBE-T expression. Other common forms of lncRNAs known to control gene expression in cis are the so-called natural antisense transcripts NATs; ref. In hypertrophic hearts, high levels of BRG1 are associated with Mhrt repression and decreased Myh6 and Myh7 transcription, whereas restoration of Mhrt protects against pathological hypertrophy by preventing aberrant fetal gene reactivation during cardiac stress YY1 controls various processes of development and differentiation 84 , is highly expressed in proliferating myoblasts, and is gradually downregulated upon initiation of differentiation. Although the mechanism is not fully understood, Yam-1 exerts its antimyogenic function in cis through the modulation of its neighboring miR gene, which in turn targets Wnt7b. The downregulation of Yam-1 upon differentiation releases inhibition of skeletal differentiation and in vivo regeneration The RNAs derived from the core enhancer region and from the distal regulatory region DRRRNA 20 kb and 5 kb upstream of the MyoD transcriptional start site [TSS], respectively facilitate the recruitment of the transcription machinery to proximal promoter regions. In addition to eRNAs in skeletal muscle, many eRNAs have been identified in cardiac development that are deregulated in several different cardiomyopathies 90 , Genomic imprinting is an important epigenetic mechanism that silences one of the parental copies of a gene. Imprinted regions encode different species of lncRNAs that in many cases bind to imprinted regions and are directly involved in silencing of the neighboring genomic loci Many parentally imprinted genes are expressed at high levels in fetal and newborn tissues and decline during late developmental stages. Notably, different skeletal muscle diseases have been associated with defects in imprinted genes. In mice and sheep, aberrant activation of the imprinted Dlk1-Dio3 cluster is responsible for the callipyge phenotype, an inherited skeletal muscle hypertrophy Deletion of one of the lncRNAs expressed from this locus, Gtl2 also known as Meg3 , led to perinatal death and skeletal muscle defects in mice Interestingly, Gtl2 interacts with the repressive PRC2 complex and is directly involved in the epigenetic silencing of many genes from the Dlk1-Dio3 region, including Dlk1 95 , Imprinting at lncRNA loci has been also identified in cancer and heart development. Misregulation of the imprinted locus containing IGF2 and H19 discussed above was in fact identified in RMS, a tumor that arises from skeletal muscle progenitors 98 â€” , while Kcnq1ot1, an antisense RNA produced from an intron of the Kcnq1 gene, is a well-characterized imprinted lncRNA required for proper heart development in the mouse Expression of Kcnq1ot1 inversely correlates with that of Kcnq1. The altered expression is due not to the formation of repressive chromatin, but to changes in the three-dimensional conformation of chromatin that results in the inactivation of heart-specific enhancers Proper Kcnq1 levels are essential for maintaining cardiac rhythm and heart function Even if its activity is not specifically restricted to skeletal muscles it was identified in the mesodermal germ layer, from which heart derives , it remains a paradigmatic example of a lncRNA participating in chromatin remodeling. Bvht has a defined role in the control of the progression of nascent mesoderm toward the cardiac fate. It acts in the same pathway as mesoderm posterior 1 Mesp1 , a master regulator of multipotent cardiovascular

progenitors, and promotes the activation of the cardiac regulatory network in trans. Bvht is also required for the commitment of embryonic stem cells ESCs toward a cardiac fate, suggesting a possible role in cardiac tissue regeneration after injury Interestingly, no human homolog has been found for Bvht thus far; however, whether the lack of conservation is due to weak pressure on the primary sequence of the lncRNA has not been established yet. Fendrr is another example of a lncRNA that promotes epigenetic modification In transgenic mice, the insertion of a premature poly A signal to disrupt the Fendrr transcript resulted in embryonic lethality due to ventral body wall defects and hypoplastic cardiac ventricles Developmental pluripotency-associated 2 upstream binding RNA Dum is a pro-myogenic lncRNA that regulates chromatin organization through the recruitment of the DNA methyltransferases DNMT-1, -3a, and -3b to silence its neighboring gene developmental pluripotency associatedâ€"2 Dppa2 The repression occurs through the formation of intrachromosomal loops between Dum and the Dppa2 promoter that culminates with the hypermethylation of CpG islands. Beyond skeletal muscle, this mechanism might play a role in satellite cell function. In line with this hypothesis, depletion of Dum in vivo decreases PAX7 levels and impairs regeneration of injured muscles.

Chapter 8 : Long non-coding RNA - Wikipedia

The class of long non-coding RNAs (lncRNAs) is a functionally diverse set of non-protein coding RNAs that regulate many processes including transcription and RNA expression. Emerging evidence suggests that lncRNAs function in vascular biology and may contribute to vascular diseases including atherosclerosis and hypertension.

Chapter 9 : JCI - Non-coding RNAs in muscle differentiation and musculoskeletal disease

Non-coding RNA Research aims to publish high quality research and review articles on the mechanistic role of non-coding RNAs in all human diseases.