Non-Coding RNA Transcriptome

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Contributor: Jelena Roganović , Nina Petrović

Non-coding RNAs (ncRNAs) represent a research hotspot by playing a key role in epigenetic and transcriptional regulation of diverse biological functions. Due to their involvement in DNA translational control, their regulation of mRNA and protein expression levels and their ability to reprogram cellular signaling pathways in oral inflammatory diseases, ncRNA could be used to diagnose and predict disease and to improve patient-tailored treatments, as integral part of precision medicine for oral inflammatory diseases.

non-coding RNA | oral inflammatory diseases | precision medicine | neuropathic orofacial pain

1. Non-Coding RNA Transcriptome

It has been proposed that approximately 70% of the human genome is transcribed into mRNA, but only around 2% are protein-coding [1][2][3], suggesting that a very tiny proportion of the human genome sequences and elements translate into proteins. According to this, a vast majority of transcribed sequences of RNA molecules are regulatory elements. Non-coding RNAs are genome elements that do not encode for amino acids [3]. They are involved in various cellular processes and interfere with signaling pathways. Non-coding RNAs are localized in almost every cellular compartment and interact with nucleic acids and proteins, thus changing their conformation and functions. Some non-coding RNAs interact with chromatin, contributing to chromatin remodeling, and thus shaping gene activity. In the backbone of every pathological condition lies non-coding RNA transcriptome changes, and their interactome. The localization and abundance of non-coding RNA are tissue-specific [4] and can change in response to a wide span of stressogenic factors and cellular and environmental events. Non-coding RNA transcriptome changes should be more closely discovered in association with disease development and have the potential to be utilized as diagnostic, predictive, and prognostic biomarkers; parameters for the stratification of patients into more specific groups; and potential targets for therapeutics. The non-coding RNA transcriptome comprises RNA molecules of various structures, lengths, and functions [3]. The basic classification on long non-coding (lncRNA) and small non-coding RNA is based on their length.

Transfer RNA (tRNAs) and ribosomal rRNAs (rRNAs) were among the first RNAs found that do not translate into proteins. However, high-throughput “whole transcriptome” techniques discovered seemingly insignificant but now very important regulators of all cellular processes in the two additional classes of non-coding RNAs: long non-coding and small non-coding RNA molecules. [5]. Classification of non-coding RNAs is based mostly on their length, but there are other types of non-coding RNA based on their special features such as packing into microvesicles, including extracellular RNAs [6].

2. Long Non-Coding RNA

LncRNAs are endogenous cellular RNAs lacking an ORF (open reading frame) or with a shorter ORF than mRNA, which is used as one of the criteria for distinguishing lncRNAs from messenger RNAs [7][8]. LncRNAs are classified as more than 200-nucleotide-long RNA molecules [9]. There are more than 16,000 lncRNA genes, while estimations suggest more than 100,000 lncRNAs [10]. The expression and abundance of lncRNAs is tissue specific; they have specific cellular localization, and have the ability to alter signaling pathways by interacting with nucleic acids and proteins. They are involved in gene expression regulation at the pre-, post-, and transcriptional level via changes in the chromatin state, and transcriptional activity, splicing, and translation [10][11]. LncRNAs can be subclassified into the groups of very long intergenic RNAs longer than 10 kb, and macroRNAs, which are pathway specific [12]. Five additional subclasses of RNA transcripts can be distinguished: intronic, intergenic, sense, antisense, and bidirectional [7]. Regarding the functional significance of lncRNA, one should be cautious, and conclusions should rely on specific studies with genetic quantitative loss-of-function or gain-of-function models in each species due to the different levels of lncRNA evolutionary conservation [8]. Namely, it has been suggested that lncRNA conservation between species could be considered at four dimensions: at the sequence level, where lncRNAs from different species can have sequence homology and thus similar transcripts; at the structural level, where similar structures could be produced despite a lack of lncRNA sequence homology; at the functional level, where similar functions could be executed despite lncRNAs' different sequences and structures; and at the transcriptional level, where the locus of transcription is conserved, thus mediating functions despite different lncRNA transcripts [8].

3. Small Non-Coding RNA

Small non-coding RNAs (sncRNAs) are 20–200-nucleotide (some around even 400 nts in length) RNA molecules involved in the regulation of gene expression, transcription, translation, splicing, RNA modification, and methylation by the interaction with target mRNA, either through full or partial complementarity [13]. Different types of snRNAs such as microRNAs (miRs), endogenous short interfering RNA (endo-siRNA), piwi-interacting RNA (pi-RNAs), transfer RNA (tRNAs), transfer RNA fragments (tRFs), small nuclear (snRNAs), small nucleolar (snoRNAs), small Cajal-body RNAs (scaRNAs), YRNAs (small stem-loop RNA structures), and short hairpin RNA (shRNA) are synthesized through various biogenesis and maturation pathways by various enzymes and by interaction with different proteins, such as Argonaute or Pi-wi like, combined into the ribonucleoproteins [13][14][15]. Ribonucleoprotein complexes guide non-coding RNA to the target and enable them to interact not only with RNA molecules but with proteins and DNA in some cases, such as microRNAs, thus forming a very complex coding-non-coding RNA-DNA-protein reactome [16][17][18].

So far, the vast number of studies have focused on microRNAs as critical molecules governing development and stress responses. Very recent studies have paid attention to other sncRNAs, tRNA and tRFs, that accumulate in the stressed cell [19]. Because both sncRNAs have a Dicer-dependent biogenesis pathway, it has been proposed that tRFs could function akin to an miR to inhibit the translation or cleave partial complementary target sites [20]. The canonical pathway of miR biogenesis requires two enzymes: Drosha and Dicer. Primary miR transcripts are first cleaved by the nuclear "microprocessor" complex, which contains the enzyme Drosha, and then exported to

the cytoplasm, where they are further processed by another enzyme, Dicer, forming the mature miR. Dicer is critical for most miRNAs, but the 5p miRNAs appear to be produced to some extent even without Dicer. Moreover, unlike canonical miR-21-5p, the synthesis of noncanonical miRs, including miR-320a-3p and miR-484–3p, is Drosha independent [21].

In addition to those described above, it is noteworthy to mention extracellular RNAs (exRNAs) [6] and competing endogenous RNAs (ceRNAs) packed into lipid or protein particles, such as exosomes, microvesicles, or oncosomes, which are especially significant for cancer research, which bare and transfer very important genetic and biological information between cells and organ systems [6]. The competing RNA (ceRNA) term is associated more with their function and role rather than the length or another structural feature or localization. The competing RNA phenomenon is associated more with interaction with long and small non-coding RNA and other transcripts, thus acting as sponges by controlling the amounts of active (free to interact with) non-coding RNA transcripts [22].

4. Challenges Related to the Clinical Application of ncRNAs

The introduction of single-cell sequencing has enabled investigation of not only the landscape of non-coding RNAs (ncRNAs) but also their cellular function. Furthermore, bioinformatic tools are becoming more sophisticated and are used for analyzing ncRNA sequencing data. However, detection of ncRNAs still remains challenging due to the low expression and unique features of certain ncRNAs and the bias of RNA sequencing and bioinformatic methods, leading to erroneous identification of ncRNA species [23].

Currently, eleven RNA-based therapeutics have been approved by the US Food and drug administration and/or the European Medicines Agency involving antisense oligonucleotides (ASOs) or small interfering RNAs (siRNAs) while others, including miRNA mimics and antimiRs, are in phase II or III clinical investigations [24].

The use of miR-based therapeutics has several advantages [25]. Namely, miRs are naturally occurring molecules in human cells, contrary to synthetic chemotherapy compounds or ASOs, and all the mechanisms in cells for their processing and downstream gene target selection are available. Additionally, miRs, by targeting multiple genes within one pathway, show a broader yet specific response [25]. It is noteworthy that circulating miRs (in serum, saliva, and other body fluids), due to their stability and distinctive function, have the advantage of being biomarkers compared with other biomarkers such as proteins (cytokines). Moreover, as controllers of gene transcription, miRNAs and their expression have a higher probability of being related to clinical variables and since they reflect cellular disturbance that occurs years before the appearance of related clinical signs, they enable disease-preventing actions [26].

Clinical applications of all RNA-based therapeutics are hindered by several issues: specificity, related to undesired effects due to uptake in non-target cells or overdosing; delivery, mainly related to inefficient intracellular delivery and the lack of suitable delivery vehicles; and tolerability, caused by the recognition of RNA molecules by pathogen-associated molecular pattern (PAMP) receptors, causing strong immune effects [24]. Therefore, in order to achieve the application of ncRNA as therapeutics and biomarkers, further research should focus on

immunogenicity screening, extensive pharmacodynamic and pharmacokinetic studies regarding delivery systems, and chemical modifications to improve specificity.

4.1. ncRNAs as salivary diagnostic markers of oral inflammatory diseases

Saliva sampling represents cost-effective and non-invasive procedure while ncRNAs, due to their short size, body fluid stability and main location inside exosomes, represent very suitable salivary biomarkers. Prominently investigated, microRNAs are engaged in the regulation of cytokine expression and established to be significant in the pathogenesis of oral inflammatory diseases. As a result, their evaluation in body fluids may be helpful in assessing the disease's status and progression, as well as evaluation of the treatment process.

4.2. ncRNAs in regenerative medicine in the field of oral inflammatory diseases

As important players in the processes of differentiation and proliferation of stem cells, ncRNAs may represent option for regenerative treatment relating to oral diseases. This mainly relies on the role of ncRNAs in osteogenic differentiation of human periodontal ligament stem cells and odontogenic differentiation of human dental pulp stem cells.

4.3. ncRNAs as biomarkers and perspective therapeutics for neuropathic and inflammatory pain

Chronic orofacial pain is usually caused by an inflammation and tissue or nerve injury, which continues even after the initial injury has healed. Engagement of ncRNA in precision oral neuropathic pain medicine represent perspective diagnostic/therapeutic strategy since ncRNA may serve as biofluid/tissue biomarkers of neuropathic orofacial pain, manifested as Temporomandibular disorders, Burning mouth syndrome or Trigeminal neuralgia.

5. Conclusions

Although still in infancy, implementation of precision medicine for oral inflammatory diseases is expected to have a significant impact on patient well-being. At the forefront of precision medicine (in dentistry) is the ability to identify unique characteristics in individual patients with oral inflammatory disease and allowing to select a tailored treatment. Among methods engaged, assessment of *in vivo* molecular characterization (signature) of the disease as well as of host (mal)adaptive immune responses, regenerative medicine, and monitoring of drug and patient outcomes, could rely on ncRNAs.

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