

Interference RNA in immune-mediated oral diseases – minireview

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Abstract

Immune-mediated oral disorders are characterised by their chronicity, and some are refractory to treatment. Interference RNA (iRNA) has been implicated in the underlying mechanism of such immune-mediate oral and refractory inflammatory oral diseases. iRNA-based understanding of the mechanism in these diseases may help to produce non-invasive diagnostic methodologies and treatment modalities of such drug non-responsive diseases. Oral lesions in these immune-mediated diseases can precede the occurrence of lesions in other regions of the body. The early diagnosis and treatment of these drug non-responsive diseases might benefit the patient by reducing chronicity and probably even resolving the disease. This aim of the present minireview is to give an overview of the possible implications of iRNA on the pathogenesis, diagnosis, and treatments of immune-mediated and inflammatory oral diseases. The manuscript can form the framework for research on iRNA in these immune-mediated oral disorders.

Key words: RNA interference, Immune disorders, oral manifestations, RNAi therapies.

(*Centr Eur J Immunol* 2017; 42 (3): 301-304)

Introduction

Andrew Fire and Craig Mello retain the credit for discovering interference RNAs (iRNA). A simple experiment in *Caenorhabditis elegans* on muscle twitching protein expression, with sense and antisense sequence of the transcripts, led to the discovery of iRNA [1]. The interference RNAs control gene expression by post-transcriptional activity and cleaving homologue transcripts [1, 2]. Furthermore, iRNA can be used to regulate the expression of proteins that are not easily accessed by traditional pharmacological approaches, such as molecules lacking ligand-binding domains or proteins that share a high degree of structural homology. Thus, iRNA-based therapeutic approaches are especially appealing to achieve a high degree of specificity and to target molecules that are considered to be “drug non-responsive diseases” [3, 4]. Common chronic oral disease are refractory to medical treatment; this group mostly encompasses of inflammatory and immune mediated diseases. The role of interference RNA in such drug non-responsive chronic diseases with oral manifestations is briefly discussed herein, which is the first of its kind.

Theoretically, literature acknowledges iRNA as small noncoding (nc) RNAs. It comprises small interference RNA (siRNA), Piwi interacting RNA (piRNA), and micro RNA

(miRNA). Short hairpin RNA (shRNA) are synthetically created interference RNAs [5, 6].

siRNAs are short linear RNAs. They consist of nucleotide sequences of 21-25 bp length derived from cleavage of a double-stranded RNA. They block translation by forming a complex with Ago (Argonaute proteins help in interference) and by endonuclease activity causing cleavage of transcripts (process of slicing) [7, 8]. Systemic therapeutic administration of siRNA's into human tumours has been a significant advance in tumour treatment [9].

piRNAs form complexes of RNA protein by their interactive action with piwi proteins [10]. piwi proteins act by targeting transposons [11]. piRNAs commonly function in germ cells, mainly during spermatogenesis [10]. They silence genes by epigenetic and post-transcriptional mechanisms [12].

miRNAs are a highly conserved, small, single-stranded, non-coding RNAs. miRNAs bind to the partial complementary site of mRNA in three different regions 3' or 5' and the coding region, and cause post-translational repression [6, 13]. The miRNA has diverse cellular functions, which include control of cellular functions, embryogenesis, and immune function [14-18]. miRNA expression and function can also be influenced by inflammation and an immunological challenge [19].

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Submitted: 12.07.2016; Accepted: 16.08.2016

In contrast to the above-mentioned interference RNA, shRNAs are artificially created iRNAs that require viral vectors or plasmids to be transcribed into the cell or can also deliver siRNA [20]. The effectiveness of shRNAs is that they are heritable, stable, and more potent in mammalian cells, on par with siRNA [21].

The iRNA subtypes may play an important role in the treatment outcome of immune-mediated oral diseases. Further communications are tailored considering the role of different iRNAs in immune-mediated oral diseases and common inflammatory oral diseases. Oral lesions are a common manifestation of certain immunologically mediated diseases and autoimmune disorders, and these diseases may be untreatable with medications [22, 23]. In autoimmune disorders such as pemphigus the oral lesions are the first manifestation of the disease process in 50-90% of patients [24]. Lesions of oral lichen planus have a greater propensity for recurrence and resistance to treatment compared to the cutaneous lesions [25]. Thus, the dilemma the oral physician faces in such scenarios could be resolved by target therapy.

There is previous literature on the role of interference RNA in oral diseases, but this article, to the best of our knowledge, is the first to focus on the possible role of immune-mediate oral diseases.

Allergic contact stomatitis

Allergic contact stomatitis tends to manifest as lichen planus-like lesions in response to certain materials such as amalgam, gold, and acrylic. The lesions do not resolve despite removal of the offending agent in 5% of cases. Under such circumstances, interference RNA can play a vital role [22]. In addition, the TNF- α expression is also increased in animal models in contact allergies. The TNF- α level is suppressed by siRNA-mediated targeting of TNF- α receptors [26, 27]. This therapeutic application can form the basis of treatment in 5% cases of persistent allergic stomatitis lesions.

Oral lichen planus

The analysis of this mucocutaneous disease exhibits an altered mRNA profile associated with T-cell activation [28]. Erosive oral lichen planus, which has a potential malignant lesion, has been controversial. The promoter of miRNA exhibits methylation in OLP patients, and the expression profile of miRNAs from oral lichen planus (OLP) patient tissue when compared to tissue from healthy individuals revealed that 11 pairs of miRNA and mRNA associated with OLP were functionally associated with the potentially malignant nature of OLP [29, 30]. In lichen planus, the miRNAs upregulated were mi-21, mi-31, mi-132, and mi-155. These miRNAs are also commonly over-expressed in precancer and cancer, thus emphasising

the malignant potential of lichen planus [30]. Oral lesions are more persistent compared to skin lesions in lichen planus [25]. iRNA-based target therapy of such refractory oral lesions could benefit the patient.

Aphthous and Bechet's disease

Alteration in T-cell regulation (Treg cells) has been implicated in the pathogenesis of both aphthous and Bechet's disease. The cardinal factors behind the altered regulatory mechanism include change functioning of the CD4+CD25+ Treg cells, abnormal variants of Toll-like receptors, abnormal cytokine cascade, and production of immunomodulatory enzyme [Indoleamine 2,3-dioxygenase (IDO)]. Decrease in IDO leads to failure of mucosal immune tolerance in aphthous ulcer patients [31]. shRNA-based suppression of IDO has been effective in cancer therapy and could possibly be implicated in the treatment of these immune-mediated diseases. miRNA profile in Treg cells has antiproliferative or proapoptotic activity for suppression of T-cells, which suggests its valuable therapeutic potential in oral aphthous ulcers in the prevention of recurrent lesions, a common concern of both patients and clinicians [32].

Sjögren's syndrome

Sjögren's syndrome is frequently identified by the dentist on the basis signs and symptoms of xerostomia [33]. Ago, GW182, and Rck/p54 are proteins that aid in the functioning of miRNAs and are localised in the cytoplasm as GW bodies (GWB). In patients with Sjögren's syndrome serum analysis revealed auto-antibodies that were generated against GWB. 31% of the patients had these auto-antibodies, denoting altered miRNA functioning [34]. miR-768-3p and miR-574 from saliva have been used as biomarkers for analysis of inflammation and salivary gland dysfunction in Sjögren's syndrome patients [35], thus implicating the role of iRNA as an effective non-invasive diagnostic tool.

Pemphigus

Oral lesions are the initial signs in the majority of pemphigus cases, later progressing to cutaneous lesions [24]. Inhibition of EGFR by shRNA (short hairpin) in human keratinocytes leads to a blockage of the pemphigus auto-antibody-induced acantholysis. This is due to prevention of the desmoglein internalisation and keratin intermediate filament retraction. PV IgG (pemphigus vulgaris antibody)-induced vesicle or blister formation was prevented in a mouse model by inhibition of EGFR both by using EGFR inhibitors and shRNA [36]. Therefore, iRNA-based therapeutic intervention could have a good prognostic outcome in pemphigus lesions that are difficult to treat.

Inflammatory oral lesions

Periodontitis and periapical lesions are the most common inflammatory lesions affecting the oral cavity. The interference RNA can have a profound effect on the suppression of these lesions.

Periodontal diseases and periapical lesions

Periodontal diseases and periapical lesions are the most common causes of tooth extraction and are associated with loss of supporting alveolar bone. Certain cases of periodontal diseases are refractory to any treatment modalities, and iRNA may be an effective tool. Mitogen-activated protein kinase (MAPK) in chronic periodontitis has been implicated in the activation of inflammatory cytokines [37]. MAPK is a molecule that has been associated with difficulty in developing an inhibitor. Hence, in chronic periodontitis, inhibition of bone loss by siRNA to MAPK in palatal regions of artificially-induced bone loss was due to decreased osteoclastogenesis and inflammatory infiltrate [38]. iRNA has a profound effect on new bone formation in areas of bone loss. iRNA in osteoblastic cells increased bone formation via activating BMP-2 signalling on alkaline phosphatase, SMAD phosphorylation, and increased expression of osteocalcin and Runx-2 [39]. Furthermore, siRNA-targeted therapy on TNF- α has prevented osteolysis in animal models of periapical lesions. shRNA-mediated knockdown of gene expression of Atp6i gene (which forms a subunit of osteoclast proton pump) prevented periapical inflammation and bone resorption in an animal model [40]. Previous reports suggest an important role of iRNA in the pathogenesis of oral inflammatory lesions and their therapeutic implications.

Conclusions

Within the limitations of the undertaken review, it is clear that iRNA may provide an insight into the pathogenesis of these immune-mediated oral diseases and refractory inflammatory oral diseases. iRNA-based analyses may prove to be an ideal tool not only for diagnosis but also for the treatment of some of these diseases. Furthermore, these molecules can also be a predictive marker in the prognosis and lead to a favourable outcome for these diseases. Further studies are required to delineate the exact role of iRNA in immune-mediated oral diseases.

The authors declare no conflict of interest.

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