Gene 594 (2016) 30–40

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Research paper

Micronome revealed miR-19a/b as key regulator of SOCS3 during cancer related inflammation of oral squamous cell carcinoma

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ARTICLE INFO

Article history:
Received 6 June 2016
Received in revised form 20 August 2016
Accepted 26 August 2016
Available online 28 August 2016

Keywords:
Oral squamous cell carcinoma
miRNA
Inflammation
Micronome
miRNA-mRNA

ABSTRACT

Although significant advances have been established in molecular biology of Oral squamous cell carcinoma (OSCC), innovative strategies are still required to further understand detailed molecular mechanisms. Using bioinformatic approach, we aim to explore the potential miRNA-mRNA pairs in cancer related inflammatory response and investigate their potential roles as signature miRNA and proteins in the signaling pathway. Firstly, the differentially expressed genes of OSCC were selected which then underwent gene ontology to identify genes engaged in inflammatory response and its regulation. Validated miRNAs were retrieved and miRNAs with complete complementarily with their targets were visualized for miRNA-mRNA regulatory network. Protein-protein interactions of inflammatory and its regulatory genes were analyzed for interacting genes involved in signaling pathway. Eight universal miRNAs were obtained for inflammation and its regulation. miRNA-19a/b showed significant influence in controlling inflammatory response in OSCC. Therefore, micronome on deregulated genes in inflammation identifies miRNA-mRNA pairs which have high potential to be targeted for diagnostic and treatment applications in OSCC.

1. Introduction

Oral cancer is a malignancy that arises from the oral cavity. More than 90% of oral cancers are squamous cells in origin and hence these cancers are often referred to a oral squamous cell carcinoma (OSCC) (Walker et al., 2003). Worldwide, OSCC is the most common cancer, with an estimated 405,000 new cases and 211,000 deaths annually (Parkin et al., 2005). In the USA, about 45,780 cases of oral cancer are

Abbreviations: OSCC, Oral Squamous Cell Carcinoma; miRNA, MicroRNA; NGS, Next Generation Sequencing; STRING, Search Tool for Retrieval of Interacting Genes/Proteins; ACTREC, Advanced Centre for Treatment Research and Education in Cancer; HNOCDB, Head Neck Oral Cancer Database; RGCB, Rajiv Gandhi Centre for Biotechnology; MTIs, miRNA Target Interactions; PPI, Protein Protein Interaction; CRI, Cancer Related Inflammation; ACVR1, Activin A receptor, type I; ADAM8, A Disintegrin and metalloproteinase domain-containing protein 8; AIM2, Absent in melanoma 2; AKT1, V-Akt Murine Thymoma Viral Oncogene Homolog 1; ANXA1, Annexin A1; APOL2, Apolipoprotein L, 2; BLNK, B-Cell Linker; C3, Complement Component 3; CCL19, Chemokine (C-C motif) ligand 19; CCL20, Chemokine (C-C motif) ligand 20; CCL4, Chemokine (C-C motif) ligand 4; CCR2, C-C chemokine receptor type 2; CCR5, C-C chemokine receptor type 5; CD40, Cluster of differentiation 40; CD44, Cluster of Differentiation 44; CEBPB, CCAAT/Enhancer Binding Protein (C/EBP), Beta; CHST2, Carbohydrate (N-Acetylglucosamine-6-O) Sulfotransferase 2; CNR2, Cannabinoid Receptor 2; CSF1R, Colony Stimulating Factor 1 Receptor; CTNNBIP1, Catenin, Beta Interacting Protein 1; CXCL1, (C-X-C motif) ligand 1; CXCL2, Chemokine (C-X-C motif) ligand 2; CXCL3, Chemokine (C-X-C motif) ligand 3; CXCL5, C-X-C motif chemokine 5; CXCL9, Chemokine (C-X-C Motif) Ligand 9; CXCL10, C-X-C motif chemokine 10; CXCL11, C-X-C motif chemokine 11; CXCL13, Chemokine (C-X-C Motif) Ligand 13; CXCR4, C-X-C chemokine receptor type 4; CYSLTR1, Cysteinyl Leukotriene Receptor 1; ELF3, E74-Like Factor 3 (Ets Domain Transcription Factor, Epithelial-Specific); EMR2, EGF-like module-containing mucin-like hormone receptor-like 2; FN1, Fibronectin 1; FOS, FBJ Murine Osteosarcoma Viral Oncogene Homolog; GJA1, Gap Junction Protein, Alpha 1,; HIF1A, Hypoxia-inducible factor 1-alpha; HMOX1, Heme Oxygenase 1); ICAM1, Intercellular Adhesion Molecule 1; IL1RN, Interleukin 1 Receptor Antagonist; IL20, Interleukin 20; IL24, Interleukin 24; IL4R, Interleukin 4 Receptor; IL6, Interleukin 6; IL8, Interleukin 8; IL10, Interleukin 10; IL18, Interleukin 18; ITGB6, Integrin, Beta 6; LYN, Tyrosine-protein kinase Lyn; MGLL, Monoglyceride Lipase; NFKB1, Nuclear Factor Of Kappa Light Polypeptide Gene Enhancer in B-Cells 1; NOS2, Nitric Oxide Synthase 2; OGG1, 8-Oxoguanine DNA Glycosylase; OLR1, Oxidized Low Density Lipoprotein (Lectin-Like) Receptor 1; PIK3CA, Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha; PIK3C2A, Phosphatidylinositol-4-Phosphate 3-Kinase, Catalytic Subunit Type 2 Alpha; PTGES, Prostaglandin E Synthase; PTGS1, Prostaglandin-Endoperoxide Synthase 1; PTGS2, Prostaglandin-Endoperoxide Synthase 2; REL, V-Rel Avian Reticuloendotheliosis Viral Oncogene Homolog; RELA, V-Rel Avian Reticuloendotheliosis Viral Oncogene Homolog A; S100A12, S100 Calcium Binding Protein A12; SDC1, Syndecan 1; SERPINA3, Serpin Peptidase Inhibitor, Clade A (Alpha-1 Antiproteinase, Antitrypsin), Member 3; SPHK1, Sphingosine Kinase 1; SPP1, Secreted Phosphoprotein 1; STAT3, Signal transducer and activator of transcription 3; TFRC, Transferrin Receptor; TGFB1, Transforming Growth Factor, Beta 1; THBS1, Thrombospondin 1; THEMIS2, Thymocyte Selection Associated Family Member 2; TLR2, Toll-like receptor 2; TLR4, Toll-like receptor 4; TNFAIP3, Tumor Necrosis Factor, Alpha-induced Protein 3; TP73, Tumor Protein P73; TSPAN2, Tetraspanin 2; CNR2, Cannabinoid Receptor 2; ETS1, V-Ets Avian Erythroblastosis Virus E26 Oncogene Homolog 1; ETS1, V-Ets Avian Erythroblastosis Virus E26 Oncogene Homolog 1; GPX1, Glutathione Peroxidase 1; GSTP1, Glutathione S-Transferase Pi 1; IER3, Immediate Early Response 3; IL4, Interleukin 4; IL10, Interleukin 10; NFKB1, Nuclear Factor Of Kappa Light Polypeptide Gene Enhancer in B-Cells 1; NT5E, 5′-Nucleotidase, Ecto; RORA, RAR-Related Orphan Receptor A; SOCS3, Suppressor of cytokine signaling 3; TNFAIP3, Tumor Necrosis Factor, Alpha-induced Protein 3; ADAM8, A Disintegrin and metalloproteinase domain-containing protein 8.

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http://dx.doi.org/10.1016/j.gene.2016.08.044
0378-1119/

diagnosed and 8650 death cases are reported annually (Siegel et al., 2015). Oral cancer has emerged as one of the top three causes of cancer related deaths in South Asian countries like India, Bangladesh and Sri Lanka. India has emerged as the epicenter of OSCC as more than half of the worldwide OSCC mortalities are reported from India (Bundela et al., 2014; Coelho, 2012). There is a considerable variation in the incidence of oral cancer for example OSCC account for less than 5% of all cancers in United States, Western Europe and Australia (Ram et al., 2011). In India, OSCC accounts for the top most cause of cancer related deaths (approximately 23% of deaths caused by all cancer type in men). Despite, the advances in surgery radiation and chemotherapy, the 5-year survival rate of OSCC have not changed in the past few decades (Bundela et al., 2014; Zini et al., 2010; Silverman et al., 1984).

The aforementioned discouraging facts mandate the need for advancement of innovative cancer treatment and therapy for OSCC (Takahashi et al., 2016). Previous studies have shown clear link between persistent inflammation and cancer via specific transcription factors that once activator, have the capacity to enhance the expression of genes regulatory the production of inflammatory mediators and to enhance the expression of genes regulatory cell survival and proliferation as well as mediatory angiogenesis, immune evasion and metastasis (Sarode et al., 2015; Feller et al., 2013; Rao et al., 2010).

MicroRNAs (miRNAs) are endogenous, small 17–25 nucleotides that regulate mRNA translation and decay. It has become evident that dysregulated expression of miRNA plays a significant role in development of human cancer, and the miRNA expression pattern is altered in many types of cancer (Bartel, 2004; Bartel, 2009). The significance of microRNAs in cancer is accentuated by the fact that they can function as oncogenes by down-regulating tumor suppressor genes (Iorio et al., 2005) or as tumor suppressor genes by down-regulating oncogenes (Kozaki et al., 2008a). In oral cancer, miRNAs have been shown to affect cell proliferation (Selcuklu et al., 2009), apoptosis (Wong et al., 2008) and even chemotherapy resistance (Yu et al., 2010) in beside cancer diagnosis (Shiiba et al., 2010).

As new structural and functional features of miRNA targeting are discovered and huge amount of expression data is produced by high-

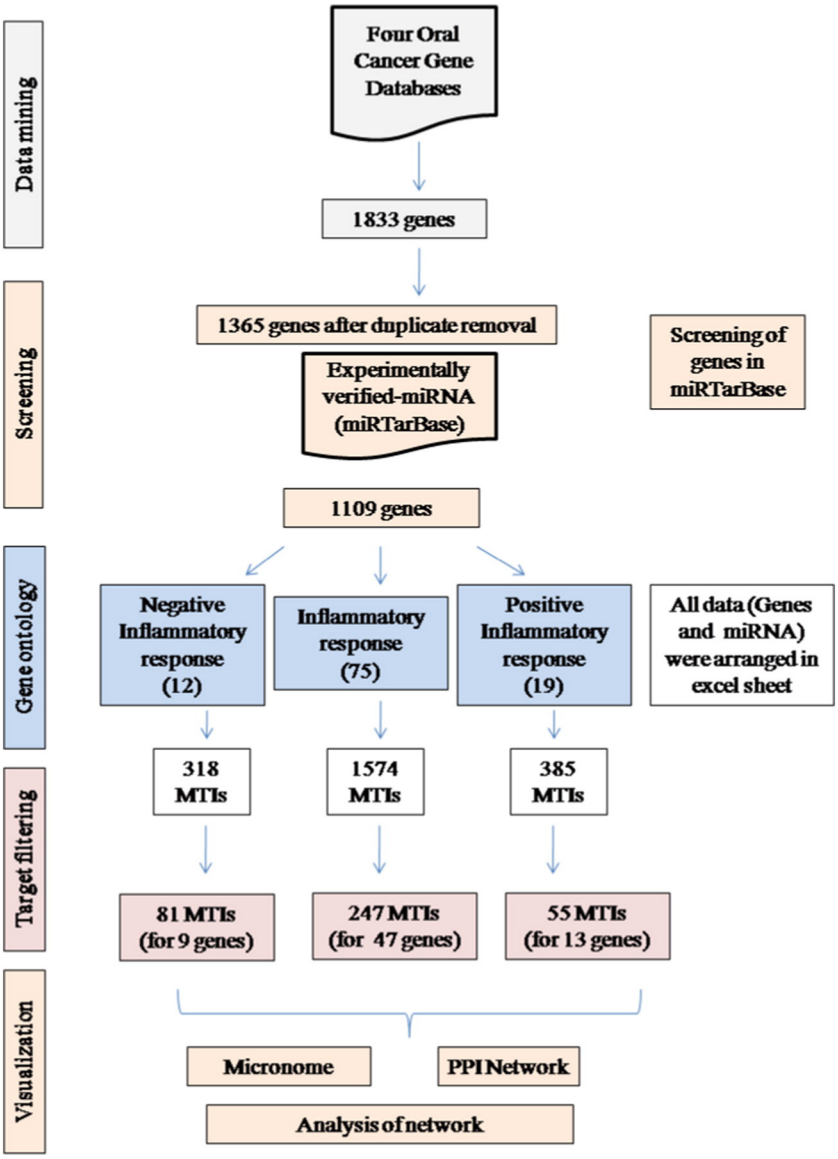

Fig. 1. An overview of the work flow: an overview for the work flow has been summarized in different steps i.e. Data Mining: Four OSCC gene databases were used to retrieve the dysregulated genes; Screening: all genes were screened in the miRTarBase; Gene Ontology: Functional classification was done according to biological processes in STRING v 10; Target filtering: All miRNAs were filtered for their direct targets and Visualization: Interactions between miRNA-mRNA were viewed and analyzed in Cytoscape 3.3.0 and further crucial interactions were evaluated through Protein-Protein Interaction (PPI). Analysis of network to determine small world networks.