Mining Potential MicroRNA Biomarkers related to IQGAPs of Thyroid Carcinoma through \textit{in silico} process.

Stefanus Satrio Hadi Wibowo 1, David Agustriawan 2, Jeremias Ivan 3, Arli Aditya Parikesit 4 and Rizky Nurdiansyah 5

1,2,3,4,5 Department of Bioinformatics, School of Life Sciences, Indonesia International Institute for Life Sciences

Email: david.agustriawan@i3l.ac.id

Abstract. Thyroid carcinoma (THCA) incidence has already increased by 6.2\% per year and become the sixth most common malignancy diagnosed in women. The IQGAP-miRNA interaction was known to affect many cancer types, including the carcinoma. Through \textit{in silico} process known as miTS, a miRNA biomarker was researched along with its molecular pathway intervention. The input of the pipeline was THCA patients from GDC Data Portal ID and it underwent data mining, statistical, and visualization process using bioinformatics tools and databases such as TCGA Assembler in R Studio, Matlab, and STRING database. The aim of this study is to discover a potential microRNA biomarker regulating the expression of IQGAP in THCA along with its acknowledged pathways. Our study shows that (1) IQGAP1 become a promoter to the growth of THCA through supporting the growth of adherens junctions in cytoskeleton, (2) IQGAP2 was a cancer suppressor, (3) miR-146b have relation with MMP16, (4) it is still unknown whether miR-146b upregulate or downregulate the PDGFRA expression in THCA. Furthermore, the pipeline of the process and command line used was provided in an open-source package (https://github.com/stefanuswibowo/miTS_Pathway).

1. Introduction

The term biomarker, a portmanteau of ‘biological marker’, refers to a broad subcategory of medical signs that can be measured accurately and reproducibly to identify whether a subject is in sick or healthy condition [1]. In oncology, the study and treatment of tumours, biomarkers identification allows molecular characterization of cancer signatures and provide information relevant for personalized treatment [2]. A research to validate biomarker would cost \$100.000-$2 million per biomarker candidate with more than one-year duration to examine it [3]. Reducing the cost and time of the research by eliminating the cancer biomarker candidate is where the bioinformatic, an interdisciplinary field that utilize computing technology to understand and solve biology problem, step in [4].

American Cancer Society estimate thyroid carcinoma (THCA) incidence already increasing by 6.2\% per year and become the sixth most common malignancy diagnosed in women [5]. Among THCA, thyroid papillary carcinoma becomes the most frequent type of thyroid malignancy due to its frequently genetic alterations which lead to difficulties in predict thyroid carcinoma’s biological behaviour [6]. In fact, there are no known effective and reliable biomarkers to distinguish benign thyroid carcinomas [7]. However, previous studies have indicated microRNA (miRNA), a class of small noncoding RNAs, profiles may be diagnostic and/or prognostic markers for numerous cancers, including THCA [8].

MicroRNA (miRNA) is a short (~22 nucleotides) non-coding RNA molecules that regulate gene expression at the post-transcriptional level by inhibiting translation or initiating mRNA degradation and are dysregulated in most of the human cancers [9]. Up until now, there are only 2000 miRNA in humans.
has been discovered, however, they regulate 30% of all genes [10] [11]. Due to their role in gene regulation, miRNAs have been identified as a high-value targets for cancer therapy [12].

IQ motif-containing GTPase-activating proteins (IQGAP) is a scaffold protein that facilitate the formation of cytoskeletal dynamics, regulate intracellular signalling and its interactions [13]. Human express three related isoforms IQGAP1, IQGAP2, and IQGAP3. With several binding factors, IQGAP1 has been shown to promote metastasis and tumorigenesis causing it to be labelled as an oncogene while IQGAP2 in the other hand is a tumour suppressor [14] [15]. Unfortunately, IQGAP3 function in thyroid carcinoma is still unknown during the time of writing. There is a growing evidence of IQGAP2 as a novel tumour suppressor counteracting the effects of IQGAP1, especially in hepatocellular carcinoma (HCC) [16] [17]. In HCC itself, it has been reported recently that miRNA with the name: miR-124 and miR-203 has regulated IQGAP1 expression [18]. Therefore, it is possible to find a relation between miRNA and IQGAPs in thyroid carcinoma.

There are many various approaches in a silico pipeline to find prominent biomarkers of miRNA related to cancer i.e. genome-wide analysis (GWA) and miTS (miRNA data and tissue specificity of diseases). GWA use a New Genome Sequencing data as the source of the research and utilize algorithm to process the data [19]. Different with miTS, they utilize available data from bioinformatics database to be computed using statistical correlation [9]. Since a New Genome Sequencing data is mostly not available in public and an effective one could cost 7-200$ per GB, utilizing a free to access tissue specific disease such as The Cancer Genome Atlas (TCGA) will greatly reduces the research run cost, therefore, making miTS a suitable approach to conduct cancer biomarker candidate screening and elimination.

Here, the study uses de novo miTS approach to identify a potent biomarker for thyroid carcinoma by performing data mining from bioinformatic databases: TCGA and MiRTarbase by using Phyton and R Studio, statistical analysis using Microsoft Excel and Matlab. The study also identifies the biomarker’s interaction into human metabolic pathway, a feature that was not present in previous miTS method, by using bioinformatics tools and database: STRING database and KEGG Pathway.

2. Methods

The method summary was provided in figure 1, the detailed was presented on paragraphs. The implementation of the pipeline was provided at https://github.com/stefanuswibowo/miTS_Pathway.

2.1. IQGAP – miRNA correlation

2.1.1. Data pre-processing

The dataset was taken from TCGA projects that were stored in the repository of GDC Data Portal (https://portal.gdc.cancer.gov/repository) [20]. In this research, the dataset was taken from thyroid carcinoma project (TCGA-THCA). The metadata of both gene and miRNA expressions dataset were selected to the cart and downloaded from the GDC Data Portal. The parameter for filtering the gene expression data was: Thyroid (Primary Site), TCGA-LGG (Project ID), HTSeq–FPKM-UQ (Workflow Type), Transcriptome Profiling (Data Category), and Gene Expression Quantification (Data Type). The parameter for filtering the miRNA expression data was: Thyroid (Primary Site), TCGA-THCA (Project ID), Transcriptome Profiling (Data Category), and miRNA Expression Quantification (Data Type). The other parameters were left unchecked. After the data filtration has finished, it was download as a metadata. The downloaded file undergoes conversion into CSV file format by using JSON to CSV Converter (https://konklone.io/json/).

The converted metadata was imported into Phyton 3.6. As the metadata contain a specific barcode (ID) to every patient, the first fifteen characters of all TCGA IDs from both metadata, which were patient-specific, were extracted and added into a new list. Then, both lists were matched: IDs that appear in both were retrieved. The process resulted in a list of IDs (patients) whose have both gene and miRNA expression data. This list of IDs was later entered TCGA Assembler 2.0.5, an implementation of R code for downloading gene and miRNA expression data [21] [22]. Here, only the first twelve characters of the ID that inserted, since it is the program requirement. The comprehensive manual to use it modules and codes were accessible from http://www.compgenome.org/TCGA-Assembler/. After the gene and
miRNA data were separately downloaded, they were imported into Microsoft Excel and saved in XLSX format.

2.1.2 Correlation analysis
The gene and miRNA expression file were imported into Matlab R2018a. Then, an automatic spearman correlation test was performed between the IQGAP gene and miRNA expression through lines of code. The test resulted IQGPA-miRNA interactions with the highest Spearman Rho (R) and significance (p) value lower than 0.05.

2.1.3 Validation
The value of Spearman Rho and significance was tested manually through a series of Microsoft Excel calculation. The top three IQGAP – miRNA interactions from the previous process were validated using available journals. Each of their presence in thyroid carcinoma was browsed by using PubMed, a trusted source to find references and abstracts on life sciences and biomedical topics created by United States National Library of Medicine using keywords “thyroid” and each of the miRNA’s name.

2.2. IQGAP – miRNA pathway

2.2.1 Protein target
The highest correlated miRNA with IQGAP in Thyroid Carcinoma was used as the keyword in MiRTarBase, a database for microRNA and its targeted protein [23] [34]. From dozens of targeted proteins, only those who recognized to have strong evidence and their interaction have been validated by reporter assay, western blot, and qPCR technique underwent the further investigation.

2.2.2 IQGAP - miRNA’s protein target relationship
The selected protein from the previous step’s interaction to IQGAP protein was figured out through using STRING, a database recording interaction of cellular process across proteins [25]. The option “multiple proteins” was selected since the relation query will need at least two protein. The inserted protein name was the name of one of the selected proteins and “IQGAP1”.

2.2.3 Validation
Validation of protein target was performed using KEGG and PubMed. KEGG is an encyclopedia of databases dealing with genomes, biological pathways, diseases, drugs, and chemical substances [26]. KEGG was used to validate since it has been used as a trusted reference within molecular biology scientist community. The KEGG database on biological pathways was utilized to discover the protein interaction by insert “IQGAP1” as the keyword. The result was accessed and the name of each protein target from the previous step was inserted as keywords in the search tab. The function of each protein and a possible or documented relation was browsed in PubMed by using keywords of a combination or independent word of “IQGAP1”, “Thyroid”, ”miR-146b” and the name of each targeted protein.
3. Results and discussion

3.1 IQGAP – miRNA correlation

The GDC Data Portal configuration resulted 571 patient ID. However, during the extraction progress in python, only 263 patient’s ID have both data of gene and miRNA. The 263 patients lead to 4638 type of miRNA which only the highest three was taken and presented to be later investigated (Table 1). The highest correlation value reaches -0.71 was owned by hsa-miR-146b. Differential overexpression of hsa-miR-146b has been studied for decade. In several types of tumor, i.e. gliomas, lung cancer, pancreatic cancer and osteosarcoma; the hsa-miR-146b has been considered as one of the inhibitors of migration and invasion [27] [28] [29]. While in thyroid carcinoma, the overexpression of hsa-miR-146b was consider positively correlated with the malignancy and aggressiveness of the cancer [30] [31]. A study to find potential prognostic microRNAs in thyroid cancer also find that miR-146b could become a prominent prognostic, along with miR-6860. In their study, miR-146b was predicted to target MMP16, Matrix metalloprotease-16, a protein family that involved in the breakdown of extracellular matrix [31]. The negative rho value of hsa-miR-146b with IQGAP2 means it is not related with IQGAP2 but related with either IQGAP1 or IQGAP3. A study concludes the effects of miR-146b-5p in papillary thyroid carcinoma are mostly associated with regulating the development of cytoskeleton [32]. Among all IQGAP, IQGAP1 has been extensively reviewed as the regulator of cytoskeletal growth and its increased expression, especially in Follicular Variant Papillary Thyroid Carcinoma [33] [34] [35].

Table 1. Top 3 IQGAP – miRNA negative correlations in THCA dataset. The table was sorted based on the Spearman Rho value (from the biggest to the smallest).

| No. | IQGAP  | miRNA         | Rho value | P value |
|-----|--------|---------------|-----------|---------|
| 1   | IQGAP2 | hsa-miR-146b  | -0.71     | < 0.001 |
| 2   | IQGAP2 | hsa-miR-6860  | -0.64     | < 0.001 |
| 3   | IQGAP3 | hsa-miR-30a   | -0.63     | < 0.001 |

3.2 IQGAP – miRNA Pathway

There are seven targets of hsa-miR-146b in MiRTarBase that their evidence has been categorized as strong (Table 2). The target consists of six protein and one RNA. Because STRING database only
consists for protein data, the RNA was removed from the study. The relationship between miRNA’s protein target and IQGAP1 was browsed in STRING database and compiled as a summary in Table 2.

**Table 2.** Protein target of hsa-miR-146b with strong evidence in miRTarBase and its relationship with IQGAP1 in STRING database.

| Target   | Description                                    | Class          | Relationship with IQGAP1          |
|----------|-----------------------------------------------|----------------|----------------------------------|
| MMP16    | Matrix metalloproteinase-16                   | Protein        | Related                          |
| TRAF6    | TNF receptor associated factor 6              | Protein        | None                             |
| IRAK1    | Interleukin-1 receptor-associated kinase 1    | Protein        | None                             |
| PDGFRA   | Plateled-derived growth factor receptor alpha | Protein        | Indirect and related             |
| ZNRF3    | Zinc and Ring Finger 3                        | Protein        | Related                          |
| SLC5A5   | Solute Carrier Family 5 Member 5              | Protein        | None                             |
| MALAT1   | Metastasis Associated Lung Adenocarcinoma Transcript 1 | RNA           | Unidentified                     |

The relation of MMP16, TRAF6, IRAK1, PDGFRA, ZNRF3, and SLC5A5 to IQGAP1 was presented in Figure 2. The relation was described through data visualization that indicated by arrow color and shape as presented in the label.
Figure 2. The relation of hsa-miR-146b protein targets with IQGAP1. (A) MMP16 (B) TRAF6 (C) IRAK1 (D) PDGFRA (E) ZNRF3 (F) SLC5A5. The legend of the graph is located at the bottom of the graph. The miRNA protein target was located on upper left, IQGAP1 was located on upper right, the molecule interaction cascade was positioned in between. The figure was taken from STRING database.

Figure 2A shows the cascade relation of MMP16 into IQGAP1. The figure show MMP16 isn’t related directly to IQGAP1, once MMP16 was deactivated by TIMP2 (TIMP metallopeptidase inhibitor 2), it will promote CDH1 (Cadherin I) to be activated which later suppress the expression of IQGAP1. The interaction explains that they are related. In our opinion, they are related because even if each have different function, both similarly promote cell growth. IQGAP1 plays a role in regulating the growth of adherens junctions in cytoskeleton while MMP16 functioned as a mediator for proteolytic switch to promote cell-cell adhesion, collagen alignment, and lymphatic invasion in melanoma [35] [36].

Figure 2B shows the cascade relation of TRAF6 into IQGAP1. The figure show that IQGAP1 was poorly related with TRAF6 because the relation of CDC42 (Cell division control protein 42 homolog) and TLR4 (Toll-like receptor 4) was defined as none/insignificant (indicated by grey line in Figure 2B). Overall, the cascade explains that the TRAF6 wasn’t related with IQGAP1. In our opinion, this make sense because TRAF6 have a different function with IQGAP1. While TRAF6 is an adaptor protein that mediates a wide array of protein-protein interactions to evade apoptosis, IQGAP1 plays a role in regulating the growth of adherens junctions in cytoskeleton [35] [37].

Figure 2C shows the cascade relation of IRAK1 into IQGAP1. The figure show that IQGAP1 was poorly related with IRAK1 since the relation between PIK3CB (Phosphatidylinositol-4,5-Biphosphate...
3-Kinase Catalytic Subunit Beta) and IRAK1 was defined as none/insignificant, indicated by grey line. Overall, the cascade explains that IRAK1 wasn’t related with IQGAP1. In our opinion, this make sense because IRAK1 have a different function with IQGAP1. While IRAK1 is associated with TRAF6 to evade apoptosis, plays a role in regulating the growth of adherens junctions in cytoskeleton [35] [38].

Figure 2D shows the cascade relation of PDGFRA into IQGAP1. The figure show that PDGFRA related indirectly to IQGAP1. In order, PDGFRA will activate: PIK3RI (Phosphoinositidase-3 Kinase Regulatory Subunit 1), RAC1 (Rac Family Small GTPase 1), CDH1 (Cadherin 1), SRC (SRC Proto-Oncogene), then lastly IQGAP1 itself. The cascade show that PDGFRA play an important role in activating IQGAP1, thus they are indirectly related. In KEGG Pathway, their relation was well described in Figure of Actin Cytoskeleton (Figure 3), together they regulate the growth of adherens junctions in cytoskeleton [43]. Figure 3 showed that RTK (Receptor tyrosine kinase) contribute in the activation of IQGAP1 (Marked by green color). Up until now, there are around 20 RTK Class, class III is the class for whole PDGFRA family [39]. To sum up, hsa-miR-146b regulate the IQGAP1 expression indirectly by regulating the expression of PDGFRA protein family or RTK Class III which later will activate/deactivade protein cascade for the activation of IQGAP1.

PDGFRA work as a mitogen, chemical substance that encourages a cell to commence cell division to trigger mitosis, by the driven of plateled-derived growth factor, written as GF in Figure 3 [48]. A study state that hsa miR-146b down-regulated the expression of target PDGFRA in hematopoietic maturation [40]. However, whether the hsa-miR-146b upregulated or downregulated the PDGFRA in THCA is still an open question since no literature explain it at the time of writing.

Figure 2E shows the cascade relation of ZNRF3 into IQGAP1. The figure show that ZNRF3 isn’t related directly to IQGAP1. ZNRF3 was known to bind, catalyze, and react with UBA52 (Ubiquitin A-52 Residue Ribosomal Protein Fusion Product 1). Later CDC42 bind and react to SRC (SCR-Proto Oncogene), promoting the IQGAP1 expression. The interaction explains that they are related. In our opinion, even if they have different function they are related because both promote cell growth. IQGAP1 plays a role in regulating the growth of adherens junctions in cytoskeleton while underexpression of ZNRF3 significantly support the cancer growth by intervening the Wnt/β-catenin pathway [35] [41].

Figure 2F shows the cascade relation of SLC5A5 into IQGAP1. The figure show that SLC5A5 don’t have any interaction with IQGAP1. The explanation of their unrelated cascade can be described by their function. SLC5A5 encodes the sodium iodine symporter which make it responsible for the uptake of iodine in tissues especially thyroid and breasts [42]. Different with IQGAP1 which plays a role in regulating the growth of adherens junctions in cytoskeleton.

Due to the limitation of sample’s population from database, miTS technique can’t replace GWA if the population sample was not available in GDC Data Portal. However, the incompleteness data of population will be fixed by the continuous improvement of data source. To sum up, our research reveals a promising approach to seeks cancer biomarker, allowing research cost and time reduction.
4. Conclusion
IQGAP1 become a promoter to the growth of THCA through supporting the growth of adherens junctions in cytoskeleton. The negative rho value of IQGAP2 into mir-146b strengthen previous study that identify it as a cancer suppressor. Our finding supports previous study that describe that miR-146b have relation with MMP16. However, it is still unknown whether mir-146b upregulate or downregulate the PDGFRA expression in THCA.

5. Author contributions
SSHW prepared the IQGAP-miRNA pathway’s pipeline and executed the protocols. DA prepared the Matlab code and supervised the research. JI prepared the Python code and helped in executing the protocols. RN and AAP reviewed the manuscript.

6. Acknowledgement
The authors would like to thanks Research and Community Engagements Institute (LPPM) and Bioinformatics Department of i3L for funding and reviewing this research.

7. References
[1] Strimbu K & Tavel JA 2010 What are Biomarkers? Curr Opin HIV AIDS, 5(6) 463–466
[2] Nalejka E, Mączyńska E & Lewandowska MA 2014 Prognostic and predictive biomarkers: Tools in personalized oncology Molecular Diagnosis and Therapy 18(3) 273–284
[3] Paulovich AG, Whiteaker JR, Hoofnagle AN & Wang P 2008. The interface between biomarker discovery and clinical validation: The tar pit of the protein biomarker pipeline Proteomics - Clinical Applications 2(10–11) 1386–1402
[4] Yousef M, Showe L, & Showe M 2009 A study of microRNAs in silico and in vivo: Bioinformatics approaches to microRNA discovery and target identification FEBS Journal 276(8) 2150–2156

[5] Jemal A, Siegel R, Ward E, Hao Y, Xu J & Thun MJ 2009 Cancer Statistics CA: A Cancer Journal for Clinicians 59(4) 225–249

[6] Xing M 2013 Molecular pathogenesis and mechanisms of thyroid cancer Nature Reviews Cancer 13(3) 184–199

[7] Yu S, Liu Y, Wang J, Guo Z, Zhang Q, Yu F, et al. 2012 Circulating microRNA profiles as potential biomarkers for diagnosis of papillary thyroid carcinoma Journal of Clinical Endocrinology and Metabolism 97(6) 2084–2092

[8] Brase JC, Wuttig D, Kuner R, & Sültmann H 2010 Serum microRNAs as non-invasive biomarkers for cancer Molecular Cancer 9(1) 306

[9] Yu L, Zhao J, & Gao L 2018 Predicting Potential Drugs for Breast Cancer based on miRNA and Tissue Specificity International Journal of Biological Sciences 14(8) 971–982

[10] Fabian MR & Sonenberg N 2012 The mechanics of miRNA-mediated gene silencing: A look under the hood of miRISC Nature Structural and Molecular Biology 19(6) 586–593

[11] Hammond SM 2015 An overview of microRNAs Advanced Drug Delivery Reviews 87 3–14

[12] Schmidt MF 2014 Drug target miRNAs: Chances and challenges Trends in Biotechnology 32(11) 578–585

[13] Hedman AC, Smith JM & Sacks DB 2015 The biology of IQGAP proteins: beyond the cytoskeleton EMBO Reports 16(4) 427–446

[14] Liu Z, Liu D, Bojdani E, El-Naggar AK, Vasko V & Xing M 2010 IQGAP1 Plays an Important Role in the Invasiveness of Thyroid Cancer Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 16(24) 6009–6018

[15] Vaitheesvaran B, Hartil K, Navare A, Zheng POB, Golden A, et al. 2014 Role of the tumor suppressor IQGAP2 in metabolic homeostasis: Possible link between diabetes and cancer Metabolomics 10(5) 920–937

[16] Schmidt VA 2012 Watch the GAP: Emerging Roles for IQ Motif-Containing GTPase-Activating Proteins IQGAPs in Hepatocellular Carcinoma International Journal of Hepatology 2012 1–8

[17] Zoheir KM, Abd-Rabou AA, Harisa GI, Kumar A, Ahmad SF, Ansari MA & Abd-Allah AR 2016 IQGAP1 gene silencing induces apoptosis and decreases the invasive capacity of human hepatocellular carcinoma cells Tumor Biology 37(10) 13927–13939

[18] Furuta M, Kozaki KI, Tanaka S, Arii S, Imoto I & Inazawa J 2009 miR-124 and miR-203 are epigenetically silenced microRNAs in hepatocellular carcinoma Carcinogenesis 31(5) 766–776

[19] Bhownick SS, Saha I, Bhattacharjee D, Genovese LM & Geraci F 2018 Genome-wide analysis of NGS data to compile cancer-specific panels of miRNA biomarkers PLoS ONE 13(7) e0200353

[20] Grossman RL, Heath AP, Ferretti V, Varmus HE, Lowy DR, Kibbe WA & Staudt LM 2016 Toward a Shared Vision for Cancer Genomic Data New England Journal of Medicine 375:12 1109-1112

[21] Zhu Y, Qiu P, & Ji Y 2014 TCGA-assembler: Open-source software for retrieving and processing TCGA data Nature Methods 11(6) 599–600

[22] Wei L, Jin Z, Yang S, Xu Y, Zhu Y & Ji Y. 2018 TCGA-assembler 2: software pipeline for retrieval and processing of TCGA/CPTAC data Bioinformatics 34(9) 1615–1617

[23] Hsu S, Lin F, Wu W, Liang C, Huang W, Chan W, et al. 2018 miRTarBase: a database curates experimentally validated microRNA – target interactions 39(August) 163–169

[24] Chou CH, Shrestha S, Yang CD, Chang NW, Lin YL, Liao KW, et al. 2018 MiRTarBase update 2018: A resource for experimentally validated microRNA-target interactions Nucleic Acids Research 46(D1) D296–D302
[25] Szklarczyk D, Morris JH, Cook H, Kuhn M, Wyder S, Simonovic M, et al. 2017 The STRING database in 2017: Quality-controlled protein-protein association networks, made broadly accessible Nucleic Acids Research 45(D1) D362–D368
[26] Kanehisa M, Furumichi M, Tanabe M, Sato Y & Morishima K 2017 KEGG: new perspectives on genomes, pathways, diseases and drugs Nucleic Acids Research 45(D1), D353–D361.
[27] Xia H, Qi Y, Ng SS, Chen X, Li D, Chen S, et al. 2009 microRNA-146b inhibits glioma cell migration and invasion by targeting MMPs Brain Res 1269(7) 158–165
[28] Katakowski M, Zheng X,jiang F, Rogers T, Szalad A & Chopp M 2010 MiR-146b-5p suppresses EGFR expression and reduces in vitro migration and invasion of glioma Cancer Invest 28(10) 24–30
[29] Patnaik SK, Kannisto E, Mallick R, & Yendamuri S 2011 Overexpression of the Lung Cancer- Prognostic miR-146b MicroRNAs Has a Minimal and Negative Effect on the Malignant Phenotype of A549 Lung Cancer Cells PLoS ONE 6(7) e22379
[30] Deng X, Wu B, Xiao K, Kang J, Xie J, Zhang X, et al. 2015 MiR-146b-5p promotes metastasis and induces epithelial-mesenchymal transition in thyroid cancer by targeting ZNRF3 Cell Physiol Biochem 35 71–82
[31] Tang J, Kong D, Cui Q, Wang K, Zhang D, Yuan Q, et al. 2018 Bioinformatic analysis and identification of potential prognostic microRNAs and mRNAs in thyroid cancer PeerJ 6 e4674
[32] Lima CR, Geraldo MV, Fuziwara CS, Kimura ET & Santos MF 2016 MiRNA-146b-5p upregulates migration and invasion of different Papillary Thyroid Carcinoma cells BMC Cancer 16(1) 1–13
[33] White CD, Khurana H, Gnatenko DV, Li Z, Odze RD, Sacks DB & Schmidt VA 2010 IQGAP1 and IQGAP2 are Reciprocally Altered in Hepatocellular Carcinoma BMC Gastroenterology 10 1–10
[34] Watanabe T, Wang S & Kaibuchi K 2015 IQGAPs as Key Regulators of Actin-cytoskeleton Dynamics Cell Structure and Function 40(2) 69–77
[35] Yuan Z, Zhang W & Tan W 2013 A Labile Pool of IQGAP1 Disassembles Endothelial Adherens Junctions International Journal of Molecular Sciences 14(7) 13377–13390
[36] Tatti O, Gucciardo E, Pekkonen P, Holopainen T, Louhimo R, Repo P, et al. 2015 MMP16 mediates a proteolytic switch to promote cell-cell adhesion, collagen alignment, and lymphatic invasion in melanoma Cancer Research 75(10) 2083–2094
[37] Zhang X, Li C-F, Zhang L, Wu C-Y, Han L, Jin G, et al. 2016 TRAF6 restricts p53 mitochondrial translocation, apoptosis and tumor suppression Molecular Cell 64(4) 803–814
[38] Li N, Jiang J, Fu J, Yu T, Wang B, Qin W, et al. 2016 Targeting interleukin-1 receptor-associated kinase 1 for human hepatocellular carcinoma Journal of Experimental & Clinical Cancer Research: CR 35(1) 140
[39] Szerlip NJ, Pedraza A, Chakravarty D, Azim M, McGuire J, Fang Y, et al. 2012 Intratumoral heterogeneity of receptor tyrosine kinases EGFR and PDGFRA amplification in glioblastoma defines subpopulations with distinct growth factor response Proceedings of the National Academy of Sciences of the United States of America 109(8) 3041–3046
[40] Ozawa T, Brennan CW, Wang L, Squatrito M, Sasayama T, Nakada M, et al. 2010 PDGFRA gene rearrangements are frequent genetic events in PDGFRA-amplified glioblastomas Genes & Development 24(19) 2205–2218
[41] Zhai P-F, Wang F, Su R, Lin H-S, Jiang C-L, Yang GH, et al. 2014 The Regulatory Roles of MicroRNA-146b-5p and Its Target Platelet-derived Growth Factor Receptor α (PDGFRA) in Erythropoiesis and Megakaryocytogenesis The Journal of Biological Chemistry 289(33) 22600–22613
[42] Qiu W, Yang Z & Zheng Q 2016 ZNRF3 is downregulated in papillary thyroid carcinoma and suppresses the proliferation and invasion of papillary thyroid cancer cells Tumour Biol 37(9) 12665-12672