A Combined Bioinformatics and Literature Based Approach for Identification of Long Non-coding RNAs That Modulate Vitamin D Receptor Signaling in Breast Cancer

Kombinovaný bioinformatický a literární přístup k identifikaci dlouhých nekódujících molekul RNA, které modulují signalizaci přes receptor vitaminu D u karcinomu prsu

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Summary

Background: Long non-coding RNAs (lncRNAs) as an important fraction of human transcriptome have been shown to exert fundamental role in regulation of signaling pathways implicated in carcinogenesis. Among them is vitamin D receptor (VDR) signaling whose participation in various cancers including breast cancer (BC) is evident. In spite of the presence of several evidences for participation of lncRNAs as well as VDR signaling in BC pathogenesis, no comprehensive study has evaluated the link between lncRNA dysregulation and VDR signaling in BC. ***Aim:*** To introduce a bioinformatics approach for identification of lncRNAs that modulate VDR signaling in BC. This approach includes co-expression analysis, in silico identification of lncRNAs that target VDR and literature search. ***Conclusions:*** Tens of lncRNAs are predicted to affect VDR signaling. Among them are some lncRNAs such as *MALAT1* which has prominent role in BC pathogenesis. Identification of the lncRNAs that influence VDR gene expression is possible through in silico analysis. Considering the prominent role of VDR in BC pathogenesis as well as availability of VDR modulating agents, evaluation of VDR signaling pathway and related networks are of practical significance and bioinformatics tools are expected to facilitate such action.

Key words

vitamin D receptor – long non-coding RNAs – co-expression – bioinformatics – calcitriol receptor – computational biology

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Souhrn

Úvod: Bylo prokázáno, že dlouhé nekódující RNA (lncRNA) jako důležitá frakce lidského transkriptomu hrají zásadní roli při regulaci signálních drah, které se podílejí na karcinogenezi. Mezi nimi je signalizace receptoru vitaminu D (VDR), jejíž účast na různých nádorech vč. nádoru prsu (breast cancer – BC) je patrná. Navzdory přítomnosti několika důkazů účasti lncRNA, stejně jako signalizace VDR v patogenezi BC, žádná souhrnná studie nehodnotila vztah mezi dysregulací lncRNA a signalizací VDR u BC. ***Cíl:*** Zavést bioinformatický přístup k identifikaci lncRNA, které modulují signalizaci VDR u BC. Tento přístup zahrnuje koexpresní analýzu, in silico identifikaci lncRNAs, které jsou zaměřeny na VDR a literární vyhledávání. ***Závěr:*** Předpokládá se, že desítky lncRNA ovlivní signalizaci VDR. Mezi nimi jsou některé lncRNA, jako je *MALAT1*, který má významnou roli v patogenezi BC. Identifikace lncRNA, které ovlivňují expresi genu VDR, je možná pomocí in silico analýzy. Vzhledem k prominentní roli VDR v patogenezi BC a dostupnosti modulačních činidel VDR je hodnocení VDR signalizační dráhy a souvisejících sítí praktického významu a nástroje bioinformatiky by měly usnadnit tuto činnost.

Key words

receptor vitaminu D – dlouhé nekódující molekuly RNA – koexprese – bioinformatika – receptor kalcitriolu – výpočetní biologie

Introduction

Breast cancer (BC) as the most common women's malignancy is regarded as an important health problem [1]. Several researchers have identified biomarkers for early detection or prognosis evaluation of BC patients [2–4]. Among pathways which involvement in BC pathogenesis has been well studied is vitamin D receptor (VDR) signaling pathway. The VDR is a member of the nuclear class II receptor family and a ligand transcription factor that facilitates the roles of 1,25-dihydroxyvitamin D3 in cell growth and differentiation [5]. In BC samples, VDR expression has been negatively associated with aggressive tumor features, such as large tumor size, hormonal receptor negativity, and triple-negative subtype [6]. In addition, elevated expression of VDR in breast tumors has been associated with a lower risk of cancer-associated mortality [7,8]. The protective effect of vitamin D against other types of human cancers, such as skin cancer, has also been documented [9]. Such effect has been associated with alterations in the expression of certain transcripts including long non-coding RNAs (lncRNAs) in a way that these lncRNAs have been suggested as skin cancer biomarkers which are secreted into the blood or urine via exosomes [10]. In general, lncRNAs comprise an important portion of human transcriptome with fundamental roles in virtually every aspect of cell physiology [11]; their aberrant expression has been associated with pathologic conditions such as cancer [12–18]. More specifically, VDR-regulated lncRNAs has been shown to participate in imprinting, tumor suppression and invasion/metastasis which implies their involvement in the protective effect of VDR signaling against skin cancer [10]. LncRNAs expression in skin cells changes in response to vitamin D in a way that diminishes their oncogenic activity while increasing their tumor suppressive role [9]. In BC, there is also evidence for the presence of a link between VDR signaling and lncRNAs. For instance, *H19* has been shown to be up-regulated in a significant proportion of BC tissues [19]. On the other hand, *H19* has been shown to suppress VDR expression via microRNA 675-5p (miR-675-5p) in colon cancer. Besides, *H19* up-regulation leads to vitamin D resistance both *in vitro* and *in vivo* [20]. Recently, we have introduced a bioinformatics approach for identification of miRNAs implicated in BC [21].

In spite of the presence of evidence supporting the individual role of lncRNAs as well as VDR signaling in BC pathogenesis, no comprehensive study has evaluated the link between lncRNA dysregulation and VDR signaling in BC. Consequently, in the present study, we introduce a bioinformatics approach for identification of lncRNAs that modulate VDR signaling in BC.

Material and Methods

Co-expression analysis

In order to find lncRNAs, which are co-expressed in breast tissues with VDR, we used co-LncRNA. This web-based computational tool facilitates detection of Gene ontology (GO) annotations and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways that are influenced by co-expressed protein-coding genes and lncRNAs. Co-expression pattern of lncRNAs and protein-coding genes has been retrieved from publicly available human RNA-Seq datasets, comprising 241 datasets from 6 560 total datasets which exemplify 28 tissue types/cell lines. Subsequently, lncRNA combinatorial influence on particular GO annotations or KEGG pathways is analyzed [22]. Spearman rank order correlation analysis was used to define the relationship between expression of VDR and certain lncRNAs. For such purpose, a Spearman correlation rank order correlation coefficient higher than 0.5 and p value less than 0.001 were regarded as statistically significant.

In silico identification of lncRNAs that target VDR

LncRNA2Target tool was used for identification of lncRNAs that function upstream of VDR. This database provides the list of lncRNA targets, which have been identified through lncRNA knockdown or overexpression experiments [23].

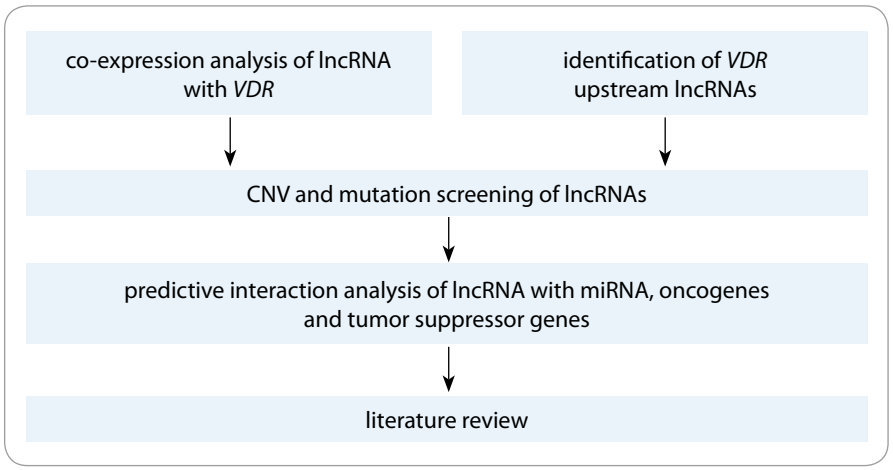
Identification of lncRNAs with genomic changes in breast cancer

Subsequently, we used the cBioPortal for Cancer Genomics tool and the Catalogue of Somatic Mutations in Cancer (COSMIC) to find lncRNAs that harbor genomic alteration in BC tissues. The cBioPortal for Cancer Genomics facilitates discovering, envisioning, and analyzing multidimensional cancer

Tab. 1. Summary of lncRNAs that possibly regulate VDR signaling in breast cancer.

lncRNA	Somatic Copy number alterations	Transcriptional regulator	Interaction with tumor suppressors or oncogenes	Interaction with tumor suppressor or oncogene miRNAs	Disease name
PVT1	amplification (14–26%)	GATA3, cMYC, ZNF217,	TP53, FGFR1, TTN		breast cancer [29], colorectal cancer [30], melanoma [31], gastric cancer [32]
FAM66A	deletion (0.5–6%)				
FAM66B	deletion (1.2–5.8%)		TP53		
FAM83 H-AS1	amplification (20%)	cMYC, ZNF217			breast cancer [33], colorectal cancer [34]
FLG-AS1	amplification (20%)		ERBB2		squamous cell carcinoma [35]
LGALS8-AS1	amplification (4–23%)		FGFR1, ERBB2		
SMG7-AS1	amplification (3–21%)		TP53, FGFR, ERBB2		
LINC00672	amplification (3–8%)		ERBB2		endometrial cancer [36]
LINC00968	amplification (4–13%)		ERBB2		non-small cell lung cancer [37]
LINC01132	amplification (4–24%)	GATA3, cMYC, ZNF217	TP53, FGFR, ERBB2, cMYC	mir-31	
MIR205HG	amplification (5–26%)		TP53, PTEN, FGFR1, TTN		
PRSS51	deletion (5%)				
ZFHX4-AS1	deletion (6–17%)		FGFR1		
WFDC21P	amplification (9%)				
RGS5	amplification (4–23%)				lung cancer [38], hepatocellular carcinoma [39]
OVAAL	amplification (20%)	cMYC, GATA3, ZNF217	ERBB2, FGFR1, MU16		endometrial cancer [40]
RUSC1-AS1	amplification (6–21%)		PTEN		
C1ORF220	amplification (3–21%)				
FAM157C	deletion (2%)		ERBB2		
FAM66E	deletion (1–6%)				
LINC01588	amplification (2%)		cMYC, ERBB2, FGFR1, TTN, GATA3		
LINC00346	deletion (1%), amplification (2–5%)				breast cancer [41], bladder cancer [42], hepatocellular carcinoma [43]
LINC00511	amplification (4–25%)	cMYC, GATA3, ZNF217	PTEN		breast cancer [44], non-small cell lung cancer [45]
SNHG6	amplification (6–15%)	cMYC	PTEN, TP53		gastric cancer [46], hepatocellular carcinoma [47]
MALAT1	deletion (1%), amplification (0.4–3%)	cMYC, GATA3		mir-155	breast cancer [48], gastric cancer [49]
SNHG16	amplification (6–11%)		PTEN, TP53	mir-31	breast cancer [50], colorectal cancer [51], bladder cancer [52], neuroblastoma [53]

lncRNA – long non-coding RNA, VDR – vitamin D receptor,



Schema 1. The pipeline used for identification of VDR related lncRNAs in breast cancer.

VDR – vitamin D receptor, lncRNA – long non-coding RNA, CNV – copy number variation

genomics data at genetic, epigenetic, gene expression, and proteomic levels [24]. COSMIC is regarded as the most all-inclusive source for discovering the effect of somatic mutations in human cancer [25].

In silico functional analysis of lncRNAs

The functional interactions of selected lncRNAs with tumor suppressor and oncogenes (including both mRNA coding and miRNA genes) which are implicated in BC have been evaluated using two online tools. AnnoLnc is an online tool which provides lncRNAs annotations including their interactions with miRNA and proteins [26]. The miRcode has provided a map of possible miRNA target sites across the complete GENCODE annotated transcriptome, including more than 10 000 lncRNA genes so facilitates the identification of miRNA-lncRNA interactions [27]. Schema 1 shows the pipeline used for identification of VDR related lncRNAs in BC.

Network construction

Pathway studio software [28] was used for construction of a network among VDR, miRNAs lncRNAs and mRNA coding genes.

Results

By using co-lncRNA tool, we could identify 304 lncRNAs which are co-expressed with VDR in BC tissues. Then, we used LncRNA2Target tool to identify VDR upstream lncRNAs which led to identification of four lncRNAs including metastasis associated lung adenocarcinoma transcript 1 (*MALAT1*), *lincFOXF1*, *lincTNS1* and *DA125942*. Application of cBioPortal and COSMIC resulted in identification of 26 lncRNAs among total 304 lncRNAs which have been the subjects of amplification, deletion or mutation in BC tissues. Finally, we have shown that these lncRNAs have interactions with transcription factors, such as *MYC, GATA3, ZNF217, TP53* and *ESR1* as well as BC related tumor suppressors or oncogenes (*RB1, PTEN, CCND1, ERBB2, FGFR1, MAP3K1, MUC16, PIK3CA* and *TTN*). In addition, the interactions of the selected lncRNAs with oncomiRs (miR-125b, miR-205, miR-17-92, miR-206, miR-200, miR-146b, miR-126, miR-335 and miR-31) as well as tumor suppressor miRNAs (miR-10b, miR-21, miR-155, miR-373 and miR-520c) have been demonstrated. Tab. 1 shows the summary of lncRNAs that possibly regulate VDR signaling in BC. Using Pathway studio, we designed a network among VDR, miRNAs, lncRNAs and mRNA coding genes. By using "regulation", "direct regulation", "binding", "promoter binding" and "expression" filters, 829 genes (including mRNA coding, lncRNAs and miRNAs) were retrieved that interact with VDR. Subsequently, we narrowed the search by exclusive inclusion of cancer related genes which led to construction of the desired network.

Discussion

In addition to protein coding mRNAs which have been documented to be regulated by VDR through application of microarray based methods, miRNAs and lncRNAs have been shown to be regulated by this signaling pathway as well. Several patterns of co-expression, co-regulation and interactions have been revealed through integrated analyses of mRNA, miRNAs and lncRNAs [54]. Animal studies have shown the effect of VDR on lncRNA expression in a way that in VDR null mouse epidermis, *mHOTAIR, MALAT1* and *SRA* are up-regulated while *Foxn2-as, Gtl2-as* and *H19-as* are down-regulated [55]. However, VDR transcriptome puzzle has many gaps which is mostly originated from the scarcity of RNA-Seq data focused on VDR function [54]. With the purpose of filling such knowledge gap, in the present study, we aimed at identification of the complex network between lncRNA expression, VDR signaling and BC using a novel bioinformatics approach. Previously, several bioinformatics approaches have been suggested for identification of disease or phenotype related VDR downstream networks – combination of VDR and chromatin immunoprecipitation (ChIP)-Seq studies with genome-wide association studies or combination of VDR ChIP-Seq with Cancer Genome Atlas (TCGA) data to evaluate the influence of VDR target genes in tumorigenesis process [56]. In the present study, using co-LncRNA tool, we assessed lncRNAs that are co-expressed with VDR in BC tissues. To find more clinically relevant candidates, we used other tools to identify those with genomic alterations in BC tissues and assess their interactions with known tumor suppressor genes and oncogenes. The final lncRNA list provided by this approach offers researchers potential candidates for functional or expression analyses. Finally, we demonstrated the interaction network between mRNA coding genes, lncRNAs and VDR. As demonstrated in this network, *LINC00261*

is among lncRNAs which bind to VDR. *LINC00261* is a tumor suppressor which decreases the stability of Slug proteins leading to inhibition of epithelial-mesenchymal transition [57]. SLUG has been previously shown to bind to the E2-box sequences of the *VDR* gene promoter leading to suppression of *VDR* gene expression through chromatin remodeling [58]. *MALAT1* as a well-known lncRNA in VDR signaling pathway has been demonstrated to interact with several genes in this network. However, due to scarcity of experimental data regarding the interactions between lncRNAs and VDR, this network does not include many of putative lncRNAs. Future experimental studies would help in enrichment of this network.

Identification of the lncRNAs that influence *VDR* gene expression is possible through genome-wide or individual gene expression analysis following silencing or overexpressing each lncRNA. However, such experiments are time-consuming and need prior identification of potential candidates which are expected to influence or be influenced by VDR signaling pathway. Considering the prominent role of VDR in BC pathogenesis as well as availability of VDR modulating agents, evaluation of VDR signaling pathway and related networks are of practical significance and bioinformatics tools are expected to facilitate such action.

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