Supportive Care in Cancer (2023) 31:223
https://doi.org/10.1007/s00520-023-07686-7

RESEARCH

Identification of potential molecular mechanisms and candidate drugs for radiotherapy- and chemotherapy-induced mucositis

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Received: 16 October 2022 / Accepted: 12 March 2023 / Published online: 20 March 2023

Abstract

Background Radiotherapy-induced oral mucositis (RIOM) and chemotherapy-induced oral mucositis (CIOM) are common complications in cancer patients, leading to negative clinical manifestations, reduced quality of life, and unsatisfactory treatment outcomes.

Objective The present study aimed to identify potential molecular mechanisms and candidate drugs by data mining.

Methods We obtained a preliminary list of genes associated with RIOM and CIOM. In-depth information on these genes was explored by functional and enrichment analyses. Then, the drug–gene interaction database was used to determine the interaction of the final enriched gene list with known drugs and analyze the drug candidates.

Results and conclusion This study identified 21 hub genes that may play an important role in RIOM and CIOM, respectively. Through our data mining, bioinformatics survey, and candidate drug selection, TNF, IL-6, and TLR9 could play an important role in disease progression and treatment. In addition, eight candidate drugs (olokizumab, chloroquine, hydroxychloroquine, adalimumab, etanercept, golimumab, infliximab, and thalidomide) were selected by the drug–gene interaction literature search additionally, as candidates for treating RIOM and CIOM.

Keywords Radiotherapy-induced oral mucositis · Chemotherapy-induced oral mucositis · Inflammatory reaction · Data mining

Introduction

Radiotherapy-induced oral mucositis (RIOM) and chemotherapy-induced oral mucositis (CIOM) are serious toxic effects of radiotherapy and chemotherapy in cancer patients [1]. As an inflammatory reaction of the oral mucosa, they lead to clinical manifestations such as erythema, hemorrhage, ulceration, and pain [2]. The pathogenesis of RIOM and CIOM is quite complex, and it is believed to be multifactorial, involving the interaction of a broad range of cellular, tissue, and oral environmental factors and many dynamic biological processes and molecular pathways [1, 3]. Currently, the pathogenesis of RIOM and CIOM is mainly based on the five-stage theory proposed by Sonis et al. [2]. In the initial stage, chemotherapy or radiotherapy causes cell or DNA damage, and many reactive oxygen species are generated in the cytoplasm [4], followed by an initial injury that up-regulates and activates the generation of messengers. Next, it enters the signal amplification phase, where pro-inflammatory cytokines amplify the damage [5]. When the damage reaches a certain level, ulceration with inflammation appears, and the epithelial barrier is disrupted [6]. Finally, in the healing phase, the basal epithelial cells migrate, proliferate, and repair the ulcer [7]. Therefore, they not only cause pain to patients but also cause dysphagia and reduced intake by patients, leading to weight loss and malnutrition, reduced quality of life, and anti-cancer treatment effects [8, 9].

Over the past several decades, extensive investigations have been conducted on the prevalence, pathogenesis, and treatment modalities of RIOM and CIOM. However, few treatment options are available, and their efficacy is still

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limited. Globally, only two drugs have been approved for intervention [10]. Benzydamine HCl is an anti-inflammatory rinse that has shown efficacy in mitigating RIOM in patients being treated with radiation only for cancers of the head and neck; however, it is ineffective for severe RIOM in patients treated with a typical standard of care for concomitant chemoradiotherapy regimens [11]. Intravenously administered palifermin can significantly reduce the incidence and severity of RIOM and CIOM. However, palifermin is only effective in 4% of the at-risk population and can produce undesired side effects such as goblet cell hyperplasia [12].

Drug repurposing is a strategy for identifying new uses for approved or investigational drugs beyond the scope of the original medical indication [13]. Compared with traditional drug development, drug repurposing can pose a lower risk, less investment, and shorter time alternative, and may reveal new targets and pathways for disease treatment [14]. A prominent example of successful drug repurposing is sildenafil (Viagra), which was developed to treat high blood pressure but was later discovered to be effective in treating erectile dysfunction. In addition, thalidomide was initially used as a sedative but was later used to treat erythema nodosum leprosy and multiple myeloma [14]. A considerable number of drugs have successfully undergone drug repurposing, providing some inspiration for discovering new drugs to treat RIOM and CIOM.

Following the repurposing paradigm, this study investigated new drug treatment options for RIOM and CIOM using computational methods to mine a continuously expanding wealth of knowledge associated with publicly available biological data [12]. Text mining of large volumes of biomedical literature has been established as an effective tool to reveal new associations between genes and diseases. In particular, it can help identify the most interesting candidate genes for a disease for further experimental analysis [15]. Furthermore, new evidence on the potential to repurpose existing drugs can be obtained by combining text mining of available literature, analyzing various databases, and using search tools and other computational resources (e.g., Metascape, STRING, DGIdb) [16]. Therefore, we used text mining, pathway analysis, database analysis, computer resources, etc., to identify existing drugs that have the potential to be repurposed to treat RIOM and CIOM.

Methods

Data mining

In order to extract related genes by data mining, the literature on RIOM and CIOM was first searched in PubMed (https://pubmed.ncbi.nlm.nih.gov/) [17]. The computer search strings were the following: RIOM: (((radiotherapy) OR (radiation therapy) OR (radiation) OR (radiochemotherapy)) AND ((induced))) AND ((oral mucositis) OR (stomatitis)). CIOM: (((chemotherapy) OR (chemoradiotherapy)) AND ((induced))) AND ((oral mucositis) OR (stomatitis)). The abstracts of the identified studies were downloaded, and data mining was conducted with the R package "pubmed.mineR" (version 1.0.19) [18]. The RIOM and CIOM genes were extracted from each identified study and used for the next steps.

GO and KEGG pathway enrichment analyses

The genes of RIOM and CIOM were used for gene ontology (GO) enrichment analysis to explore the biological process, cellular components, and molecular functions of these genes [19]. Furthermore, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was conducted to explore the signaling pathways these genes participated in [20]. GO and KEGG enrichment analyses were conducted by the Metascape database (https://metascape.org/), which can provide comprehensive analysis and interpretation for OMICs-based data [21]. False discovery rate (FDR) was used to assess the statistical significance of the results, and FDR < 0.05 was considered statistically significant [22].

Protein-to-protein interaction (PPI) network

PPI network analysis was conducted to explore the interactions among these genes and further identify hub genes in this network. The web-based database String (http://string-db.org/) was used to perform the PPI analysis among the identified genes [23]. This database integrated PPI evidence from the experiment, database association, co-expression, and PubMed data mining. The PPI data were exported from the String database and imported into Cytoscope software (version 3.9.1) for depicting the PPI network [24]. The confidence parameter used to infer the interaction was set at high (70%). The hub genes (genes that play a significant role in the interaction network) in this PPI network were identified by algorithms including maximal clique centrality (MCC) [25], the density of maximum neighborhood component (DMNC) [26], maximum neighborhood component (MNC) [27], edge percolated component (EPC) [28], and degree [29]. These algorithms were integrated into "Cytohubba," a plug-in of Cytoscope software [30]. The final list of hub genes was the sum of hub genes identified by the five algorithms (MCC, DMNC, MNC, EPC, and Degree).

Drug–gene interaction

The hub genes were used as the potential treatment targets for exploring drugs or small organic compounds in the DGIdb database (https://dgidb.genome.wustl.edu/), which aggregates drug–gene interaction data from 27 sources,

including DrugBank, PharmGKB, ChEMBL, NCBI Entrez, Ensembl, PubChem, various clinical trial databases, and literature available through NCBI PubMed [31]. To ensure the predicated drugs had desirable therapeutic effects on R/CIOM, the drug–gene interactions were evaluated in the context of the gene's association with mucositis and the drug's correlation with the gene. The linked references were also explored to extract the related metadata, including the administration and approved use. Drugs or small organic compounds were included in the final drug list if they reached the criteria of targeting at least one of the identified hub genes through appropriate interaction. Furthermore, the clinical trials of these drugs for oral mucositis were screened using ClinicalTrials.gov (https://clinicaltrials.gov) to evaluate their treatment efficiency [32]. Figure 1 presents the overall design of our study.

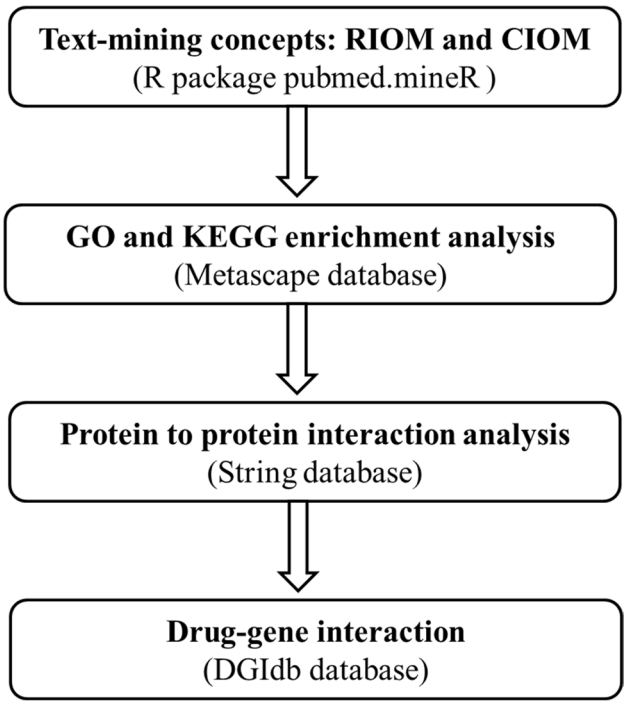

Fig 1 The overall design of the study

Results

Genes identified through data mining

A literature search in PubMed provided 1413 studies of RIOM and 4528 studies of CIOM. Then, the abstracts of these studies were downloaded and used for data mining. Data mining identified 109 genes in RIOM and 209 genes in CIOM (Fig. 2). The lists of RIOM genes are presented in Supplementary file 1 (sheet 1) and CIOM genes in Supplementary file 1 (sheet 2).

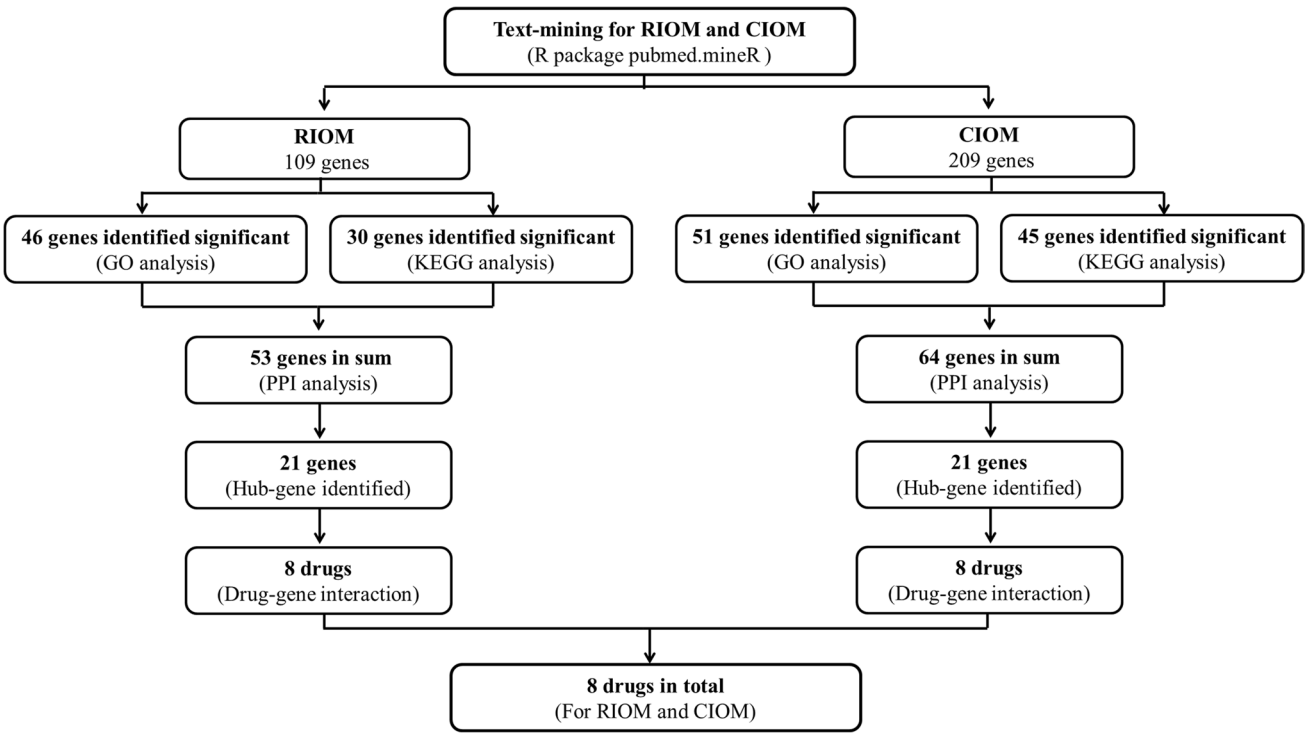

Fig 2 The summary of data mining, GO and KEGG pathway enrichment analyses, PPI analysis, and drug–gene interaction results

Results of GO and KEGG pathway enrichment analyses

GO and KEGG pathway enrichment analyses were conducted to clarify the molecular functions of these genes and the signaling pathway they participated in. The top five significant annotation terms were identified (Table 1). In RIOM, the top 5 terms of GO enrichment analysis were "response to molecule of bacterial origin," "ERK1 and ERK2 cascade," "positive regulation of DNA metabolic process," "positive regulation of peptidyl-tyrosine phosphorylation," and "response to lipopolysaccharide." The top 5 terms of KEGG pathway enrichment analysis were "FoxO signaling pathway," "toll-like receptor signaling pathway," "NF-kappa B signaling pathway," "MAPK signaling pathway," and "PI3K-Akt signaling pathway." In CIOM, the top 5 GO terms enriched were "response to molecule of bacterial origin," "response to lipopolysaccharide," "cellular response to lipopolysaccharide," "positive regulation of cytokine production," and "cellular response to biotic stimulus." The top 5 KEGG terms enriched were "toll-like receptor signaling pathway," "NF-kappa B signaling pathway," "Chemokine signaling pathway," "TNF signaling pathway," and "NOD-like receptor signaling pathway." In the meanwhile, all of the GO and KEGG terms of RIOM were presented in Supplementary file 1 (sheet 3 and sheet 4) and terms of CIOM Supplementary file 1 (sheet 5 and sheet 6).

Results of PPI network analysis

First, the PPI network analysis was conducted, combining the top 5 terms in GO enrichment analysis and the top 5 signaling pathways in KEGG pathway enrichment analysis. Then, the interaction data were imported into Cytoscope software. Second, hub genes in this network were identified using the algorithms in Cytohubba. Furthermore, the final list of hub genes was the sum of hub genes identified by the five algorithms (MCC, DMNC, MNC, EPC, and Degree). The results of each algorithm for RIOM were presented in Supplementary file 1 (sheet 7) and CIOM in Supplementary file 1 (sheet 8). Third, the high-confidence PPI networks of hub genes in RIOM (Fig. 3A) and CIOM (Fig. 3B) were exhibited, respectively. Connecting lines with different colors represents different types of interaction, and the confidence parameter used to infer the interaction was set at a high level (70%).

Results of exploring drug–gene interaction

Table 2 presents the candidate drugs for treating RIOM and CIOM predicted by drug–gene interactions. To ensure that the predicated drugs had desirable therapeutic effects, the drug–gene interactions were evaluated in the context of the gene's association with mucositis and the drug's correlation with the gene. The linked references were also explored to extract the related metadata, including the administration and approved use. Drugs or small organic compounds were included in the final drug list if they reached the criteria of targeting at least one of the identified hub genes through appropriate interaction. Using these hub genes identified from the PPI network, we reached candidate drugs that met our inclusion criteria. The targets of these potential drugs are interleukin 6 (IL-6), toll-like receptor 9 (TLR9), and tumor necrosis factor (TNF). Furthermore, eight approved drugs (olokizumab, chloroquine, hydroxychloroquine, adalimumab, etanercept, golimumab, infliximab, and thalidomide) were identified through drug–gene interactions. Table 2 presents their related clinical evidence.

Discussion

This study explored the potentially important genes and pathways in RIOM and CIOM and identified the candidate drugs for treatment. First, we obtained a preliminary list of genes associated with RIOM and CIOM using text mining. Then, to validate the association of our genes and generate a targeted set of targets, we integrated in-depth information on these genes in a functional analysis and enrichment manner. Next, the extracted genes were analyzed for their function and gene ontology using Metascape, resulting in an enriched gene list of high-priority targets. Finally, the drug–gene interaction database was used to determine the interaction of the final enriched gene list with known drugs and analyze the drug candidates. We analyzed three potential candidate genes (IL-6, TLR9, and TNF) and eight approved drugs (olokizumab, chloroquine, hydroxychloroquine, adalimumab, etanercept, golimumab, infliximab, and thalidomide) were identified, which could play an important role in the treatment of RIOM and CIOM.

TNF plays a vital role in OM. Adalimumab, etanercept, golimumab, infliximab, and thalidomide are inhibitors of TNF, playing important anti-inflammatory and immunosuppressive roles. Adalimumab was effective in treating aphthous stomatitis in three case reports [33–35], and a randomized clinical trial demonstrated its effect on Crohn's disease (NCT01562951). Golimumab was also effective in treating ulcerative colitis, supported by a case report and two non-randomized clinical trials. According to a case report, infliximab relieved the pembrolizumab-induced steroid refractory oral mucositis, but further evidence is still necessary [36]. However, in preclinical trials, infliximab could not improve mucositis, which might restrict its potential in further research [37, 38]. Finally, thalidomide has been supported by a multicenter, open-label, randomized controlled trial. Patients with locally advanced nasopharyngeal

Table 1 Results of GO and KEGG pathway enrichment analyses. The top 5 terms in GO enrichment analysis and the top 5 signaling pathways in KEGG pathway enrichment analysis were identified and exhibited in this table

Terms	Description	FDR	Gene counts	Genes
RIOM				
GO enrichment analysis				
GO:0002237	Response to molecule of bacterial origin	2.97E-12	20	ABCC2/EDN1/EPO/FGFR2/FOS/CXCL2/GSTP1/HMGB1/IL6/CXCL8/MIF/MPO/ADAM17/TGFB1/TLR2/TLR4/TNF/SIRT2/TLR9/NLRP3
GO:0070371	ERK1 and ERK2 cascade	4.93E-11	18	BRAF/CD4/EGF/EGFR/EPO/FGF2/FGF4/FGFR2/GSTP1/HMGB1/LIF/MIF/TGFB1/TLR4/TNF/FGF20/TRPV4/SPRY4
GO:0051054	Positive regulation of DNA metabolic process	4.93E-11	16	ATM/ATR/BAX/CD40/EGFR/ERCC1/FGF2/HMGB1/IL6/MRE11/RAD51/TGFB1/WAS/XRCC1/TNKS/SIRT1
GO:0050731	Positive regulation of Peptidyl-tyrosine phosphorylation	4.93E-11	15	CD4/CD40/EGF/EPO/FGF7/IL6/LIF/MIF/ADAM17/TEC/TGFB1/TNF/TNFRSF1A/TP53/GHRL
GO:0032496	Response to lipopolysaccharide	5.62E-11	18	ABCC2/EDN1/EPO/FGFR2/FOS/CXCL2/GSTP1/HMGB1/IL6/CXCL8/MIF/MPO/ADAM17/TGFB1/TLR2/TLR4/TNF/NLRP3
KEGG pathway enrichment analysis				
hsa04068	FoxO signaling pathway	8.04E-08	12	ATM/CCND1/BRAF/CAT/EGF/EGFR/IKBKB/IL6/MDM2/SOD2/TGFB1/SIRT1
hsa04620	Toll-like receptor signaling pathway	6.11E-07	10	CD40/FOS/IKBKB/IL6/CXCL8/TLR2/TLR4/TLR5/TNF/TLR9
hsa04064	NF-kappa B signaling pathway	4.51E-06	9	ATM/CD40/EDA/CXCL2/IKBKB/CXCL8/TLR4/TNF/TNFRSF1A
hsa04010	MAPK signaling pathway	5.13E-06	14	BRAF/EGF/EGFR/FGF2/FGF4/FGF7/FGFR2/FOS/IKBKB/TGFB1/TNF/TNFRSF1A/TP53/FGF20
hsa04151	PI3K-Akt signaling pathway	7.87E-06	15	CCND1/EGF/EGFR/EPO/FGF2/FGF4/FGF7/FGFR2/IKBKB/IL6/MDM2/TLR2/TLR4/TP53/FGF20
CIOM				
GO enrichment analysis				
GO:0002237	Response to molecule of bacterial origin	1.62E-20	35	ADM/ASS1/CD14/CD80/CD86/CD68/CCR7/ABCC2/EDN1/EPO/FGFR2/FOS/CXCL1/CXCL2/GSTP1/HDAC2/HMGB1/IFNAR1/IL6/IRF3/MIF/MPO/CCL2/CXCL11/SRC/TGFB1/TH/TLR2/TLR4/TNF/TNFAIP3/TRAF6/TLR9/SRR/NLRP3
GO:0032496	Response to lipopolysaccharide	2.75E-20	34	ADM/ASS1/CD14/CD80/CD86/CD68/CCR7/ABCC2/EDN1/EPO/FGFR2/FOS/CXCL1/CXCL2/GSTP1/HDAC2/HMGB1/IFNAR1/IL6/IRF3/MIF/MPO/CCL2/CXCL11/SRC/TGFB1/TH/TLR2/TLR4/TNF/TNFAIP3/TRAF6/SRR/NLRP3
GO:0071222	Cellular response to lipopolysaccharide	4.89E-14	23	ASS1/CD14/CD80/CD86/CD68/ABCC2/CXCL1/CXCL2/GSTP1/HMGB1/IL6/IRF3/MIF/CCL2/CXCL11/SRC/TGFB1/TLR2/TLR4/TNF/TNFAIP3/TRAF6/NLRP3
GO:0001819	Positive regulation of cytokine production	4.89E-14	32	C3/CD2/CD4/CD14/CD80/CD86/CD34/CD40/CCR7/HDAC2/HGF/HMGB1/IL6/IL6R/IRF1/IRF3/LPL/MIF/CCL19/SRC/STAT1/STAT3/TGFB1/TLR2/TLR4/TLR5/TNF/TRAF6/FADD/TLR9/TRPV4/NLRP3

Table 1 (continued)

Terms	Description	FDR	Gene counts	Genes
GO:0071216	Cellular response to biotic stimulus	4.89E-14	24	ASS1/BTK/CD14/CD80/CD86/CD68/ABCC2/CXCL1/CXCL2/GSTP1/HMGB1/IL6/IRF3/MIF/CCL2/CXCL11/SRC/TGFB1/TLR2/TLR4/TNF/TNFAIP3/TRAF6/NLRP3
KEGG pathway enrichment analysis				
hsa04620	Toll-like receptor signaling pathway	6.14E-11	18	CD14/CD80/CD86/CD40/FOS/IFNAR1/IFNAR2/IL6/IRF3/CXCL11/STAT1/TLR2/TLR4/TLR5/TNF/TRAF6/FADD/TLR9
hsa04064	NF-kappa B signaling pathway	1.68E-08	15	PARP1/ATM/BTK/CD14/CD40/EDA/CXCL1/CXCL2/CCL19/CXCL12/TLR4/TNF/TNFAIP3/TNFRSF1A/TRAF6
hsa04062	Chemokine signaling pathway	8.36E-07	17	BRAF/CCR7/CXCL1/CXCL2/CXCR2/ITK/KRAS/CCL2/CCL19/CCL20/CXCL11/CXCL12/SRC/STAT1/STAT3/WAS/CXCR4
hsa04668	TNF signaling pathway	1.01E-06	13	FAS/EDN1/FOS/CXCL1/CXCL2/IL6/IRF1/CCL2/CCL20/TNF/TNFAIP3/TNFRSF1A/FADD
hsa04621	NOD-like receptor signaling pathway	1.62E-06	16	GBP1/CXCL1/CXCL2/IFNAR1/IFNAR2/IL6/IRF3/OAS1/CCL2/STAT1/TLR4/TNF/TNFAIP3/TRAF6/FADD/NLRP3

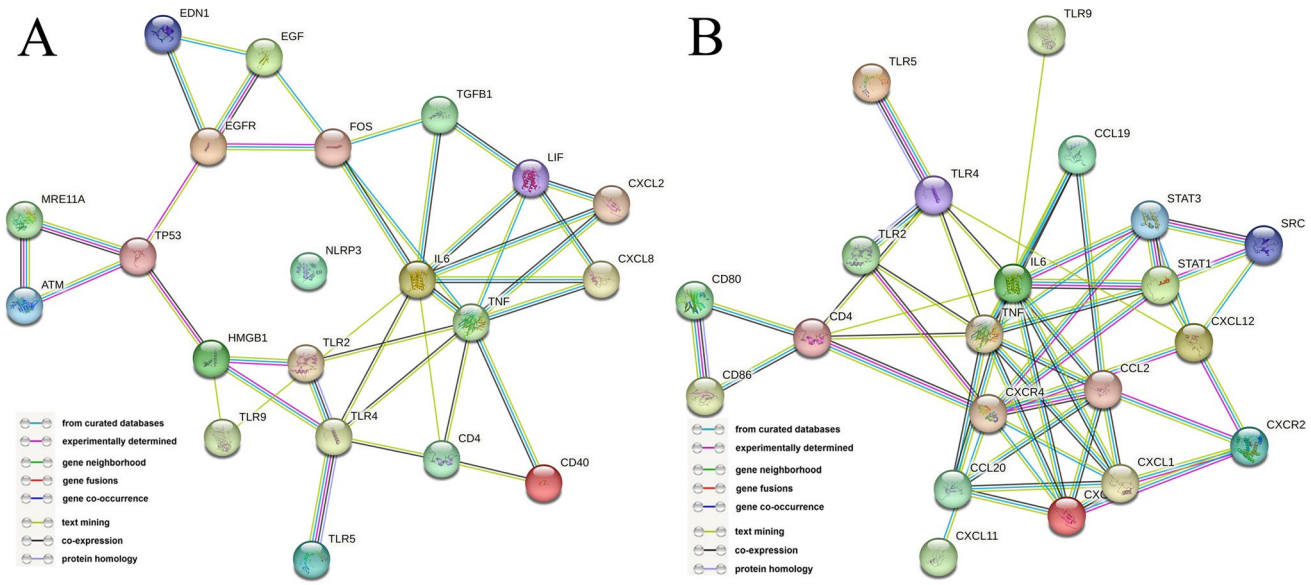

Fig 3 High-confidence PPI network of the hub genes. **A** RIOM, **B** CIOM. Connecting lines with different colors represent different types of interaction. The confidence parameter used to infer the interaction was set at a high level (70%)

carcinoma undergoing concurrent chemoradiotherapy were recruited and treated with thalidomide. The results indicated that thalidomide prolonged the latency period, reduced the incidence of oral mucositis, and did not affect the short-term efficacy of concurrent chemoradiotherapy [39].

IL-6 is a pro-inflammation cytokine in oral mucositis [40]. IL-6 induces the breakdown of vascular endothelial calmodulin on endothelial cells either directly or by inducing VEGF, leading to vascular hyper-permeability and tissue damage [41]. IL-6 could also induce tissue factor expression on the surface of monocytes and trigger the coagulation cascade, leading to thrombin activation and clot formation [42]. Olokizumab, as a newly designed inhibitor of IL-6, was suggested as a candidate. However, further clinical evidence is still required.

The role of TLR9 in RIOM and CIOM is still not well documented. TLR9 is mainly expressed on the membrane of endosomes and binds nucleic acids, including DNA

Table 2 Candidate drugs for treating R/CIOM predicted by drug–gene interaction

Identified for (RIOM, CIOM)	Drug	Gene	Drug-gene interaction	Approval status	Approved use	Case reports (PMID)	Clinical trials (PMID, ClinicalTrials.gov)
Both	Olokizumab	IL6	Inhibitor	Approved	Anti-inflammatory	NA	NA
Both	Chloroquine	TLR9	Inhibitor	Approved	Anti-rheumatic	5664916,	NA
Both	Hydroxychloroquine	TLR9	Antagonist	Approved	Anti-rheumatic	32654931,32970835	NA
Both	Adalimumab	TNF	Inhibitor	Approved	Anti-inflammatory	16209159,18482322, 31588588,	NCT01562951*
Both	Etanercept	TNF	Inhibitor	Approved	Anti-inflammatory	14568829,23619454, 24365222,30528070	NCT00031551
Both	Golimumab	TNF	Inhibitor	Approved	Immunosuppressive	34559136*	34812437* 34959224*
Both	Infliximab	TNF	Inhibitor	Approved	Anti-inflammatory	33024767	NA
Both	Thalidomide	TNF	Inhibitor	Approved	Immunosuppressive	NA	34910297

*Focus on mucositis of gastrointestinal tract except for oral mucositis (references without * focused on oral mucositis)

and RNA from both bacteria and viruses. In addition, it is expressed in oral mucosal epithelial cells and multiple mucosal immune cells, with an important role in innate and adaptive immunity [43]. After chemotherapy, TLR9 is more likely to recognize a part of the intestinal microbiota, send downstream signals, produce pro-inflammatory mediators, and mediate the development of gastrointestinal mucositis. Therefore, TLR9 antagonists may reduce anti-tumor drug-induced intestinal injuries. Several studies have also found that deletion of the TLR9 receptor gene improves animal survival and reduces intestinal injury and bacteremia. Also, it reduces the expression of inflammatory markers, such as NF-κB, IL-1, IL-18, and COX-2 [44]. Wong et al. noted that TLR9 knockout preserved mucosal structure, bacterial translocation, and IL-1β expression compared to wild-type mice injected with saline or irinotecan to induce intestinal mucositis [45]. Therefore, TLR9 could be a promising target in the treatment. Case reports have reported that hydroxychloroquine is a TLR9 antagonist and might alleviate RIOM and CIOM [46, 47]. Nevertheless, further clinical evidence is required.

Since radiotherapy and chemotherapy will also lead to epithelial injury besides mucositis, the similarity and differences between R/CIOM and radio/chemotherapy-induced epithelial injury should be noticed. On the issue of similarity, radiation and chemo drugs can damage liquid and DNA, leading to destruction of epithelial cell. In addition, in the mucosa, radiation-induced loss of stem cells from the basal layer interferes with the replacement of cells in the superficial mucosal layers when they are lost through normal physiological sloughing [48]. Changes of the process of neovascularization have also been observed in both R/CIOM and radio/chemotherapy-induced epithelial injury. Neovascularization requires signaling through the vascular endothelial growth factor (VEGF) family. After exposure to 10Gy irradiation, the synthesis of angiogenic factor VEGF in the blood of rat tumor carriers was significantly hindered [49]. Preclinical studies supported this by showing that irradiated rat bladder epithelium administrated with VEGF resulted in a marked reduction in fibrotic tissue and enhanced tissue angiogenesis, which suggested the potential value of VEGF in radio/chemotherapy-induced epithelial injury [50]. However, there also exist differences between R/CIOM and radio/chemotherapy-induced epithelial injury. It has been reported that transforming growth factor β (TGF-β), a peptide which has a fundamental role in controlling proliferation of many cell types, is intricately involved in the development of chronic radiation dermatitis. It activates fibroblasts to secrete extracellular matrix protein, leading to epithelium fibrosis. In the irradiated tissue of pigs, TGF-β plays an important role in promoting and regulating the late fibrotic process [51]. However, mice oral mucosa lacks Smad3, a downstream mediator of TGF-b, which demonstrates decreased tissue damage and fibrosis after irradiation, as well as accelerated healing [52]. IL-10 is capable of inhibiting the inflammatory response and reducing the activity of macrophages in radio/chemotherapy-induced epithelial injury, but it has been reported not expressed in RIOM [53]. When it comes to RIOM and CIOM, keratinocyte growth factor-1 (KGF-1) has been demonstrated as a valuable target for treatment. Palifermin, a kind of recombinant KGF-1 use, has been approved by FDA to decrease the incidence and severity of RIOM and CIOM [54]. Recent studies also reported that Wnt/β-catenin signaling activator has a protective effect on post irradiation tissues and promotes regeneration of colonic epithelium after chemical damage [55, 56]. Furthermore, LiCl has been indicated to promote the renewal of tongue mucosa, thus diminishing oral mucositis and taste dysfunction of irradiated mice by activating Wnt/β-catenin signaling pathway [57]. By verifying the special mechanisms of RIOM and CIOM, further studies could explore more valuable targets and more effective drugs.

The importance of the kinetics of genomic expression should also be noticed in treating RIOM and CIOM. The

overexpression of TNF and IL-6 usually occurs after the inflammation cascade is active, which means the progress of OM enters the signal amplification phase, and pro-inflammatory cytokines amplify the damage [58]. From a therapeutic perspective, this time may be too late to inhibit TNF and IL-6. Therefore, applying phosphodiesterase-5 (PDE5) agents could be a good reference. By inhibiting PDE5, these drugs prevent the degradation of cGMP, which can activate protein kinase G [59]. Therefore, it could be promising to develop drugs that could inhibit the injury cascade beforehand.

This study had some limitations and should be interpreted with caution. First, the genomic data we used was widely and roughly associated with RIOM and CIOM, which reduces the accuracy of outputs. Second, there was heterogeneity in the data we analyzed, including different anti-cancer treatments, vacations in OM trajectory, and the time of sample collection, which would affect the signals. Third, the data mining was conducted only in PubMed, possibly including limited genes and their function or ways in a specific pathway. Fourth, not all existing drug–gene interactions were clear and included in the database. Potential drugs might have been ignored because their drug–gene interactions have not yet been fully demonstrated or could have had detrimental effects. Finally, further high-quality clinical research is required to confirm and verify our findings.

Conclusion

Through our data mining, bioinformatics survey, and candidate drug selection, TNF, IL-6, and TLR9 could play important roles in the progression and treatment of R/CIOM. In addition, eight candidate drugs (olokizumab, chloroquine, hydroxychloroquine, adalimumab, etanercept, golimumab, infliximab, and thalidomide) were selected by drug–gene interaction literature search as candidates for treating RIOM and CIOM.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-023-07686-7.

Authors' contribution Y. W. and S. H. contributed to the overall conceptualization and design of the study. S. H., Y. J., and Y. Y. conducted the literature search, carried out the data extraction and quality assessment, analyzed the data. S. H. and Y. W. drafted the manuscript. J.W. and J.Z. revised the manuscript. All authors have read and approved the manuscript.

Funding This study was supported by Natural Science Foundation of Sichuan Province (Youth Science Foundation Project) (2022NSFSC1482 to YW) and Science & Technology Department of Sichuan province (2023YFS0349 to JW). None of the funders participated in this study.

Declarations

Ethical approval This study is a data mining study which did not include any experiments on live vertebrates. Therefore, it did not need approval, accordance, and (for human subjects) informed consent. All data of this study was from available public databases which did not need ethical approval.

Competing interests The authors declare no competing interests.

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