REVIEW ARTICLE

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Activity of Matrix Metalloproteinase-7 (MMP-7) Related to Heparin-Binding Epidermal Growth Factor (HB-EGF) Activation in Squamous Cell Carcinoma as Diagnostic Biomarker for Early Detection And Treatment of Maxilarian Cancer: Review Article

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ABSTRACT

Background: Squamous cell carcinoma (SCC) has a higher chance of occurance and progression in maxillary sinus cancer than other paranasal sinus cancers (80%). Matrix metalloproteinase-7 (MMP-7) is a protease specified in collagen type IV degradation and Heparin Binding Epidermal Growth Factor activation, which causes an increase in squamous cell carcinoma proliferation and metastasis.

Methods: This review aims to identify the potential role of MMP-7 as a target for prevention and therapeutic modality to manage SCC sinus maxillary cancer. We did literature searching in several databases to elucidate the importance of the MMP-7 pathway in SCC sinus maxillary cancer progression.

Results: Increasing expression and activity of MMP-7 are associated with maxillary sinus cancer progression. Squamous cells, the most impacted in maxillary sinus cancer, sustain dysplasia due to heparin-binding epidermal growth factor (HB-EGF) activation into EGF by MMP-7 and Cluster of Differentiation 44 (CD44) binding complexes that trigger high proliferation and mitogenic activity. The therapeutic function of MMP-7 occurs by affecting the protein 53 (p53) in cancer cell apoptosis initiation by specific interaction with CD44.

Conclusion: MMP-7 could be an alternative therapeutic target and potential treatment option for maxillary sinus cancer. Furthermore, more trials should be done to test the relevancy of MMP-7 uses as an SCC sinus maxillary cancer modality.

INTRODUCTION

Maxillary sinus cancer incidence is rated from 1 case per 10,000 people to four from 5 people with sinus cancer maxillary over 55 years [1,2]. Commonly, sinus maxillary cancer cases do not cause any symptoms in an early stadium, so it is often detected when reaching a high stadium due to metastasis induced by extracellular matrix (ECM) components degradation by MMP-7 [3–5]. SCC dominates the development of sinus cancer maxillary because of tumor protein 53 (TP53) mutation, marked by Epidermal Growth Factor (EGF) overexpression due to plenty of MMP-7 that binds CD44. Thus, the binding will activate EGF from HB-EGF and bind with TIMP, reconstructing the maxillary sinus structure and leading to basal membrane destruction [3–6]. These circumstances stimulate malignancy in squamous cell carcinoma among maxillary sinus cancer patients. In squamous cells, EGF that bind to Epidermal Growth Factor Receptor (EGFR) will increase cyclin A and cyclin D2 expression, causing an increase of cellular mitogenic activity and maxillary sinus cancer [7,8].

Currently, the screening method is microRNA (miRNA) detection in a polymerase chain reaction (Taq-RT PCR).

Among all miRNAs, miR-874 lowered most significantly. It is related to the miR-874 function that directly regulates protein phosphatase protein catalytic subunit alpha (PPCA) in sequent 11q13, contributing to proliferation suppression and cancer cell invasion. However, this method still needs to be proven to identify SCC in polymorphism conditions [9]. Therefore, another method that could be used with MMP-7 as an alternative SCC sinus maxillary marker and therapy due to its capability to represent the polymorphic characteristic of cancer cells [10].

Sinus maxillary cancer is not a common cancer that occurs, but that does not mean this cancer could be underestimated. It is shown from diagnosis that made mostly when the cancer is already in a high stadium. SCC is the manifestation of MMP-7, followed by a significant effect focused on p53 mutation in the role of inducing apoptosis [11,12]. Furthermore, sinus maxillary chemotherapy management has not been optimized yet, which survival rate is only 50%, and the chemotherapy still needs drug combinations like cisplatin with doxorubicin, methotrexate, vinblastine, or gemcitabine [13]. Moreover, the side effects occurring when and after therapy [14]. Therefore, specific therapy that targets some micromolecules should be considered because efficacy and effectiveness could be increased by maintaining a clear target and minimalizing side effects [15].

MMP-7 known as Matrilysin is one of the endopeptidase enzymes linked to Zn(II) ions, which degrade collagen type IV on sinus maxillary cancer progression, where the macromolecules are the structural backbone of the basement membrane that barrier the spread and metastasis of SCC [7,16–19]. In maxillary sinus cancer, MMP-7 binds with CD44 and activates HB-EGF and TIMP to induce SCC proliferation, so MMP-7 overproduction causes migration progression and cancer cell proliferation related to metastasis and increase in cancer stage [7,8].

High MMP-7 activity in sinus maxillary cancer could be explicitly detected using an enzyme-linked immunoabsorbent assay with two types of antibodies (Sandwich ELISA) and adding a Eu3+ platting agent to detect fluorescence [20]. Furthermore, MMP-7 is targeted in sinus maxillary cancer treatment related to apoptosis function and activation of the first apoptosis signal (FAS) receptor by the p53 protein [8,21]. MMP-7 is used as a preventive and curative modality of SCC by its role as a biomarker and apoptosis activator in sinus maxillary SCC. As compare to MMP-8 and MMP-9 that are only expressed in polymorphonuclear neutrophils, especially MMP-9also expressed in osteoclast and ameloblastoma, thus unsuitable to be a biomarker and therapeutic target [22].

This review, therefore, presents information on the development of current knowledge related to the potential utilization of MMP-7 as a diagnostic marker and therapeutic target in managing squamous cell carcinoma. Elaboration on this literature review aims to evaluate the potential of MMP-7 as a diagnostic marker considering the rarely discussed squamous cell carcinoma of maxillary sinus cancer.

METHODS

The study was done using the literature review method. The author used the keywords MMP-7, CD44, HB-EGF, maxillary sinus cancer, ELISA, Fas, and p53 with Boolean logic “AND” in searching international scientific journals. The search was conducted on the NCBI, ScienceDirect, Elsevier, and PubMed database pages. The information obtained was organized according to the discussed problem topic from March 13, 2014, to December 21, 2021. A total of 178 studies related to our topic were identified. Studies that provide information about the effect of MMP-7 on solid cancer or SCC are included in this review, either in general or specific cancers. The articles were screened based on the abstracts to evaluate the relevancy of the articles, followed by the availability of the articles. A total of 82 articles were selected and analyzed. The remaining were excluded because of a lack of relevancy or non-English articles. The quality of the studies/articles is evaluated based on articles published in the PubMed journal index, according to the reference site of the article publication. The articles also consider the author’s skill in producing the piece, and the articles used as references have just been published in the last ten years.

RESULT

Maxillary Sinus Cancer Curative Efforts through Utilization of MMP-7

MMP-7 is a good indicator of the concentration of soluble Fas (sFas) and Fas/Fasl ligand (sFasl) [23]. This function is related to the role of MMP-7 in MUC-1 SEA cleavage, which facilitates the p53 regulation by nucleolin in the nucleus [24]. SEA (Sea urchin sperm protein, enterokinase, and again) is a domain found in many proteins as regulators of carbohydrate binding [25]. p53 will be phosphorylated and activated via the CDK (cyclin-dependent kinase) pathway to respond to DNA damage in mucosal cells [26]. Through this mechanism, there is an increase in the senescence phase of the cell cycle, DNA repair, and apoptosis. P53 activity is regulated by two tandem transcription activation domains (TADS), namely TADS 1 and TADS 2 [27]. p53 carries out the process of apoptosis through Fas induction [28]. Apoptosis begins with the activation of caspase enzymes that break down cellular components in the form of the cytoskeleton and nuclear proteins. The decomposed cells then pass through the plasma membrane and trigger phagocytic signaling by macrophages [29].

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p53 acts as a tumor suppressor that causes chemosensitivity in SCC. In addition, p53 suppresses the expression of zinc finger e-box-binding homeobox 1 (ZEB1), which counteracts the emergence of EMT and the invasive phenotype [30]. The p53 mutation will trigger EMT activity which causes a decrease in miR-130b and an impact on increasing ZEB1 expression [31]. Under normal conditions, microRNA-130b (miR-130b) acts as a regulator of the apoptotic process, which inhibits cancer progression by binding to B-cell lymphoma 2 (BCL-2) signaling [32].

ZEB1 can influence cancer progression by silencing E-cadherin on epigenetic regulation that affects the functionality of multiple chromatin enzymes in the E-cadherin promoter [33]. Loss or reduction of E-cadherin affects SCC metastasis. In addition, E-cadherin will help the process of tissue morphogenesis by segregation and differentiation. Network binding by E-cadherin or -catenin is required in the role of cell adhesion, where interference with this process is associated with mutations of the catenin and actin complexes in E-cadherin [34].

Apoptosis by p53 can also occurs through binding to the miR-200c promoter, which increases the number of miR-200c via transcriptional activation [35]. The role of miR-200c relates to the prevention of metastasis and invasion by cancer cells through the regulation of EMT [36]. Therefore, decreased miR-200c activity in cancer cells could be associated with a reduced risk of invasion and metastasis of SCC cancer cells [37].

The protein of p53 mutation causes a reduction, or even loss of the transcriptional ability of wild-type protein 53 (WT-p53) to the target gene and is more commonly found in advanced cancers. p53 plays a vital role in treating SCC by modulating the actions of other tumor suppressors and transcriptional regulators. In chronic cancer patients, it was found that there was a suppression of the number of p53 by the Mouse Double Minute 2 (MDM-2) protein. In addition, the reduction in the number of p53 under normal conditions could be due to the resistance of cells to the function of apoptosis induced by Trp53 (transformation-related protein 53) [38].

Alternative treatment through cancer cell degradation is carried out through the translocation of DNA sequences by MMP-7 to modulate apoptosis in p53 mutants. The binding site function occurs in the pro-apoptotic Puma and Noxa genes. Puma and Noxa act as transcription factors [39]. Once transcribed, Puma will produce Puma-α and Puma-β, which interact with other types of Bcl-2 (B-cell lymphoma 2), particularly BH-3 (Bcl-2 homology 3), in the stimulation of apoptosis [40,41].

MMP-7 Specificity and Sensitivity as SCC Biomarker in Maxillary Sinus Cancer

Research aimed at determining the specificity of MMP-7 as a biomarker for detecting SCC here in maxillary sinus cancer has not been published. As a comparative reference, Schummer et al. [42] reported an increase in MMP-7 in SCC patients with oral cancer andconcluded that SCC has a sensitivity of 73.7% and a specificity of 55.3%, with the cut-off value (CT-value) used is more than 183,91 pg/mL. SCC in the oral cavity and sinus cavity has different characteristics of cancer, with a survival probability ratio of 56.8% and 21.6%, respectively. It can be interpreted that the activity and progression of SCC in maxillary sinus cancer are higher than in oral cancer, and the activity of MMP-7, which can provide higher specificity and sensitivity values as SCC biomarkers in maxillary sinus cancer [43].

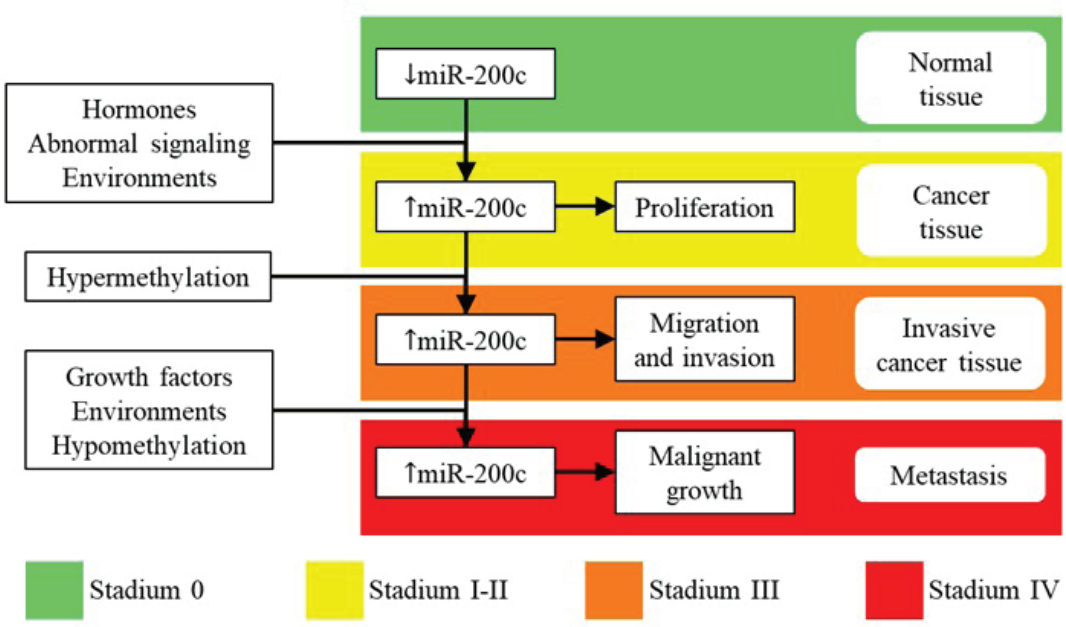

Figure 1. The activity of miR-200c in cancer progression [35-37]

The utilization of MMP-7 as a marker of squamous cell carcinoma of the maxillary sinus still needs to be clearly defined through further research. The analysis conducted in this literature review is based on the mechanisms of the utilization of MMP-7 components in serum types of squamous cell carcinoma from other organs [44]. MMP-7 markers could detect malignancy in the maxillary sinus with an accuracy of up to 92.5% [45]. However, these results tend to illustrate the association of this component with advanced malignancies [45]. Limitations related to patients who tend to report cancer when it has reached high severity,pose a challenge in the identification of the utilization of this type of marker in squamous cell carcinoma of the maxillary sinus.

DISCUSSION

Sinus Maxillary Cancer Pathogenesis and Pathophysiology

Sinus maxillary cancer is paranasal sinus cancer often marked by malignant degradation of squamous cells, especially under the cavum nasal. Maxillary sinus cancer develops among bone and border sinuses body around the nasal. The symptoms that occur during maxillary sinus cancer tend to be asymptomatic and seen during the advanced stage of malignancy [46].

Sinus maxillary cancer could occur in all age categories but frequently in people aged 55–65 years old. Sinus maxillary cancer needs more attention because of its domination in paranasal cancer prevalency with worse prognosis compared to other sinonasal cancer. Moreover, research has shown that maxillary sinus cancer occurs more in Asians [47].

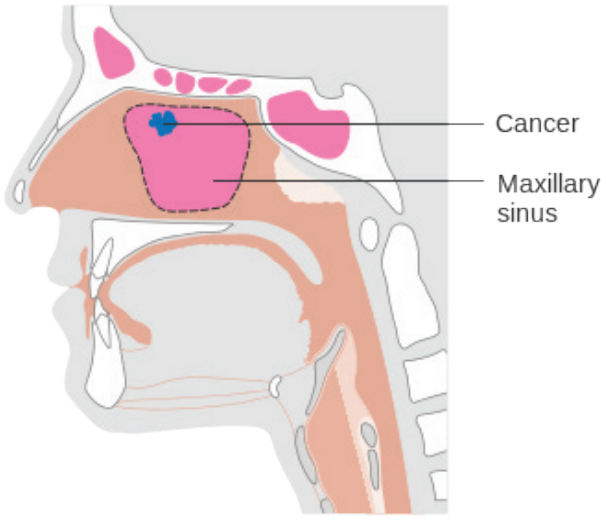

Figure 2. Maxillary Sinus Cancer [48]

The drug for maxillary sinus cancer is now by excision dissection, continued with radiotherapy for patients with continuing local symptoms. That management could cause hippo pituitary disruption, which leads to hormonal deficiency due to over-toxicity because of radiation induction in the endocrine system. Moreover, in some cases, dissection and radiotherapy only give 45–60% life expectancy for patients with dissection and 52% for patients with radiotherapy management [49,50].

Maxillary sinus cancer management is adapted to the patient's cancer stadium, which contains excision dissection, continued excision, radiotherapy post-operation, craniofacial recession, and chemotherapy. Dissection management of sinonasal cancer could only be done on the subsequent stadium cancer to omit tumors, accommodate fluid drainage on the sinus with cancer, and continue post-operation therapy. Radiotherapy uses a high dose to control cancer permanently, which involves the entire maxillary cavity and area around the hemiparanasal sinus, except the eye cavity and organ inside it. There is a chance that this therapy is not successful and causes maxillary sinus cancer to relapse [46].

Chemotherapy as maxillary sinus cancer management currently uses a cisplatin-adriamycin combination to induce sister chromatids to exchange on leukocytes in peripheral blood vascular. This drug therapy is possible to cause mutation in an individual. The drug usage in hamster embryos showed abrasion in chromosomes and micronucleus in humans and rodents during in vitro experiments [51]. Hence, there needs to be a consideration to innovate a way to manage maxillary sinus cancer with milder side effects.

Some internal and external factors could cause squamous cell carcinoma. Internal factors that cause SCC are genodermatosis, immunosuppression, changes in dermal composition, keratosis, acinic, skin pigmentation, photosensitivity, and ulcer [52–54]. External factors that affect SCC are ion radiation, human papillomavirus (HPV), and chemical substances (hydrocarbon, arsenic, tobacco). A combination of those factors could cause SCC [54]. Early mutation of p53 also be a cancer inducer due to inhibition of cellular apoptosis on abnormal cells; HB-EGF as the target will cause precancer lesions and manifest into invasive metastasis [53,55]. Protein 53 inhibits HB-EGF related to cell proliferation and prevents cancer cell apoptosis [56].

Pathogenesis development of SCC is explained by several sequences of cellular activity, according to multistep neoplasm theory. The cellular activity could affect many parts of genetics and transform into malignancy in the cell. Changes in cell malignancy from the genetic level could be explained in 3 steps: tumor initiation, promotion, and progression. In the initiation part, etiologic factors interact with host genetic material, affecting cell development and proliferation regulation. Tumour promotion explains additional factors with elements already available to the tumor environment.

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Tumor progression step, the cell is already through 2 stages of genetic and epigenetic activities that cause keratinocyte growth in the stroma [54].

By arranging the exon sequence that gene to mutate due to SCC dominated by tumor suppressor. Genetic mutation of SCC could occur on FAT Atypical Cadherin 1 (FAT 1), Caspase 8 (CASP8), Cyclin-Dependent Kinase Inhibitor 2A (CDKN 2A), NOTCH1, Harvey rat sarcoma viral oncogene (HRAS), and Phosphatidylinositol-4-5-Biphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA). Genetic mutation distribution varies among the human population, with a high risk in smokers and those infected with HPV [57,58].

Roles of MMP-7 Activity in Maxillary Sinus

Cancer Progression

MMP-7 or known as matrilysin has a gene on chromosome 11q21-q22 with 13 exons. A polymorphism at the A-1813 gene MMP-7 construct promoter modulates the transcription gene and links with nuclear protein. If matrilysin-1 or MMP-7 is produced in mucosal epithelial, the production will increase due to pathogen infection [59,60]. MMP-7 activity is related to changes in β4-integrin, Tumour Necrosis Factor α (TNF-α), Fas ligand, HB-EGF, IGF-binding protein, and plasminogen to induce cell migration, proliferation, and apoptosis [61,62]. According to in vitrostudies, it is known that another role of MMP-7 is related to epithelial cadherin (E-cadherin) shedding to increase the malignancy and invasion of carcinoma, MMP-7 causing cleavage in the

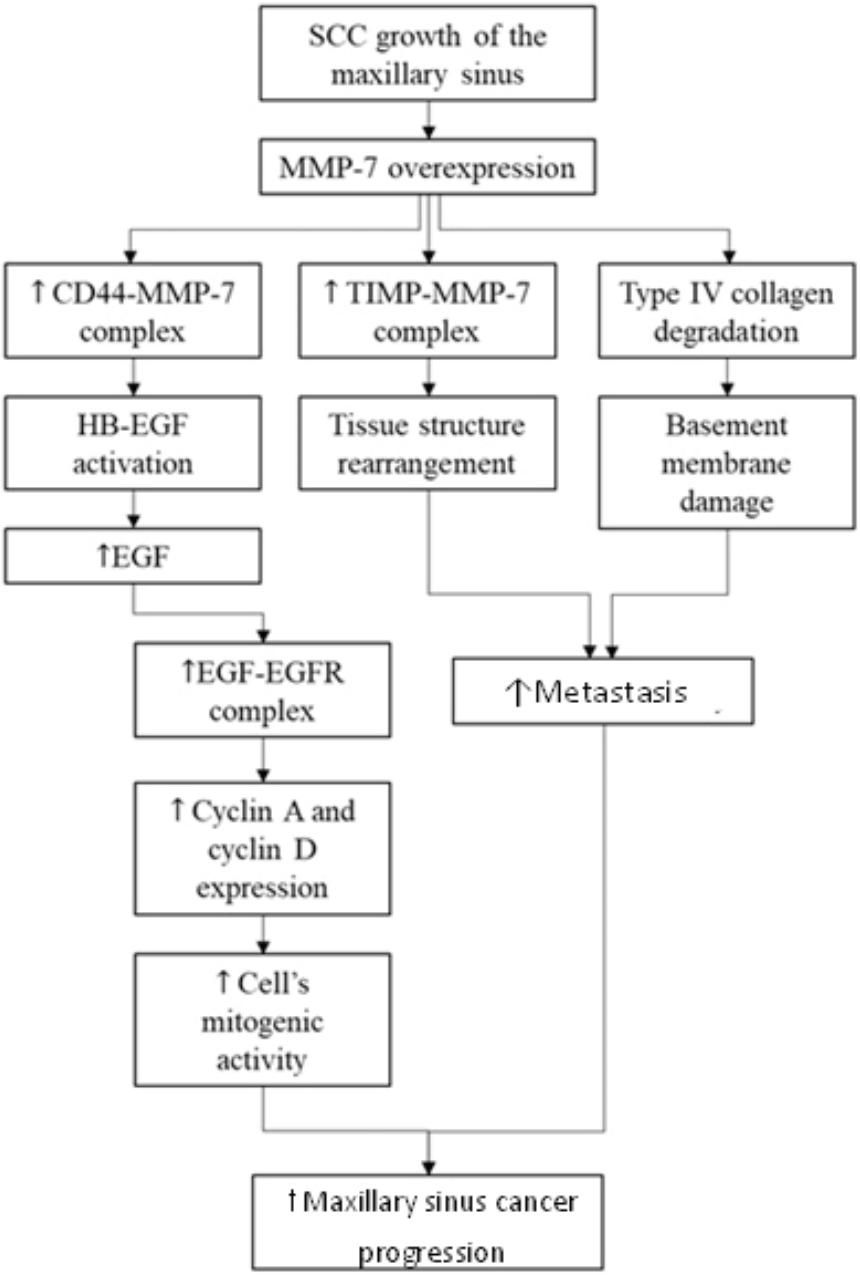

Figure 3. Sinus maxillary cancer pathogenesis [7,8].

syndecan-1/KC complex from mucous layer, causing neutrophils influx [63].

MMP-7 in people with epithelial mucous cancer has increased TNF-α and Interleukin-6 (IL-6), accompanied by decreasing in Interleukin-10 (IL-10) [64]. TNF-α is a pleiotropic cytokine that increases prothrombic and initiates mobility, adhesion, and polymorphonuclear (PMN) phagocytosis in tissue with cancer [65]. The increasing activity of IL-6 in cancer would be resistant to cell damage potential and proliferate faster [66]. Increasing TNF-α, as a pleiotropic cytokine, would increasing the opportunity of thrombosis on vascular.

Roles ff HB-EGF in Sinus Maxillary Cancer Progression

HB-EGF is part of EGF with a molecule weight of around 22 kD, composed of ectodomain shedding transmembrane pro-HB-EGF, the juxtacrine growth factor. HB-EGF could bind with EGF receptor in carcinoma cells, actively supporting proliferation and angiogenesis in epithelial neoplasia, and its C-terminal fragment could translocate into the nucleus to increase the expression of cyclin A and cyclin D2. Consequently, HB-EGF has an important role in supporting mitogenic activity [67,68].

HB-EGF is a biological molecule that link with a membrane and could be removed by proteolysis cleavage from the extracellular domain. HB-EGF is involved in increasing proliferation and apoptosis prevention physiologically and pathologically. HB-EGF's ability to bind with proteoglycan heparan-sulfate would increase the biological activity and secrete molecules as the effect of integral membrane metalloprotease (MMP) binding with disintegrin domain (ADAMs) type 9, 10, 12, and 17. The molecule secretion is also involved in the paracrine activity of HB-EGF in MMP [69]. Membranes that are connected or soluble In HB-EGF have an essential role in epithelial-to-mesenchymal transition (EMT) [70].

Interaction of MMP-7, TIMP-1, and HB-EGF in Sinus Maxilary Cancer Progression

MMP-7 overexpressed by SCC could degrade type IV collagen in maxillary sinus cancer progression so that the basement membrane that acts as a barrier to metastasis is damaged [7,16-18]. MMP-7 interacts with CD-44 on the receptor cluster of differentiation 44 receptor isoform variant 3 (CD44v3) and will associate with surrounding proteinases to form a pro-HB-EGF membrane complex [71].

Activated HB-EGF can form EGF, which plays a role in growth, proliferation, and differentiation, and inhibits apoptosis of epithelial cells [72,73]. EGF will interact with the epidermal growth factor receptor (EGFR) on the ectodomain to form a transmembrane glycoprotein site for tyrosine kinase binding [74]. Through dimerization, mutations in EGFR can activate tyrosine kinase [75,76]. Tyrosine kinase then affects growth, metabolism, differentiation, and apoptosis according to the needs of cancer cells [76].

TIMP plays a significant role in rearranging the network structure that changes due to MMP-7 activity [77]. Overexpression of TIMP inhibits cell polarization and prevents cancer progression and vice versa if TIMP expression is not high enough and cannot express MMP adequately [78]. So in the case of maxillary sinus cancer caused by the progressive proliferation of SCC, an unbalanced interaction between TIMP-1 and MMP-7 was found where the expression of MMP-7 molecules weretoo high so that the inhibitory activity of MMP-7 by TIMP molecules had no significant effect on the decreased progression of maxillary sinus cancer, this condition can be associated with cancer progression and metastases [79].

Effectiveness of MMP-7 as Sinus Maxillary Cancer Early Detection and Treatment

Early detection and treatment include screening procedures to discover certain specific markers in cancer that are often latent and, therefore, difficult to detect. Early detection and treatment are important to study further its effect on the patient's higher chance of recovery. When detected, the severity of the disease can be minimized, especially in people with risk factors for maxillary sinus cancer. Several prevention efforts and early detection have already been conducted for people with SCC. These early detection methods include scalpel biopsy, co-axial tomography (CT) scan, magnetic resonance imaging (MRI), and salivary metabonomics test. The scalpel biopsy method requires time and proficient analytical skills, and a CT scan can only detect a malignant carcinoma mass. The detection method of salivary metabonomics as an SCC test has only been studied in this decade as an easy, economical, and effective way. This saliva metabonomics test will use a swift metabonomic approach to salivary DNA and proteins, namely high-performance liquid chromatography-mass spectrometry (HPLC-MS), nuclear magnetic resonance (NMR) spectroscopy, and ultrahigh-performance liquid chromatography-mass spectrometry (UPLC-mass spectrophotometry). UPLC-MS detects the presence of oral, colorectal, and other types of cancer. These three tools can sensitively detect disease diagnoses in highly reproducible cells [80].

The review includes multiple research that analyzed the impact of MMP-7 on the growth and spread of many types of solid cancer with similar characteristics to sinus maxillary cancer as the reference; specifically, results showed that overexpression of MMP-7 significantly affected the proliferation and metastasis of SCC. Further research is necessary to compare MMP-7 expression in SCC patients with maxillary sinus cancer to healthy individuals and to develop early detection

methods for maxillary sinus cancer related to excessive MMP-7 activity and expression. Therefore, a more comprehensive explanation of the correlation between SCC and maxillary sinus cancer with MMP-7 is required, along with more information on the necessary technology to implement this finding in practice. Additionally, it is necessary to investigate the suitability of this method for different SCC sinus maxillary cancer grades.

CONCLUSIONS

Maxillary sinus cancer is frequently associated with squamous cell carcinoma (SCC). Timely identification of this disease is crucial, and monitoring MMP-7 activity levels is one way to achieve this. Nevertheless, no guidelines exist for recommending MMP-7 levels linked to maxillary sinus cancer advancement in SCC cases. Despite this, MMP-7 treatment exhibits promise as a viable therapeutic option for managing this form of cancer. It is recommended that future research efforts focus on establishing precise benchmarks and implementing treatment approaches targeting MMP-7. By exploring the relevance of MMP-7 in maxillary sinus cancer, we may unveil its potential as a reference point for the early detection or treatment of this disease. This heightened research may ultimately lead to improved outcomes for patients.

DECLARATIONS

Competing interest

The author(s) declare no competing interest in this study

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