BRIEF COMMUNICATION

https://doi.org/10.5125/jkaoms.2025.51.2.123
pISSN 2234-7550 · eISSN 2234-5930

Growth differentiation factor 15: a promising biomarker in oral cancer

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Abstract (J Korean Assoc Oral Maxillofac Surg 2025;51:123-125)

Growth differentiation factor 15 (GDF-15), a cytokine within the transforming growth factor-β superfamily, is involved in various malignancies, with implications in oral squamous cell carcinoma (OSCC). Elevated GDF-15 levels are correlated with unfavorable prognosis, tumor progression, and chemotherapy resistance, and the protein has been identified as a potential diagnostic and prognostic biomarker for OSCC. Personalized treatment strategies based on GDF-15 expression could improve treatment outcomes.

Key words: Growth differentiation factor 15, Cachexia, Squamous cell carcinoma, Mouth neoplasms, Biomarkers

[paper submitted 2025. 2. 3 / revised 2025. 3. 10 / accepted 2025. 3. 10]

Growth differentiation factor 15 (GDF-15) is a distinctive protein within the transforming growth factor-β superfamily. It exhibits divergent properties that distinguish it from other members of this family. It is encoded by a two-exon gene located on human chromosome 19p13.11[1]. Depending on its tissue-specific expression or functional roles, GDF-15 is alternatively referred to as macrophage inhibitory cytokine 1, placental transforming growth factor-β, placental bone morphogenetic protein, prostate-derived factor, and nonsteroidal anti-inflammatory drug activated gene 1[2-4].

GDF-15 was initially cloned based on its upregulation in response to macrophage activation[5]. In healthy individuals, the placenta is the primary tissue expressing high levels of GDF-15 for prenatal development followed by the prostate. GDF-15 expression has also been detected in the urinary bladder, heart, stomach, pancreas, liver, colon, rectum, kidney, and endometrium. However, except in the placenta and prostate, GDF-15 levels remain minimal under physiological conditions in healthy individuals[6,7]. GDF-15 is a stress-induced cytokine whose expression is significantly increased in response to pathological conditions such as inflammation, hypoxia, tissue injury, and tumor development. Elevated circulating levels of GDF-15 have been reported in various malignancies, including prostate, pancreatic, colorectal, endometrial, and lung cancers, suggesting its potential as a diagnostic or prognostic biomarker[8-12]. These elevated levels are associated with reduced survival rates. Furthermore, the overexpression of GDF-15 promotes distant metastasis in cancers such as prostate, colorectal, and gallbladder[6]. Recent studies have reported decreased symptoms, positive weight gain, and improved physical activity levels in patients with cancer cachexia and elevated GDF-15 levels when treated with ponsegromab, a highly selective antibody that inhibits circulating GDF-15. These results support the involvement of GDF-15 in the progression of cachexia[13,14].

In oral squamous cell carcinoma (OSCC), most cases are diagnosed at an advanced stage, which is associated with a poor prognosis. Early detection is crucial for reducing cancer-specific morbidity and mortality. Therefore, identifying biomarkers for OSCC could be beneficial for improving treatment outcomes[15,16]. Recent studies have reported the high sensitivity of Chemerin and matrix metalloproteinase-9 as salivary biomarkers for OSCC, while carcinoembryonic antigen, cancer antigen 125, and cytokeratin 19 fragment antigen (CYFRA 21-1) have been identified as potential serological biomarkers[17,18]. Another study reported the six proteins, I309 (C-C motif chemokine ligand 1; CCL1), GDF-15, AXL re-

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ceptor tyrosine kinase, matrix metalloproteinase-3, CTACK (C-C motif chemokine ligand 27; CCL27), and macrophage colony-stimulating factor as potential diagnostic serological markers for OSCC. Among these, only GDF-15 was found to have a significant association with OSCC prognosis[19].

A research group in Germany was the first to report serum GDF-15 as a diagnostic and prognostic biomarker for OSCC[20]. They also described, for the first time, the involvement of GDF-15 in both tumorigenesis and radio-resistance in OSCC. Due to its anti-apoptotic effects, GDF-15 may promote tumor progression and protect carcinoma cells from irradiation[21].

A research group in China reported that elevated GDF-15 levels may function as a diagnostic marker for oral leukoplakia and as a prognostic marker, associated with reduced response to induction chemotherapy for OSCC[22]. They further suggested that GDF-15 expression could act as a prognostic biomarker for OSCC and a predictive marker for patients likely to benefit from cisplatin, docetaxel, and 5-fluorouracil (TPF) induction chemotherapy. Additionally, GDF-15 has been implicated in tumorigenesis and progression in OSCC[23]. In addition, patients with GDF-15 mutations experience significantly poorer outcomes compared to those with wild-type GDF-15, suggesting that these mutations may serve as an independent risk factor for poor prognosis in OSCC patients[24]. Another study proposed that elevated GDF-15 expression may serve as a prognostic marker for poor treatment outcomes in locally advanced OSCC as it predicted a significant survival benefit from induction chemotherapy with the TPF regimen in OSCC[25]. Moreover, OSCC overexpressing GDF-15 has been shown to be sensitive to TPF chemo-agents. Overexpression of GDF-15 promotes cellular proliferation in OSCC through phosphorylation, and phosphorylation inhibitors could potentially be employed as targeted drugs for affected patients. A customized treatment was proposed based on the GDF-15 expression levels in biopsies obtained from patients with locally advanced OSCC[26].

Recently, a research group in India reported that salivary GDF-15 levels gradually increase from healthy subjects to cases of oral leukoplakia, with the highest levels observed in the OSCC group. An increase in GDF-15 concentration was also noted with progression of OSCC grade. Therefore, variation in salivary GDF-15 levels could potentially serve as a key therapeutic target[27].

GDF-15 is considered a promising biomarker and potential therapeutic target in OSCC management, with implications for personalized treatment regimens in both chemotherapy and radiotherapy. Despite significant advances in GDF-15 research, its specific pathological roles remain elusive owing to its pleiotropic effects. Clarifying the molecular mechanisms of GDF-15 in cancer pathogenesis and progression is imperative. Further investigation is necessary to establish a solid foundation for developing optimized, personalized treatment strategies in OSCC.

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Authors' Contributions

All authors have read and approved the final manuscript. H.J.O. conducted the literature review and wrote the manuscript. J.H.L. provided guidance for the study. S.M.K. conceptualized the study and designed the entire manuscript.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2022R1F1A1069624).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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How to cite this article: Oh HJ, Lee JH, Kim SM. Growth differentiation factor 15: a promising biomarker in oral cancer. J Korean Assoc Oral Maxillofac Surg 2025;51:123-125. https://doi.org/10.5125/jkaoms.2025.51.2.123