The role of ghrelin and its receptors in colorectal cancer progression

Nur Maya Sabrina Tizen Laim[1], Muaatamarulain Mustangin[1], Faridah Abd Rahman[2], Badrul Iskandar Abdul Wahab[2], Nurwahyuna Rosli[1], Farah Hanis Juhari[3]

[1]Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Cheras, Kuala Lumpur, Malaysia, [2]Department of Diagnostic Laboratory Services, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, 56000 Cheras, Kuala Lumpur, Malaysia, [3]Department of Biosciences, Faculty of Science, Universiti Teknologi Malaysia, 81300 Johor Bahru, Johor, Malaysia

ABSTRACT

Introduction: Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide. In Malaysia, CRC represents a significant burden, particularly among males. Despite advancements in screening and treatment, late-stage diagnosis remains prevalent, highlighting the need for improved biomarkers for early detection and therapeutic targeting. Ghrelin, a 28-amino-acid peptide hormone predominantly secreted in the stomach, has gained attention for its role in appetite regulation, metabolism and potential involvement in cancer biology, including inflammation, proliferation, and tumour progression. This narrative review aims to explore the role of ghrelin and its receptors i.e. GHSR1a and GHSR1b in the development and progression of CRC and to assess their potential as diagnostic and therapeutic biomarkers. **Materials and Methods and Results:** Ghrelin is encoded by the GHRL gene and synthesized as pre-proghrelin before being processed into acylated ghrelin via the enzyme ghrelin O-acyltransferase (GOAT). The acyl-ghrelin form binds to GHSR1a, a functional receptor widely expressed in the hypothalamus and peripheral tissues including the gastrointestinal tract. GHSR1b, a truncated receptor isoform unable to bind ghrelin is believed to modulate GHSR1a signalling through heterodimerization. Both receptors have been identified in colonic tissues including malignant cells, thus raising questions about their role in CRC progression. Studies on circulating ghrelin levels in CRC patients have shown mixed results. Several investigations reported decreased serum ghrelin levels particularly in more advanced CRC stages, suggesting a potential inverse relationship with tumour progression. Other studies found increased or unchanged levels, reflecting inconsistencies in the literature. Furthermore, tissue-level studies using immunohistochemistry (IHC) and reverse transcription polymerase chain reaction (RT-PCR) have demonstrated variable expression patterns. Some findings indicated increased expression of ghrelin and GHSR1b in high-grade adenomas and well- to moderately-differentiated adenocarcinomas, while GHSR1a expression was reduced or absent in poorly differentiated tumours. **Discussion:** The functional implications of these findings remain unclear. While ghrelin has been shown to activate pathways like PI3K/Akt, promoting cell proliferation and inhibiting apoptosis, other studies suggest that ghrelin might have protective roles particularly in early carcinogenesis or inflammation-associated CRC. The differential expression of GHSR1a and GHSR1b across disease stages suggests they may play distinct or even opposing roles in CRC pathogenesis. In addition to tissue-level expression, several studies have linked GHSR1a downregulation and GHSR1b upregulation with increasing tumour grade, further supporting the idea that the ghrelin system reflects tumour behaviour. However, inconsistencies in study design, sample size, and methodology limit the generalisability of findings. Moreover, while ghrelin-targeted therapies are under consideration in other cancers, their role in CRC remains speculative. **Conclusion:** In conclusion, the ghrelin system shows potential as a biomarker and therapeutic target in colorectal cancer. However, conflicting evidence regarding its expression and function necessitates further investigation using standardised methods and larger cohorts. Clarifying the roles of ghrelin, GHSR1a and GHSR1b may lead to novel strategies for CRC diagnosis, prognosis and treatment.

Keywords: Colorectal cancer, Ghrelin, GHSR1a, GHSR1b, Biomarker, Immunohistochemistry, RT-PCR