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MINI-REVIEW ARTICLE

Molecular Regulatory Roles of Long Non-coding RNA *HOTTIP*: An Overview in Gastrointestinal Cancers

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Abstract: Gastrointestinal (GI) cancers presented an alarmingly high number of new cancer cases worldwide and are highly characterised by poor prognosis. The poor overall survival is mainly due to late detection and emerging challenges in treatment, particularly chemoresistance. Thus, the identification of novel molecular targets in GI cancer is highly regarded as the main focus. Recently, long non-coding RNAs (lncRNAs) have been discovered as potential novel molecular targets for combating cancer, as they are highly associated with carcinogenesis and have a great impact on cancer progression. Amongst lncRNAs, *HOTTIP* has demonstrated a prominent oncogenic regulation in cancer progression, particularly in GI cancers, including oesophageal cancer, gastric cancer, hepatocellular carcinoma, pancreatic cancer, and colorectal cancer. This review aimed to present a focused update on the regulatory roles of *HOTTIP* in GI cancer progression and chemoresistance, as well as deciphering the associated molecular mechanisms underlying their impact on cancer phenotypes and chemoresistance and the key molecules involved. It has been reported that it regulates the expression of various genes and proteins in GI cancers that impact cellular functions, including proliferation, adhesion, migration and invasion, apoptosis, chemosensitivity, and tumour differentiation. Furthermore, *HOTTIP* was also discovered to have a higher diagnostic value as compared to existing diagnostic biomarkers. Overall, *HOTTIP* has presented itself as a novel therapeutic target and potential diagnostic biomarker in the development of GI cancer treatment.

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1. INTRODUCTION

Gastrointestinal (GI) cancers refer to malignant conditions of the digestive system, composed of the oesophagus, stomach, biliary system (*e.g.*, liver, gallbladder, and bile duct), small intestine, large intestine, rectum, and anus. It is considered one of the most prominent cancers, as GI cancers have occupied the top ten leading cancers in recent decades. In terms of the newest cancer cases reported in 2018 worldwide, colorectal cancer (CRC) ranked fourth (1,096,601 cases), stomach cancer ranked sixth (1,033,701 cases) and liver cancer ranked seventh (841,080 cases). While rectum cancer and

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oesophageal cancer (OC) ranked eighth (704,376 cases) and ninth (572,034 cases), respectively. Besides, GI cancers also have a poor survival rate as stomach cancer is the leading cause of death worldwide, with 782,685 deaths reported in 2018 [1]. Treatments for GI cancers include surgery, chemotherapy, and radiotherapy, depending on the stage and severity of each cancer type [2]. Based on the recent findings, there is no specific treatment for cancer that could lead to significant benefits for patients [3].

The challenge of cancer treatment is the rise of resistance towards chemotherapy that leads to difficulty in the management of cancer [4, 5]. In fact, there is no single drug treatment that could completely cure cancer; thus, drug combination treatment is much preferred. However, this treatment strategy could increase the risk of gaining toxicity, thus becoming a limiting factor for drug combination treatment [3]. In this regard, most GI cancer patients suffer from chemotherapy-related toxicity, which reduces their quality of life. Although the first choice of GI cancer treatment is surgical resection; however, it is not a preferred treatment, as most patients are diagnosed at the late stage, which is unfavourable for surgery, and the tumour is enlarged or has been metastasised to the other parts of the body. Other than that, most patients have relapse episodes after surgery, making surgical treatment less efficacious for GI cancers [2]. Thus, it is an urgent need to discover new potential therapeutic targets to improve the management of GI cancers.

According to genome-wide association studies on cancer, over 80% of cancer-associated single nucleotide polymorphisms occur in non-coding regions of the genome [6]. Besides, it is reported that most of the cancer risk loci are in the non-coding regions that subsequently affect the relevant gene expression, as these regions have regulatory elements [7]. Non-coding RNAs (ncRNAs) are defined as an RNA molecule that is transcribed from DNA but not translated into protein. They function as a regulator of gene expression at both transcriptional and post-transcriptional levels [8]. They can be divided into two distinct classes, mainly based on the length of the nucleotides, namely long non-coding RNAs (lncRNAs) and small non-coding RNAs (sncRNAs). SncRNAs consist of less than 200 nucleotides, for example, small interfering RNAs, microRNAs, and picoRNAs, whereas lncRNAs comprise over 200 nucleotides [9]. LncRNAs play a significant role in many cancers, including GI cancers, in which they act as either an oncogene or tumour suppressor [10, 11]. Additionally, it has been reported that lncRNAs could affect cancer phenotypes by regulating chromatin remodelling, transcription co-activation and repression, protein inhibition, post-transcriptional modifications, and decoy elements [6].

To date, many lncRNAs have been discovered, and amongst which, *HOTTIP* plays significant biological roles in GI cancers [12]. For example, several studies have revealed that high *HOTTIP* expression is associated with lymph node metastasis, distant metastasis, poor tumour differentiation, and poor clinical stage [13, 14], all of which cause a poor prognosis that subsequently leads to a poor survival rate. Moreover, other studies have also reported that the expression levels of *HOTTIP* significantly affect the overall survival of cancer patients [13, 15]. This finding demonstrated that *HOTTIP* plays a significant role in cancer progression and could act as a cancer prognostic biomarker.

Thus, this review aims to provide a focused update on the regulatory roles of *HOTTIP* on various genes and proteins expression in the aspects of GI cancer progression and chemoresistance, as well as the underlying mechanism of actions and the key molecules that are involved in each mechanistic response. Therefore, it enables the evaluation of *HOTTIP* as a potential candidate becoming a novel therapeutic target for GI cancers.

2. LONG NON-CODING RNA *HOTTIP*

The human genome sequencing of ENCODE project showed that only 2% of the human genome is protein-coding, while 98% is non-protein coding. This non-protein-coding region is transcribed into an RNA molecule that regulates the overall gene expression to influence growth, organ function, and disease progression [9]. Among ncRNAs, lncRNAs show significant molecular regulatory roles in cancer progression. It is transcribed by RNA Polymerase II and can be further categorised based on the location of the genome relative to the protein-coding genes, including antisense transcripts, bidirectional promoter transcription, enhancer-associated lncRNA, long intergenic ncRNA, and repetitive element-associated ncRNA [16, 17], as shown in Figure **1**. LncRNAs can interact with other molecules, such as protein, RNA, and DNA, to exert their functions in chromatin organisation, epigenetic regulation, gene transcription and translation, RNA turnover, and genome defence [18].

HOTTIP, which is located within the *homeobox (HOX)* genes, plays a vital role in tumorigenesis through regulating various genes expression [19]. In general, *HOX* genes encode transcription factors that regulate embryonic development and tissue homeostasis. A total of 39 transcription factors encoded by *HOX* genes have been identified in regulating a series of targeted genes in a downstream manner. There are four *HOX* gene clusters in humans, namely *HOXA, HOXB, HOXC,* and *HOXD*. Each cluster consists of nine to ten *HOX* genes [20], except for the *HOXA* cluster comprising 11 *HOX* genes. The gene expression along the body from proximal to distal is in the gradient pattern that is colinear with the position of the gene from 3′ to 5′. *HOTTIP* is a long intergenic ncRNA that is encoded at the 5′ end of the *HOXA* cluster, as illustrated in Figure **2**. Its expression is highly concentrated at the anatomically distal human fibroblast, such as hand, foot, and foreskin; thus, it is termed as '*HOXA* transcript at the distal tip' (*HOTTIP*) [21]. Furthermore, *HOTTIP* is also known as a locus

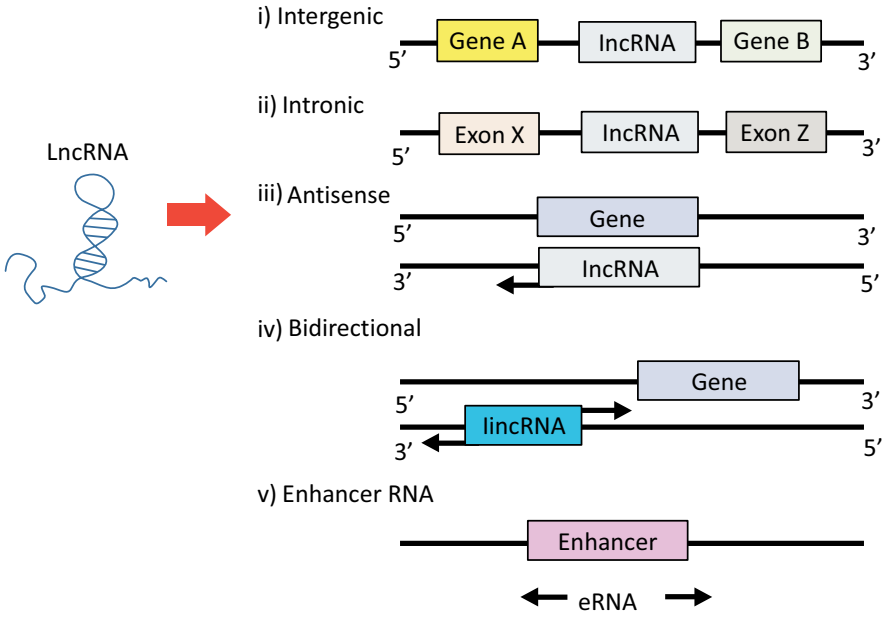

Fig. (1). Different types of lncRNAs. LncRNAs can be divided into bidirectional, intronic (within an intron), sense, intergenic (between two genes), antisense, and enhancer based on the location on the genome relative to the nearby protein-coding gene. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

control element of the *HOXA* gene, as it coordinates the activation of 59 *HOXA* genes *in vivo*. This is due to the chromosomal looping at which two genomic loci are brought into close proximity by DNA-binding protein via epigenetic mechanisms. Chromosomal looping brings *HOTTIP* closes to 5′ *HOXA* genes. The close proximity with the target genes enables *HOTTIP* to induce their expression [22]. *HOTTIP* is one of the lncRNAs that exhibits enhancer-like properties. Enhancer is defined as a DNA element that acts at a distance to regulate protein-coding genes. It consists of a specific sequence that requires the binding of transcriptional factors to enhance the transcription of targeted genes. It has been reported that *HOTTIP* plays critical roles in regulating gene expression, either as a transcriptional activator or repressor, which certainly imitates the properties of enhancers [23].

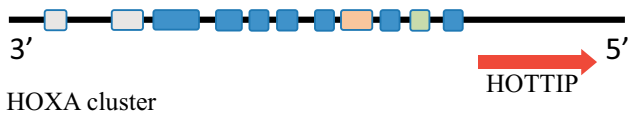

Fig. (2). *HOTTIP* transcription. The transcription of **HOTTIP** starts at the region nearby 5′ end of the *HOXA* gene cluster.

3. REGULATORY ROLES OF *HOTTIP* IN GASTROINTESTINAL CANCERS

It has been reported that *HOTTIP* extensively regulates cancer progression [12]. In particular, it has shown significant regulatory roles in EC [24], gastric cancer (GC), hepatocellular carcinoma (HCC), pancreatic cancer (PC), and CRC [12], as summarised in both Table **1** and Fig. (**3**). The regulatory roles of *HOTTIP* and the associated molecular mechanisms, as well as key molecules involved along the mechanistic pathways, are discussed in the following sections based on different GI cancers.

3.1. Oesophageal Cancer

EC is one of the fatal cancers having a poor prognosis, with an overall 5-year survival of only about 19% [25]. EC has two subtypes, namely oesophageal adenocarcinoma (EAC) and oesophageal squamous cell carcinoma (ESCC). In comparison, ESCC contributes about 90% of the reported EC cases worldwide [1]. Currently, there is still no definite treatment for ESCC that could lead to significant survival benefits. The mainstay treatment for ESCC patients is surgery, and the combination of radiotherapy and chemotherapy is often given as preoperative therapy. While palliative treatment is used to prolong their survival rate, the patients cannot opt for surgery and/or chemotherapy [26]. Besides, ESCC is commonly diagnosed at the late stage; thus, palliative care is the only treatment option [27]. However, it has been reported that the response rate towards chemotherapy is only 19-40%, and about half of these patients do not achieve a good response [28]. This phenomenon increases the difficulty in managing ESCC patients and may increase the mortality rate and contribute to the poor prognosis of metastatic ESCC [29].

Chen *et al.* [30] reported that the expression of *HOTTIP* was significantly elevated in ESCC cells as compared to normal oesophageal cells. Additionally, *HOTTIP* expression was more prominent in the late-stage tumour tissue and influenced the tumour size. It also affected cancer cell proliferation through cell cycle regulation. The percentage of cells in the G0/G1 cell

phase was increased, while that in the S phase was decreased in response to the downregulation of *HOTTIP*. This result signified that *HOTTIP* silencing caused cell arrest at G0/G1 phase and subsequently inhibited the progression of ESCC cells to the S phase. In addition, the percentage of cell viability significantly decreased in *HOTTIP*-silenced ESCC cell lines, all of which indicating that *HOTTIP* silencing promotes cell cycle arrest that leads to decreased ESCC cell proliferation. Besides, *HOTTIP* was shown to promote metastasis of ESCC cells through epithelial-mesenchymal transition (EMT). Interestingly, *HOTTIP* silencing resulted in the change of EMT-inducing protein expression levels, including E-cadherin, N-cadherin, and vimentin [30]. According to Heerboth *et al.* [31], these proteins are vital for the metastasis of cancer cells. For example, E-cadherin is a marker of epithelial phenotype, and a decrease in its protein level can cause the loss of cell adhesion, which is favourable in promoting metastasis. In contrast, both vimentin and N-cadherin are the markers of the mesenchymal phenotype, whereby mesenchymal morphology confers cancer cells with the ability to migrate and differentiate into different types of cells. The increase in the mesenchymal markers is concomitant with the decrease of E-cadherin expression in cancer cell migration [31].

Apart from these, *HOTTIP* has also been found to activate *HOXA13* to promote cancer progression. An *in vitro* study showed that *HOTTIP/HOXA* promoted EC cell progression through the inhibition of apoptosis. This claim was evidenced by the increased levels of apoptotic proteins, including cleaved caspase-3, cleaved caspase-9, and Bax after *HOTTIP/HOXA* gene silencing. Similarly, Lin *et al.* [32] also reported that *HOTTIP* promoted metastasis via EMT, except that *HOXA13* also plays a role in inducing EMT. The *in vitro* effects of *HOTTIP* on promoting tumour metastasis were supported by the results obtained from the *in vivo* nude mouse model. For example, it was measured that the number of migrating cells in the tissues of nude mice with a high level of *HOTTIP/HOXA13* gene expression was much higher than in the control group. They further reported that *HOTTIP* could regulate *HOXA13* through WDR5 and miR-30b. The downregulation of *HOTTIP* caused a decrease in the protein levels of WDR5 and H3K4me3 at the *HOXA13* promoter, thus leading to decreased gene transcription. This result indicated that *HOTTIP* plays a role in maintaining WDR5 at the promoter of the *HOXA13* locus to activate the transcription of the *HOXA13* gene. Besides, *HOTTIP* silencing upregulated the expression of *miR-30b*. The transfection of *miR-30b* mimic into ESCC cells resulted in decreased mRNA levels of *HOXA13.* This may be due to that *HOTTIP* acts as a ceRNA that binds to *miR-30b* and consequently inhibits its function [32]. Thus, Lin *et al.* [32] deduced that *HOTTIP* could induce miRNA degradation in ESCC. MiR-30b functions as a tumour suppressor microRNA in ESCC through the integrin subunit alpha 5 (ITGA5), platelet-derived growth factor receptor beta (PDGFRB), and signalling pathways, such as PI3K/Akt, involved in ESCC regulation [33].

Compared to Chen *et al.* [30], Lin *et al.* [32] demonstrated much clearer evidence regarding the effects of *HOTTIP* on metastasis by conducting an *in vivo* study, which showed an increased tumour volume and intensity of cell migration. Additionally, they found that nude mice bearing overexpression of *HOTTIP/HOXA13* had markedly higher intensity of cell migration and metastasis of nodule in lungs and liver area as compared to the control group [32]. Other than that, *HOXA13* downregulation could reduce the expression of *HOTTIP* in ESCC cells. However, further investigation is required to determine whether *HOXA13* upregulation alone could regulate *HOTTIP* expression to be implicated in ESCC progression [31].

3.2. Gastric Cancer

GC ranks fifth among the most diagnosed cancers and ranks third among the deadliest cancers, with a survival rate of about 31%. About 90% of GC tumours are adenocarcinoma, which is defined as a malignant tumour formed from a glandular structure in epithelial. Risk factors of GC include *Helicobacter pylori* infection that is considered the primary cause in GC. Besides, environmental factors also play a significant role in developing GC, for example, intake of high dietary salt and processed meat [34-36]. It is commonly detected at the metastasis stage that results in a poor prognosis [37]. The early stages of GC are commonly asymptomatic compared to advanced stages, in which persistent abdominal pain, anorexia, weight loss, hematemesis, and persistent vomiting are observed [35, 36].

Comparatively, *HOTTIP* has a higher potential to be a prognostic and diagnostic biomarker in GC patients than other GI cancers. A study showed that exosomal *HOTTIP* levels were abnormally high in patients with advanced tumour stage. In addition, the diagnostic capability of exosomal *HOTTIP* was higher than an existing diagnostic biomarker of GC [38]. To support this claim, several studies have also demonstrated that *HOTTIP* positively associates with the tumour size, tumour invasion, and overall survival of GC patients [39, 40]. Interestingly, Wang *et al.* [41] also found that *HOTTIP* was correlated with the metastasis of GC, as its expression levels were higher in malignant GC cells than non-malignant GC cells.

Chang *et al.* [40] reported that *HOTTIP* regulated GC progression by activating the *HOXA13* gene. After *HOTTIP* silencing, it was observed that the mRNA levels of several *HOXA* genes (e.g., *HOXA9, HOXA10*, *HOXA11,* and *HOXA13*) were downregulated. Among *HOXA* genes, *HOXA13* showed a significant decrease in the mRNA levels. Additionally, the downregulation of the *HOXA13* gene demonstrated an inhibitory effect on cell growth, migration, and invasion, which are very similar to the effects of *HOTTIP* gene silencing. Furthermore, Wang *et al.* [41] demonstrated that *HOXA13 gene* silencing significantly downregulated *HOTTIP*, stipulating that *HOXA13* may influence

HOTTIP expression. Thus, it was concluded that the *HOXA13* gene is involved in *HOTTIP*-induced GC phenotypes [40]. Intriguingly, similar to the ESCC, the *HOXA13* gene also initiated GC cells by regulating a variety of EMT, namely, MSS/TP53+, MSS/TP53-, MSI, and MSI/EMT that further promotes metastases invasion [42]. The invasion capability of GC cells decreased when the mRNA levels of *HOXA13* were downregulated. Also, *HOXA13* downregulation could increase E-cadherin expression but not N-cadherin and vimentin [43].

In GC, it was discovered that *HOTTIP* regulated *HOXA13* gene expression by increasing the recruitment of the WDR5/MLL complex at the 5'-end of the *HOXA* cluster [41]. The increase of the WDR5/MLL complex was observed when the expression levels of *HOTTIP* were upregulated. Subsequently, the H3K4me3 level was increased at the E1 site of the *HOXA13* promoter, thus initiating gene transcription. Other than that, *HOXA13* was also positively associated with insulin growth factor-binding protein 3 (IGFBP3). Homeobox protein Hox-A13 and IGFBP3 were overexpressed in GC patients, with 63.2% (homeobox protein Hox-A13) and 28.6% (IGFBP3), respectively. Increased *HOXA13* activated *IGFBP-3* promoter activity due to mutations in two putative HOX-binding sites on the *IGFBP3* promoter. Additionally, Wang *et al.* [41] also demonstrated a clear mechanism on how *HOXA13* increased IGFBP3 protein levels by using a luciferase assay. The *IGFBP-3* promoter was cloned to the luciferase reporter, and the *HOXA13*-expressing construct was co-transfected into CS12 cells. The result showed an increase in luciferase activity, signifying that *HOXA13* enhanced the activation of the *IGFBP-3* promoter. To further clarify whether the protein levels of IGFBP3 correlates with *HOXA13* in regulating cancer progression, malignant GC cells were transfected with *HOXA13* siRNA. It was found that *HOXA13* gene silencing resulted in a significant reduction of IGFBP3 protein levels. Consequently, the reduced IGFBP3 also decreased the migration and invasion capacities of highly malignant GC cells [41]. Collectively, *HOTTIP* is associated with *HOXA13* via WDR5/MLL and H3K4me3 to indirectly promote metastasis in GC through EMT and IGFBP3 by increasing *HOXA13* mRNA levels.

Insulin-like growth factors (IGF) play a significant role in regulating cancer cell proliferation, differentiation, and apoptosis. IGFBP3 is the protein that binds to IGF in the extracellular milieu to inhibit IGF-induced migration and antiapoptotic features. Apart from that, IGFBP3 also has IGF-independent functions, such as antiproliferative and proapoptotic effects. Among IGFBP members, IGFBP3 is found as the most abundant in the serum and tightly bound to IGF. It is expressed in most human tissues and various cell lines, including gastric cells. In conclusion, IGFBP3 acts as a tumour suppressor that stimulates cell apoptosis and inhibits cell migration, as evidenced in a study that the suppression of IGFBP3 through hyper-methylation of promoter *IGFBP3* gene could trigger cancer cell proliferation [44]. However, the findings of Wang *et al.* [41] showed contradictory results, in which IGFBP3 induced GC cell proliferation. Furthermore, *IGFBP3* gene silencing reduced cancer cell growth, proliferation, invasion, and migration. Thus, IGFBP3 may act as a tumour oncogene that promotes GC cell growth, which contradicts the findings of its role as a tumour suppressor, particularly in GC. The contrasting differences of IGFBP-3 role might be due to the complex interplay between cellular microenvironment and the presence of cellular IGFBP-3 binding partners and growth factor receptors in which IGFBP-3 expression levels vary between cell lines and tumour tissues [45] and in different cell culture systems [46]. It could also be explained that either circulating levels of IGFBP-3 do not play a role or are non-reflective of the tumour microenvironment [47].

Besides, it has been reported that lncRNAs aberrantly regulate various cell functions, such as cell cycle, apoptosis, autophagy, and metabolisms, which are associated with chemosensitivity [48]. Similarly, several studies have demonstrated *HOTTIP* upregulation in cisplatin-resistant GC cells. Wang *et al*. [49] further indicated that extracellular *HOTTIP* could be incorporated into exosomes via the activation of HMGA1 and transmitted to sensitive cells, possibly to disseminate cisplatin resistance. The underlying mechanism of *HOTTIP* expression in promoting cisplatin resistance in GC cells is through sponging miR-216a-5p overexpression to further decrease Bcl-2 expression and enhance Beclin1 expression, which leads to active autophagy [50].

3.3. Hepatocellular Carcinoma

HCC is characterised by high mortality and short survival time, with an estimated 5-year survival rate of only 6.9%. The poor survival rate may be due to the late detection in most HCC patients [51]. It is commonly asymptomatic at the early stages but shows symptoms when the tumour diameter exceeds 10 cm. The preferred treatment of HCC is surgical resection for early stages patients when the tumour is still small and limited to one lobe of the liver. However, liver transplantation is required for advanced stages [52]. It has a high prevalence in Asian countries, contributing about 76% of all reported cases [53]. The primary risk factor of HCC is a chronic infection of viral hepatitis. Other risk factors include cirrhosis, chronic viral hepatitis, alcohol abuse, obesity, hemochromatosis, $alfa_1$-antitrypsin deficiency, and aflatoxin-like toxins [52, 54, 55].

Compared to normal liver tissue, it was reported that the expression of *HOTTIP* was 4.67-fold higher in HCC tissue. Besides, its expression was highly dominant in the late stages of HCC, particularly third and fourth [56]. This finding was also supported by the findings of Tsang *et al.* [56], in which *HOTTIP* mRNA expression was significantly high in most HCC patients (81.4%). However, they also discovered that *HOTTIP* was overexpressed at the early stage of HCC, resulting in a potential biomarker for HCC diagnosis. This result is opposed to the findings of Zhang *et al.* [57]. It was

also observed that *HOTTIP* upregulation was positively associated with tumour progression, as evidenced in an *in vivo* model. In the nude mice injected with HCC cells, it was observed that reduced levels of *HOTTIP* significantly suppressed the tumour growth. Besides, *HOTTIP* silencing also decreased the migration rate and pulmonary metastasis of HCC, implying its significant role in HCC progression [57]. In another study carried out by Wu *et al.* [58], the expression levels of *HOTTIP* were markedly higher in cancerous tissues compared to healthy liver tissues, which is consistent with the findings of Zhang *et al.* [51]. Additionally, they found that high *HOTTIP* expression levels in HCC patients positively implicated the overall survival rate, tumour recurrence after liver transplant, and sensitivity towards chemotherapy, such as doxorubicin, etoposide, and oxaliplatin [58].

Apart from these, several studies have reported that regulating *HOTTIP* in HCC is related to the *HOXA13* gene [59, 60]. For example, increased expression of both *HOTTIP* and *HOXA13* was detected in HCC biopsies. Furthermore, it was observed that the expression levels of the *HOXA13* gene were downregulated to 42.3% after reducing the mRNA levels of *HOTTIP* to 53.3% in HCC cells by using the RNAi-mediated technique. This result indicated that *HOTTIP* regulated *HOXA13* expression levels. The reduced expression of both *HOTTIP* and *HOXA13* also led to decreased cell proliferation index [59]. Furthermore, it is also postulated that *HOXA13* may influence *HOTTIP* expression, as *HOXA13* gene silencing reduced *HOTTIP* expression, resulting in a significant reduction in HCC cell proliferation. However, *HOXA13* upregulation showed no significant increase in *HOTTIP* expression and did not affect HCC cell migratory properties but induced a higher apoptosis rate and reduced proliferation rate [55].

As it has been detected that *HOTTIP* regulates the *HOXA13* gene, thus HCC patients with high *HOXA13* expression levels also showed poor tumour differentiation and poor prognosis rate. In addition, *HOXA13*-overexpressed cells showed resistance towards sorafenib treatment, as their proliferation was not affected [60]. The regulation of the *HOXA* gene by *HOTTIP* is via a cis-manner, where *HOTTIP* is located at the distal end of the *HOXA* cluster, as depicted in Figure **3**. It has been shown that *HOTTIP* upregulation positively regulates the neighbouring *HOXA* gene, as a marked increase in the *HOXA* gene has been observed, particularly in *HOXA13* [57].

3.4. Pancreatic Cancer

PC is the fourth leading cause of cancer-related deaths worldwide [61, 62]. Statistically, it ranked fourteenth as the most cancer cases reported and seventh in terms of mortality in 2018 [1]. As it is difficult to treat, it is known as a rapidly fatal cancer. This condition is due to the fact that there is currently no diagnostic marker for early diagnosis, and the biological features of PC are aggressive that results in multiple resistance towards treatment and rapidly progressive metastasis [63]. Unlike other tumours, no sensitive and specific markers have been detected to aid the detection of PC. Besides, the treatment options for PC are limited, as it is known to be complex at genomic, epigenetic, and metabolic levels, with multiple activated pathways and evident crosstalk [64].

High *HOTTIP* expression has been observed in several PC cell lines, such as Panc1, L3.6pL, and MiaPaCa2, and can influence their proliferation [65]. Besides, *HOTTIP* downregulation induced a cell cycle arrest at the G_2/M phase, indirectly inhibiting PC progression. Additionally, reduced mRNA levels of *HOTTI*P also triggered cell apoptosis, as evidenced by an increase in Annexin V and PARP cleavage [66]. Apart from these, Cheng *et al.* [66] also investigated the regulatory effect of *HOTTIP* on other genes by conducting bead chip array analysis. The analysis showed that *HOTTIP* could regulate the expression of several pancreatic carcinogenesis-promoting genes, including *AURKA, AHNAK, GDF15, SGK1,* and *CD44* [66]. They further investigated the effect of *AURKA* gene silencing on carcinogenesis because *AURKA* has played an important role in carcinogenesis, particularly in PC [67, 68]. A decrease in *AURKA* gene expression caused a decrease in Panc1 cell growth in which the percentage of cells in the G0/G1 phase was significantly decreased, whereas the percentage of cells in both S and G2/M phases increased. *AURKA* gene silencing also increased Annexin V staining and PARP cleavage, as well as inhibited cancer cell migration. Overall, downregulation of the *AURKA* gene in PC cells causes inhibition of cell growth through cell cycle arrest, induction of cell apoptosis, and inhibition of cell migration [66].

Unlike the findings observed in other GI cancers, Cheng *et al.* [66] further demonstrated that *HOTTIP* did not regulate the expression of the *HOXA13* gene, as only a slight decrease in *HOXA13* mRNA levels was observed after *HOTTIP* silencing. Nonetheless, *HOTTIP* silencing led to a marked decrease in the expression of *HOXA10* (>80%), *HOXB2* (>60), *HOXA11* (>75%), *HOXA9* (>80%), and *HOXA1* (>60%) genes [66]. However, this finding is opposed to the findings reported by Li *et al.* [69], in which *HOTTIP* can regulate the expression of the *HOXA13* gene to implicate PC progression. For example, when *HOTTIP* was downregulated, *HOXA13* mRNA levels also markedly decreased compared to the other *HOXA* genes. To further prove the correlation between *HOTTIP* and *HOXA13* gene, a correlation scatterplot (Spearman test) of *HOTTIP* and *HOXA13* expression in PC was conducted. The result showed a positive correlation between *HOTTIP* and *HOXA13* gene (r_s = 0.7008) [69]. Spearman rho (r_s) value was between 0.61 to 0.80, indicating a strong and positive correlation between them [70]. Such a contrast finding reported in both studies could be due to different PC cells used. For example, Cheng *et al.* [63] used Panc-1 cells, while Li *et al.* [66] used SW1990 and MIA PaCa-2 cells. Both SW1990 and Panc1 cells are different in the expression of several proteins and growth characteristics [71]. For Panc1 and MIA PaCa-2 cells,

they have different phenotype and genotype characteristics [72].

Similarly, Li *et al.* [69] further identified that *HOTTIP* induced PC cell metastasis via EMT. This claim is supported by the results that both mRNA and protein levels of vimentin and Snai1 were downregulated, while the opposite was observed for E-cadherin after *HOTTIP* silencing in SW1990 and MIA PaCa-2 cells. In another study, it was found that *HOTTIP* regulated *HOXA9* gene expression in PC stem cells, leading to a rapid cancer progression. *HOTTIP* regulated *HOXA9* through binding to WDR5. In RNA immunoprecipitation using WDR antibody, HOTTIP precipitated with WDR5, and a *HOTTIP* fragment was bound to WDR5. When WDR5 was downregulated, the mRNA levels of *HOXA9* were also reduced [73]. Apart from these, Ye *et al.* [74] discovered that *HOTTIP* regulated metabotropic glutamate receptor 1 (mGluR1) pathway in PC. For example, low *HOTTIP* expression in PC cells resulted in decreased protein levels of mGluR1, phosphoinositide 3-kinase (PI3K), p-protein kinase B (Akt) and p-mTOR, which are known to play a crucial role in cell growth and survival. mGluRs are a family of G-protein-coupled receptors, which are mostly located in the brain because of their functions in synaptic transmission and neuronal excitability in the central nervous system [75]. mGluR1 can activate PI3K/Akt and mitogen-activated protein kinase pathways, at which these pathways play a significant role in regulating cell proliferation and restraining apoptosis [74, 76]. Thus, mGluR1 inhibition could reduce the activation of PI3K/Akt mechanistic target of rapamycin pathway in PC [74].

In addition to cancer progression, *HOTTIP* also regulates PC chemosensitivity. Li *et al.* [69] reported that *HOTTIP* downregulation increased the chemosensitivity of PC in response to the treatment of first-line chemotherapy, gemcitabine, as evidenced in both *in vitro* and *in vivo* models. A lower IC_{50} (1.956 ± 0.353 μM) for gemcitabine was observed in *HOTTIP*-silenced PC cells compared to the control group. Interestingly, the combination treatment of gemcitabine and *HOTTIP* silencing in nude mice promoted a marked reduction in the tumour volume as compared to individual treatment. Besides, Yin *et al.* [77] demonstrated that *HOTTIP* regulated miR-137 to exert its chemoresistance-inducing role in PC. *HOTTIP* expression levels were elevated, while miR-137 expression was reduced in chemoresistant-PC cells. It further found that *HOTTIP* downregulation in chemoresistant-PC cells significantly increased miR-137 expression levels. This finding indicated that *HOTTIP* regulated miR-137 expression in chemoresistant PC cells [77]. MiR-137 is reported to function as a tumour suppressor in PC, in which it inhibits tumour formation by reducing the size and weight of tumour *in vivo* [78]. Additionally, it has also been shown to increase the chemosensitivity among PC patients and halts the tumour invasion. These conditions are due to miR-137 overexpression in PC cells that restrain cancer cell invasion and increase the sensitivity towards 5-fluorouracil. However, the development of chemoresistance towards 5-fluorouracil is along with the markedly reduced expression of miR-137 [78].

3.5. Colorectal Cancer (CRC)

In 2018, CRC ranked third in the highest incidence rate and the second-highest in the mortality rate [1]. It is estimated that CRC cases and deaths will increase up to over 2.2 million and 1.1 million, respectively, by 2030 [79]. Besides, it has a limited early diagnosis with vague and non-specific symptoms presented in patients [80]. It has been shown that a delay in diagnosis may lead to late treatment, eventually resulting in cancer progression [81, 82]. The development of CRC is closely related to the genetic mutation of both tumour suppressors and oncogenes. The CRC epigenome is found to have hundreds to thousands of abnormally methylated genes, which control the CRC features and biological behaviours [83]. The most common genetic mutations are chromosomal changes and translocations that affect important pathways (*e.g.*, WNT, MAPK/PI3K, TGF-β, and TP53) and genes (*e.g.*, c-MYC, *KRAS*, *BRAF*, *PIK3CA*, *PTEN*, *SMAD2*, and *SMAD4*). Besides, alterations in ncRNAs, such as lncRNAs or miRNAs, also contribute to CRC development and progression [84].

For CRC, *HOTTIP* has been reported to be associated with proliferation, invasion, and prognosis. *HOTTIP* overexpression was detected in malignant CRC tissues compared to non-malignant tissues [85, 86]. CRC cell proliferation was significantly decreased after *HOTTIP* silencing by inducing apoptosis and inhibiting cancer cell migration. Furthermore, *HOTTIP* mediated CRC cell proliferation by enhancing the cell cycle, as evidenced by a high percentage of cells in the G_1/G_0 phase after *HOTTIP* downregulation compared to the control group [85].

Similarly, it was reported that *HOTTIP* regulated CRC metastasis through EMT induction. *HOTTIP* downregulation significantly decreased the protein levels of mesenchymal markers (*e.g.*, vimentin and N-cadherin) and increased E-cadherin. This result indicated that *HOTTIP* induces proliferative and mesenchymal phenotypes in CRC cells, enabling them to acquire invasive properties [85]. Besides, the regulatory roles of *HOTTIP* in CRC involve the participation of several proteins, such as p21 [12], SGK1 [18], and DKK1 [87]. For example, reduced mRNA levels of *HOTTIP* caused a cell cycle arrest in the G_1/G_0 phase, which may involve cell cycle inhibitor proteins, namely p53, p21, or p27 [12]. Given the important role played by p21 in the CRC cell cycle, Lian *et al.* [12] investigated whether *HOTTIP* could reduce p21 protein levels to enhance CRC cell proliferation using both *in vitro* and *in vivo* models. The results demonstrated that p21 protein was significantly elevated in *HOTTIP*-silenced DLD-1 and SW480 cells. Additionally, the inhibition of tumour growth was shown in the histopathological and immunohistochemical analyses, and upregulation of *p21* mRNA levels was

observed in *HOTTIP*-silenced xenograft mouse [12]. These findings suggested that *HOTTIP* regulates the expression of cell cycle inhibitory protein, particularly p21, to regulate CRC cancer cell proliferation.

The regulatory role of *HOTTIP* also requires serum and glucocorticoid regulated kinase 1 (SGK1) protein to affect CRC cell proliferation, invasion, and migration. This claim is supported by the evidence that when *HOTTIP* was silenced, SGK1 protein levels were markedly decreased in HCT-116 and SW620 cells. It has been reported that the target sequence of *HOTTIP* can suppress *SGK1* expression levels, as measured in luciferase reporter assay, indicating that *HOTTIP* can regulate SGK1 expression. The upregulation of *SGK1* gene expression caused an increase in the protein levels of glycogen synthase kinase 3 beta (GSK3β), β-catenin, c-myc, vimentin, and matrix metallopeptidase 7 (MMP-7), and a decrease in the protein levels of E-cadherin, Forkhead box O3 (FoxO3a), p27, and Bim in both cells [18]. The importance of GSK3β, β-catenin, c-myc, and MMP-7 is due to their involvement in the Wnt/β-catenin pathway to promote colon tumour proliferation, survival, and metastasis [88]. At the same time, both vimentin and E-cadherin are associated with cell invasion [89]. Lastly, FoxO3a, p27, and Bim have been demonstrated to involve in cell cycle arrest and apoptosis [90]. SGK1 protein is a member of the AGC kinase family, whereby it can phosphorylate various proteins to regulate cell growth, proliferation, apoptosis, and survival [91]. For example, SGK1 phosphorylates glycogen synthase kinase 3 (GSK3) to prevent GSK3 from degrading β-catenin that can eventually lead to the accumulation of oncogenic β-catenin [92]. Increased β-catenin subsequently promotes the transcription of Wnt-triggered genes to increase cancer cell proliferation [93]. Additionally, SGK1 can also phosphorylate and suppress FoxO3a protein. FoxO3a protein is a family of FOXO proteins, which function as a tumour suppressor to confer anti-proliferative and pro-apoptotic properties [94]. Phosphorylated FoxO3a by SGK1 at the regulatory sites (Thr32 and Ser315) consequently lead to the inhibition of cell cycle arrest and apoptosis induced by FoxO3a protein [95]. Thus, *HOTTIP* is claimed to regulate SGK1 to implicate in CRC cell proliferation.

In addition to cancer progression, *HOTTIP* can be involved in CRC metastasis through the inhibition of tumour suppressors, such as the *Dickkopf-1 (DKK1)* gene [87]. Rui *et al.* [87] investigated the possible mechanism of CRC metastasis by examining the

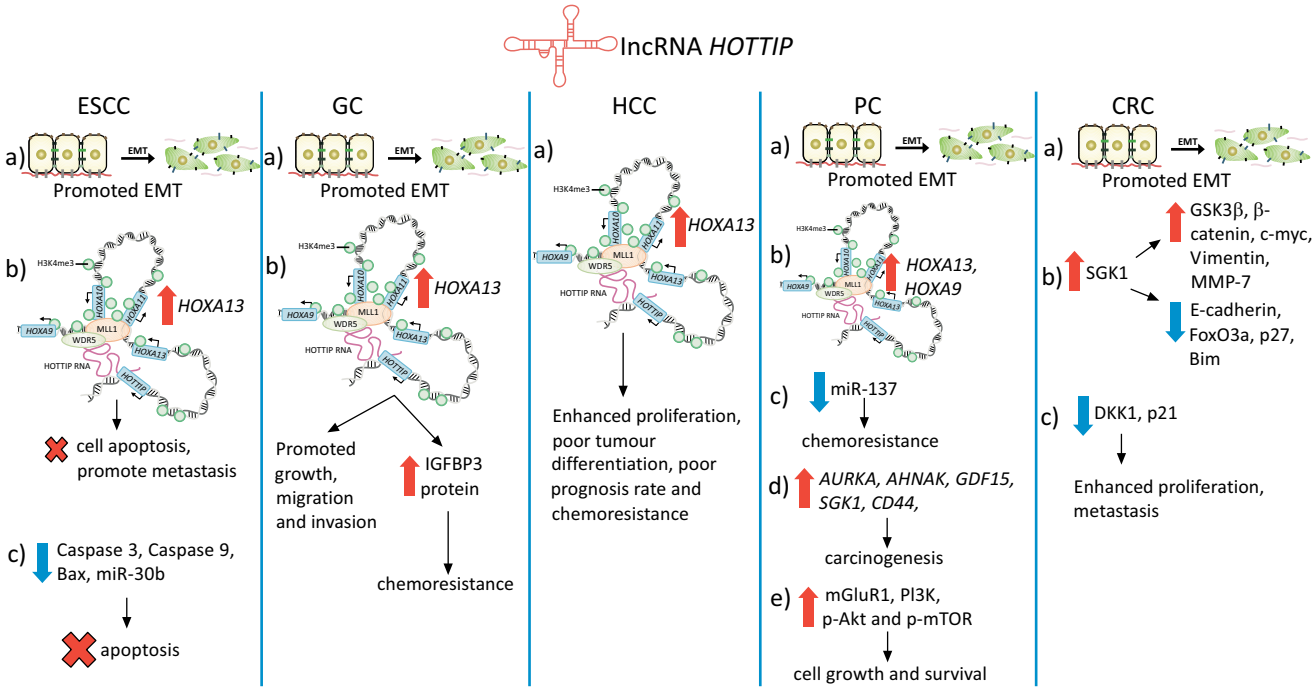

Fig. (3). Summary of regulatory mechanisms of *HOTTIP* in gastrointestinal cancers. *HOTTIP* regulates different GI cancers through different mechanisms. Some GI cancers share similar mechanisms, for instance, via *HOXA13* and EMT proteins (*e.g.*, Vimentin, N-cadherin, and E-cadherin). It decreases the protein levels of epithelial marker (E-cadherin) while increases that for mesenchymal markers (*e.g.*, N-cadherin and vimentin) to induce EMT for promoting metastasis in ESCC, GC, PC, and HCC. Besides, *HOTTIP* also increases *HOXA13* expression levels through WDR5/MLL binding complex in ESCC, GC, HCC, and PC. Increased HOXA13 expression upregulates IGFBP3 protein levels in GC. Apart from these, *HOTTIP* also inhibits cell apoptosis by reducing the protein levels of Caspase 3, Caspase 9, and Bax in ESCC cells. Other genes that are also regulated by *HOTTIP* include *AURKA, AHNAK, GDF15, SGK1, CD44, p21, DKK1, miR-30b,* and *miR-137*, which are associated with metastasis, invasion, migration, cell growth, cell survival, cell apoptosis and/or chemoresistance of GI cancers.

Table 1. Regulatory roles of *HOTTIP* in GI cancers.

Type of GI Cancer	Disease Model	Expression of LncRNA *HOTTIP*	Regulated Molecule (Gene/Protein)	Expression of Regulated Molecule	Biological Activity	Refs.
EC	*In vitro*	Upregulated	N-cadherin, Vimentin	Upregulated	Enhanced migration; promoted metastasis	[30]
			E-cadherin	Downregulated	Loss of cell adhesion	
	In vitro and *in vivo*		*HOXA13*	Upregulated	Inhibited cell apoptosis, promote metastasis	[32]
			Cleaved-caspase 3, cleaved caspase 9, Bax	Downregulated	Inhibited cell apoptosis	
			miR-30b	Downregulated	Inhibited cell apoptosis; promoted metastasis	
GC	*In vitro*	Upregulated	*HOXA13*	Upregulated	Promoted growth, migration, and invasion	[40]
	In vitro		E-cadherin	Downregulated	Loss of cell adhesion	[43]
			N-cadherin, Vimentin	Upregulated	Promoted metastasis; enhanced migration	
	In vitro and *in vivo*		IGFBP3	Upregulated	Promoted migration, invasion and chemoresistance	[41]
HCC	*In vitro*	Upregulated	*HOXA13*	Upregulated	Increased proliferation, poor tumour differentiation, poor prognosis rate, and chemoresistance	[59, 60]
PC	*In vitro* and *in vivo*	Upregulated	Annexin V	Downregulated	Inhibited cell apoptosis	[66]
			AURKA, AHNAK, GDF15, SGK1, CD44	Upregulated	Promoted carcinogenesis	
			HOXA13	Upregulated	Promoted cancer progression	[69]
			Vimentin, Snai1	Upregulated	Promoted metastasis	
			E-cadherin	Downregulated	Induced loss of cell adhesion	
			HOXA9	Upregulated	Induced rapid cancer progression	[73]
	In vitro		mGluR1, PI3K, p-Akt, p-mTOR	Upregulated	Promoted cell growth and survival	[74]
	In vitro		miR-137	Downregulated	Promoted chemoresistance	[77]
CRC	*In vitro* and *in vivo*	Upregulated	Vimentin, N-cadherin	Upregulated	Promoted invasion	[85]
			E-cadherin	Downregulated	Induced loss of cell adhesion	
			p21	Downregulated	Enhanced proliferation	[12]
	In vitro		*SGK1*	Upregulated	Induced cell proliferation, invasion, migration; inhibited the apoptosis	[18]
	In vitro and *in vivo*		*DKK1*	Downregulated	Enhanced metastasis	[87]

mRNA levels of metastasis-associated and EMT-associated genes (*e.g.*, *E-cadherin*, *N-cadherin*, *vimentin*, *DKK1*, *EMP1,* and *FN1*) in silenced-*HOTTIP* SW480 cells. Among these genes, *DKK1* expression significantly increased at both mRNA (2.5-fold) and protein (2.0-fold) levels. In contrast, *HOTTIP* expression did not influence the expression of EMT-associated genes in SW480 cells. Furthermore, the percentage of migratory cells after co-transfection with both *HOTTIP* and *DKK1* siRNA was significantly higher than *HOTTIP*-silenced CRC cells [87]. This result indicated that *DKK1* downregulation could delete the silencing effect of *HOTTIP* in CRC cells. DKK1 functions as an inhibitor of the Wnt signalling pathway, which has been shown to regulate the proliferation of multiple cancers, including CRC [96, 97], HCC [98], and GC [99, 100]. Therefore, an alteration in any molecular component that links to the Wnt signalling

pathway would trigger carcinogenesis. In CRC, DKK1 expression suppressed by *HOTTIP* can also cause the loss of its function to antagonise the Wnt signalling pathway, thus activating the pathway to induce cell proliferation [87, 101, 102].

CONCLUSION

In summary, the regulatory roles of *HOTTIP* in GI cancers show pronounced effects in carcinogenesis through various underlying mechanisms of actions involving numerous key molecules in exerting biological effects that are prominently in cancer progression and chemoresistance. *HOTTIP* aids in proliferation, invasion, migration, and chemoresistance through regulating various genes and proteins in GI cancers. Notably, the most common gene regulated by *HOTTIP* in GI cancers is *HOXA13*. However, in PC, there are contradictory findings between studies that used different cells, whereby one study found that the *HOXA13* gene did not regulate by *HOTTIP*, while the other study found the opposite. Thus, further investigations should be conducted to fully understand the regulatory roles of HOTTIP in cancer phenotypes. Another noteworthy view is that it has been shown that *HOXA13* downregulation can suppress *HOTTIP* expression; however, its regulatory roles in *HOTTIP* expression and mediated cancer progression and chemoresistance are still limited and deserve further confirmation. Other than that, *HOTTIP* commonly promotes metastasis by regulating EMT-related genes and proteins, such as vimentin, E-cadherin, N-cadherin, and Snai1 in most GI cancers. It also plays a crucial role in promoting GI cancer chemosensitivity, particularly GC, HCC, and PC, via the regulation of miRNAs, particularly miR-216a-5p and miR-137. However, compared to cancer progression, the regulatory roles of *HOTTIP* in GI cancer chemoresistance are still limited and require more investigations. Whether GI cancer phenotypes could affect the regulation of *HOTTIP* in inducing chemoresistance and whether *HOTTIP* is greatly implicated in GI chemoresistance, more future research is required to have a better understanding. Based on the studies reviewed above, *HOTTIP* represents a potential therapeutic target for GI cancer treatment, as well as a diagnostic biomarker for early detection. Due to high *HOTTIP* expression in GI cancers, *HOTTIP* downregulation greatly decreases cell proliferation in both *in vivo* and *in vitro* studies, making it possible to be a novel therapeutic target in clinical application and presenting an excellent opportunity for further advancement in GI cancer treatment. This claim is because biological treatments, particularly targeted therapy, including RNA-targeted drugs, are on the rise in precision oncology. In general, this review has deciphered that *HOTTIP* is potentiated to be developed as an RNA-targeted drug for combating GI cancers.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394-424. http://dx.doi.org/10.3322/caac.21492 PMID: 30207593

[2] Sung JJ, Ng EK, Lin JT, *et al.* Digestive cancer management in Asia: Position statements: A report on GI Oncology Summit in 2011. J Gastroenterol Hepatol 2012; 27(9): 1417-22. http://dx.doi.org/10.1111/j.1440-1746.2012.07194.x PMID: 22694174

[3] Zugazagoitia J, Guedes C, Ponce S, Ferrer I, Molina-Pinelo S, Paz-Ares L. Current challenges in cancer treatment. Clin Ther 2016; 38(7): 1551-66. http://dx.doi.org/10.1016/j.clinthera.2016.03.026 PMID: 27158009

[4] Wu YS, Lee ZY, Chuah LH, Mai CW, Ngai SC. Epigenetics in metastatic breast cancer: Its regulation and implications in diagnosis, prognosis and therapeutics. Curr Cancer Drug Targets 2019; 19(2): 82-100. http://dx.doi.org/10.2174/1568009618666180430130248 PMID: 29714144

[5] Ramakrishnan P, Loh WM, Gopinath SCB, *et al.* Selective phytochemicals targeting pancreatic stellate cells as new anti-fibrotic agents for chronic pancreatitis and pancreatic cancer. Acta Pharm Sin B 2020; 10(3): 399-413. http://dx.doi.org/10.1016/j.apsb.2019.11.008 PMID: 32140388

[6] Cheetham SW, Gruhl F, Mattick JS, Dinger ME. Long noncoding RNAs and the genetics of cancer. Br J Cancer 2013; 108(12): 2419-25. http://dx.doi.org/10.1038/bjc.2013.233 PMID: 23660942

[7] Sud A, Kinnersley B, Houlston RS. Genome-wide association studies of cancer: Current insights and future perspectives. Nat Rev Cancer 2017; 17(11): 692-704. http://dx.doi.org/10.1038/nrc.2017.82 PMID: 29026206

[8] Hombach S, Kretz M. Non-coding RNAs: classification, biology and functioning. Adv Exp Med Biol 2016; 937: 3-17. http://dx.doi.org/10.1007/978-3-319-42059-2_1 PMID: 27573892

[9] Slack FJ, Chinnaiyan AM. The role of non-coding RNAs in oncology. Cell 2019; 179(5): 1033-55. http://dx.doi.org/10.1016/j.cell.2019.10.017 PMID: 31730848

[10] Bhan A, Soleimani M, Mandal SS. Long noncoding RNA and cancer: a new paradigm. Cancer Res 2017; 77(15): 3965-81. http://dx.doi.org/10.1158/0008-5472.CAN-16-2634 PMID: 28701486

[11] Ramli S, Sim MS, Guad RM, *et al.* Long noncoding RNA *UCA1* in gastrointestinal cancers: molecular regulatory roles and patterns, mechanisms, and interactions. J Oncol 2021; 2021: 5519720. http://dx.doi.org/10.1155/2021/5519720 PMID: 33936199

[12] Lian Y, Ding J, Zhang Z, *et al.* The long noncoding RNA HOXA transcript at the distal tip promotes colorectal cancer growth partially *via* silencing of p21 expression. Tumour Biol 2016; 37(6): 7431-40.

http://dx.doi.org/10.1007/s13277-015-4617-2 PMID: 26678886

[13] Fan Y, Yan T, Chai Y, Jiang Y, Zhu X. Long noncoding RNA HOTTIP as an independent prognostic marker in cancer. Clin Chim Acta 2018; 482: 224-30. http://dx.doi.org/10.1016/j.cca.2017.07.031 PMID: 28778381

[14] Li W, Li N, Kang X, Shi K, Chen Q. Prognostic value of the long noncoding RNA *HOTTIP* in human cancers. Oncotarget 2017; 8(35): 59563-9. http://dx.doi.org/10.18632/oncotarget.19166 PMID: 28938659

[15] Chen Z, He A, Wang D, Liu Y, Huang W. Long noncoding RNA HOTTIP as a novel predictor of lymph node metastasis and survival in human cancer: A systematic review and meta-analysis. Oncotarget 2017; 8(8): 14126-32. http://dx.doi.org/10.18632/oncotarget.12981 PMID: 27806342

[16] Salehi S, Taheri MN, Azarpira N, Zare A, Behzad-Behbahani A. State of the art technologies to explore long non-coding RNAs in cancer. J Cell Mol Med 2017; 21(12): 3120-40. http://dx.doi.org/10.1111/jcmm.13238 PMID: 28631377

[17] Atkinson SR, Marguerat S, Bähler J. Exploring long non-coding RNAs through sequencing. Semin Cell Dev Biol 2012; 23(2): 200-5. http://dx.doi.org/10.1016/j.semcdb.2011.12.003 PMID: 22202731

[18] Liu T, Yu T, Hu H, He K. Knockdown of the long non-coding RNA HOTTIP inhibits colorectal cancer cell proliferation and migration and induces apoptosis by targeting SGK1. Biomed Pharmacother 2018; 98: 286-96. http://dx.doi.org/10.1016/j.biopha.2017.12.064 PMID: 29274585

[19] Botti G, De Chiara A, Di Bonito M, *et al.* Noncoding RNAs within the HOX gene network in tumor pathogenesis and progression. J Cell Physiol 2018; 234(1): 395-413. http://dx.doi.org/10.1002/jcp.27036 PMID: 30132877

[20] Li B, Huang Q, Wei GH. The role of HOX transcription factors in cancer predisposition and progression. Cancers (Basel) 2019; 11(4): E528. http://dx.doi.org/10.3390/cancers11040528 PMID: 31013831

[21] Burgess DJ. Non-coding RNA: HOTTIP goes the distance. Nat Rev Genet 2011; 12(5): 300. http://dx.doi.org/10.1038/nrg2992 PMID: 21483457

[22] Wang KC, Yang YW, Liu B, *et al.* A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. Nature 2011; 472(7341): 120-4. http://dx.doi.org/10.1038/nature09819 PMID: 21423168

[23] Lam MT, Li W, Rosenfeld MG, Glass CK. Enhancer RNAs and regulated transcriptional programs. Trends Biochem Sci 2014; 39(4): 170-82. http://dx.doi.org/10.1016/j.tibs.2014.02.007 PMID: 24674738

[24] Su M, Xiao Y, Ma J, *et al.* Long non-coding RNAs in esophageal cancer: Molecular mechanisms, functions, and potential applications. J Hematol Oncol 2018; 11(1): 118. http://dx.doi.org/10.1186/s13045-018-0663-8 PMID: 30223861

[25] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69(1): 7-34. http://dx.doi.org/10.3322/caac.21551 PMID: 30620402

[26] Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet 2013; 381(9864): 400-12. http://dx.doi.org/10.1016/S0140-6736(12)60643-6 PMID: 23374478

[27] Siti-Azrin AH, Wan-Nor-Asyikeen WA, Norsa'adah B. Review of the burden of esophageal cancer in Malaysia. Asian Pac J Cancer Prev 2016; 17(8): 3705-9. PMID: 27644604

[28] Kelsen DP, Winter KA, Gunderson LL, *et al.* Long-term results of RTOG trial 8911 (USA Intergroup 113): A random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol 2007; 25(24): 3719-25. http://dx.doi.org/10.1200/JCO.2006.10.4760 PMID: 17704421

[29] Lau MC, Ng KY, Wong TL, *et al.* FSTL1 promotes metastasis and chemoresistance in esophageal squamous cell carcinoma through NFκB-BMP signaling cross-talk. Cancer Res 2017; 77(21): 5886-99. http://dx.doi.org/10.1158/0008-5472.CAN-17-1411 PMID: 28883005

[30] Chen X, Han H, Li Y, Zhang Q, Mo K, Chen S. Upregulation of long noncoding RNA HOTTIP promotes metastasis of esophageal squamous cell carcinoma *via* induction of EMT. Oncotarget 2016; 7(51): 84480-5. http://dx.doi.org/10.18632/oncotarget.12995 PMID: 27806322

[31] Heerboth S, Housman G, Leary M, *et al.* EMT and tumor metastasis. Clin Transl Med 2015; 4: 6. http://dx.doi.org/10.1186/s40169-015-0048-3 PMID: 25852822

[32] Lin C, Wang Y, Wang Y, *et al.* Transcriptional and posttranscriptional regulation of HOXA13 by lncRNA HOTTIP facilitates tumorigenesis and metastasis in esophageal squamous carcinoma cells. Oncogene 2017; 36(38): 5392-406. http://dx.doi.org/10.1038/onc.2017.133 PMID: 28534516

[33] Xu J, Lv H, Zhang B, *et al.* miR-30b-5p acts as a tumor suppressor microRNA in esophageal squamous cell carcinoma. J Thorac Dis 2019; 11(7): 3015-29. http://dx.doi.org/10.21037/jtd.2019.07.50 PMID: 31463131

[34] Piazuelo MB, Correa P. Gastric cáncer: Overview. Colomb Med (Cali) 2013; 44(3): 192-201. PMID: 24892619

[35] Correa P. Gastric cancer: Overview. Gastroenterol Clin North Am 2013; 42(2): 211-7. http://dx.doi.org/10.1016/j.gtc.2013.01.002 PMID: 23639637

[36] Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. Lancet 2016; 388(10060): 2654-64. http://dx.doi.org/10.1016/S0140-6736(16)30354-3 PMID: 27156933

[37] Rawla P, Barsouk A. Epidemiology of gastric cancer: Global trends, risk factors and prevention. Prz Gastroenterol 2019; 14(1): 26-38. http://dx.doi.org/10.5114/pg.2018.80001 PMID: 30944675

[38] Zhao R, Zhang Y, Zhang X, *et al.* Exosomal long noncoding RNA HOTTIP as potential novel diagnostic and prognostic biomarker test for gastric cancer. Mol Cancer 2018; 17(1): 68. http://dx.doi.org/10.1186/s12943-018-0817-x PMID: 29486794

[39] Ye H, Liu K, Qian K. Overexpression of long noncoding RNA HOTTIP promotes tumor invasion and predicts poor prognosis in gastric cancer. OncoTargets Ther 2016; 9: 2081-8. PMID: 27103834

[40] Chang S, Liu J, Guo S, *et al.* HOTTIP and HOXA13 are oncogenes associated with gastric cancer progression. Oncol Rep 2016; 35(6): 3577-85. http://dx.doi.org/10.3892/or.2016.4743 PMID: 27108607

[41] Wang SS, Wuputra K, Liu CJ, *et al.* Oncogenic function of the homeobox A13-long noncoding RNA HOTTIP-insulin growth factor-binding protein 3 axis in human gastric cancer. Oncotarget 2016; 7(24): 36049-64. http://dx.doi.org/10.18632/oncotarget.9102 PMID: 27144338

[42] Tan H, Zhang S, Zhang J, *et al.* Long non-coding RNAs in gastric cancer: New emerging biological functions and therapeutic implications. Theranostics 2020; 10(19): 8880-902. http://dx.doi.org/10.7150/thno.47548 PMID: 32754285

[43] He YX, Song XH, Zhao ZY, Zhao H. HOXA13 upregulation in gastric cancer is associated with enhanced cancer cell invasion and epithelial-to-mesenchymal transition. Eur Rev Med Pharmacol Sci 2017; 21(2): 258-65. PMID: 28165563

[44] Kim ST, Jang HL, Lee J, *et al.* Clinical significance of IGFBP-3 methylation in patients with early stage gastric cancer. Transl Oncol 2015; 8(4): 288-94. http://dx.doi.org/10.1016/j.tranon.2015.06.001 PMID: 26310375

[45] Johnson MA, Firth SM. IGFBP-3: A cell fate pivot in cancer and disease. J Growth Hormone Res 2014; 24(5): 164-73.

[46] Baxter RC. Nuclear actions of insulin-like growth factor binding protein-3. Gene 2015; 569(1): 7-13. http://dx.doi.org/10.1016/j.gene.2015.06.028 PMID: 26074086

[47] Zielinska HA, Bahl A, Holly JM, Perks CM. Epithelial-to-mesenchymal transition in breast cancer: A role for insulin-like growth factor I and insulin-like growth factor-binding protein 3? Breast Cancer (Dove Med Press) 2015; 7: 9-19. PMID: 25632238

[48] Li Z, Lü M, Zhou Y, *et al.* Role of long non-coding RNAs in the chemoresistance of gastric cancer: a systematic review. OncoTargets Ther 2021; 14: 503-18. http://dx.doi.org/10.2147/OTT.S294378 PMID: 33500626

[49] Wang J, Lv B, Su Y, Wang X, Bu J, Yao L. Exosome-mediated transfer of lncRNA HOTTIP promotes cisplatin resistance in gastric cancer cells by regulating HMGA1/miR-218 axis. OncoTargets Ther 2019; 12: 11325-38. http://dx.doi.org/10.2147/OTT.S231846 PMID: 31908497

[50] Zhao R, Zhang X, Zhang Y, *et al.* HOTTIP predicts poor survival in gastric cancer patients and contributes to cisplatin resistance by sponging miR-216a-5p. Front Cell Dev Biol 2020; 8(348): 348. http://dx.doi.org/10.3389/fcell.2020.00348 PMID: 32457911

[51] Zhao Z, Malhotra A, Seng WY. Curcumin modulates hepatocellular carcinoma by reducing UNC119 expression. J Environ Pathol Toxicol Oncol 2019; 38(3): 195-203. http://dx.doi.org/10.1615/JEnvironPatholToxicolOncol.2019029549

[52] Motola-Kuba D, Zamora-Valdés D, Uribe M, Méndez-Sánchez N. Hepatocellular carcinoma. An overview. Ann Hepatol 2006; 5(1): 16-24. http://dx.doi.org/10.1016/S1665-2681(19)32034-4 PMID: 16531960

[53] Ozakyol A. Global epidemiology of hepatocellular carcinoma (HCC epidemiology). J Gastrointest Cancer 2017; 48(3): 238-40. http://dx.doi.org/10.1007/s12029-017-9959-0 PMID: 28626852

[54] Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: Consider the population. J Clin Gastroenterol 2013; 47(Suppl 1): S2-6.

[55] Balogh J, Victor D III, Asham EH, *et al.* Hepatocellular carcinoma: A review. J Hepatocell Carcinoma 2016; 3: 41-53. http://dx.doi.org/10.2147/JHC.S61146 PMID: 27785449

[56] Zhang Y, Huang JC, Cai KT, *et al.* Long non-coding RNA HOTTIP promotes hepatocellular carcinoma tumorigenesis and development: A comprehensive investigation based on bioinformatics, qRT-PCR and meta-analysis of 393 cases. Int J Oncol 2017; 51(6): 1705-21. http://dx.doi.org/10.3892/ijo.2017.4164 PMID: 29039502

[57] Tsang FH, Au SL, Wei L, *et al.* Long non-coding RNA HOTTIP is frequently up-regulated in hepatocellular carcinoma and is targeted by tumour suppressive miR-125b. Liver Int 2015; 35(5): 1597-606. http://dx.doi.org/10.1111/liv.12746 PMID: 25424744

[58] Wu L, Yang Z, Zhang J, Xie H, Zhou L, Zheng S. Long noncoding RNA HOTTIP expression predicts tumor recurrence in hepatocellular carcinoma patients following liver transplantation. Hepatobiliary Surg Nutr 2018; 7(6): 429-39. http://dx.doi.org/10.21037/hbsn.2018.10.07 PMID: 30652087

[59] Quagliata L, Matter MS, Piscuoglio S, *et al.* Long noncoding RNA HOTTIP/HOXA13 expression is associated with disease progression and predicts outcome in hepatocellular carcinoma patients. Hepatology 2014; 59(3): 911-23. http://dx.doi.org/10.1002/hep.26740 PMID: 24114970

[60] Quagliata L, Quintavalle C, Lanzafame M, *et al.* High expression of HOXA13 correlates with poorly differentiated hepatocellular carcinomas and modulates sorafenib response in *in vitro* models. Lab Invest 2018; 98(1): 95-105. http://dx.doi.org/10.1038/labinvest.2017.107 PMID: 29035381

[61] Wu YS, Looi CY, Subramaniam KS, Masamune A, Chung I. Soluble factors from stellate cells induce pancreatic cancer cell proliferation *via* Nrf2-activated metabolic reprogramming and ROS detoxification. Oncotarget 2016; 7(24): 36719-32. http://dx.doi.org/10.18632/oncotarget.9165 PMID: 27167341

[62] Wu YS, Chung I, Wong WF, Masamune A, Sim MS, Looi CY. Paracrine IL-6 signaling mediates the effects of pancreatic stellate cells on epithelial-mesenchymal transition *via* Stat3/Nrf2 pathway in pancreatic cancer cells. Biochim Biophys Acta, Gen Subj 2017; 1861(2): 296-306. http://dx.doi.org/10.1016/j.bbagen.2016.10.006 PMID: 27750041

[63] Oberstein PE, Olive KP. Pancreatic cancer: why is it so hard to treat? Therap Adv Gastroenterol 2013; 6(4): 321-37. http://dx.doi.org/10.1177/1756283X13478680 PMID: 23814611

[64] Kleeff J, Korc M, Apte M, *et al.* Pancreatic cancer. Nat Rev Dis Primers 2016; 2(1): 16022. http://dx.doi.org/10.1038/nrdp.2016.22 PMID: 27158978

[65] Han T, Hu H, Zhuo M, *et al.* Long non-coding RNA: an emerging paradigm of pancreatic cancer. Curr Mol Med 2016; 16(8): 702-9. http://dx.doi.org/10.2174/1566524016666160927095812 PMID: 27686798

[66] Cheng Y, Jutooru I, Chadalapaka G, Corton JC, Safe S. The long non-coding RNA HOTTIP enhances pancreatic cancer cell proliferation, survival and migration. Oncotarget 2015; 6(13): 10840-52. http://dx.doi.org/10.18632/oncotarget.3450 PMID: 25912306

[67] Katsha A, Belkhiri A, Goff L, El-Rifai W. Aurora kinase A in gastrointestinal cancers: Time to target. Mol Cancer 2015; 14(1): 106. http://dx.doi.org/10.1186/s12943-015-0375-4 PMID: 25987188

[68] Xie Y, Zhu S, Zhong M, *et al.* Inhibition of aurora kinase A induces necroptosis in pancreatic carcinoma. Gastroenterology 2017; 153(5): 1429-1443.e5. http://dx.doi.org/10.1053/j.gastro.2017.07.036 PMID: 28764929

[69] Li Z, Zhao X, Zhou Y, *et al.* The long non-coding RNA HOTTIP promotes progression and gemcitabine resistance by regulating HOXA13 in pancreatic cancer. J Transl Med 2015; 13: 84. http://dx.doi.org/10.1186/s12967-015-0442-z PMID: 25889214

[70] Prion S, Haerling KA. Making sense of methods and measurement: spearman-Rho ranked-order correlation coefficient. Clin Simul Nurs 2014; 10(10): 535-6. http://dx.doi.org/10.1016/j.ecns.2014.07.005

[71] Zhang H, Lv L, Liu H, *et al.* Profiling the potential biomarkers for cell differentiation of pancreatic cancer using iTRAQ and 2-D LC-MS/MS. Proteomics Clin Appl 2009; 3(7): 862-71. http://dx.doi.org/10.1002/prca.200800029 PMID: 21136992

[72] Gradiz R, Silva HC, Carvalho L, Botelho MF, Mota-Pinto A. MIA PaCa-2 and PANC-1 - pancreas ductal adenocarcinoma cell lines with neuroendocrine differentiation and somatostatin receptors. Sci Rep 2016; 6: 21648. http://dx.doi.org/10.1038/srep21648 PMID: 26884312

[73] Fu Z, Chen C, Zhou Q, *et al.* LncRNA HOTTIP modulates cancer stem cell properties in human pancreatic cancer by regulating HOXA9. Cancer Lett 2017; 410: 68-81. http://dx.doi.org/10.1016/j.canlet.2017.09.019 PMID: 28947139

[74] Ye Y, Li Y, Wei Y, *et al.* Anticancer effect of HOTTIP regulates human pancreatic cancer *via* the metabotropic glutamate receptor 1 pathway. Oncol Lett 2018; 16(2): 1937-42. http://dx.doi.org/10.3892/ol.2018.8870 PMID: 30008887

[75] Niswender CM, Conn PJ. Metabotropic glutamate receptors: Physiology, pharmacology, and disease. Annu Rev Pharmacol Toxicol 2010; 50: 295-322. http://dx.doi.org/10.1146/annurev.pharmtox.011008.145533 PMID: 20055706

[76] Prickett TD, Samuels Y. Molecular pathways: Dysregulated glutamatergic signaling pathways in cancer. Clin Cancer Res 2012; 18(16): 4240-6. http://dx.doi.org/10.1158/1078-0432.CCR-11-1217 PMID: 22648273

[77] Yin F, Zhang Q, Dong Z, Hu J, Ma Z. LncRNA HOTTIP participates in cisplatin resistance of tumor cells by regulating miR-137 expression in pancreatic cancer. OncoTargets Ther 2020; 13: 2689-99. http://dx.doi.org/10.2147/OTT.S234924 PMID: 32280243

[78] Xiao J, Peng F, Yu C, *et al.* microRNA-137 modulates pancreatic cancer cells tumor growth, invasion and sensitivity to chemotherapy. Int J Clin Exp Pathol 2014; 7(11): 7442-50. PMID: 25550779

[79] Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017; 66(4): 683-91. http://dx.doi.org/10.1136/gutjnl-2015-310912 PMID: 26818619

[80] Vega P, Valentín F, Cubiella J. Colorectal cancer diagnosis: Pitfalls and opportunities. World J Gastrointest Oncol 2015; 7(12): 422-33. http://dx.doi.org/10.4251/wjgo.v7.i12.422 PMID: 26690833

[81] Granados-Romero J, Valderrama-Treviño A, Contreras Flores E, Barrera-Mera B, Herrera M, Uriarte-Ruíz K. Colorectal cancer: A review. Int J Res Med Sci 2017; 5: 4667. http://dx.doi.org/10.18203/2320-6012.ijrms20174914

[82] Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet 2019; 394(10207): 1467-80. http://dx.doi.org/10.1016/S0140-6736(19)32319-0 PMID: 31631858

[83] Lao VV, Grady WM. Epigenetics and colorectal cancer. Nat Rev Gastroenterol Hepatol 2011; 8(12): 686-700. http://dx.doi.org/10.1038/nrgastro.2011.173 PMID: 22009203

[84] Mármol I, Sánchez-de-Diego C, Pradilla Dieste A, Cerrada E, Rodriguez Yoldi MJ. Colorectal carcinoma: a general overview and future perspectives in colorectal cancer. Int J Mol Sci 2017; 18(1): E197. http://dx.doi.org/10.3390/ijms18010197 PMID: 28106826

[85] Liu T, Wang H, Yu H, *et al.* The long non-coding RNA HOTTIP is highly expressed in colorectal cancer and enhances cell proliferation and invasion. Mol Ther Nucleic Acids 2020; 19: 612-8. http://dx.doi.org/10.1016/j.omtn.2019.12.008 PMID: 31945724

[86] Ren YK, Xiao Y, Wan XB, *et al.* Association of long non-coding RNA HOTTIP with progression and prognosis in colorectal cancer. Int J Clin Exp Pathol 2015; 8(9): 11458-63. PMID: 26617875

[87] Rui Y, Hu M, Wang P, *et al.* LncRNA HOTTIP mediated DKK1 downregulation confers metastasis and invasion in colorectal cancer cells. Histol Histopathol 2019; 34(6): 619-30. PMID: 30229808

[88] Reabroi S, Saeeng R, Boonmuen N, *et al.* The anti-cancer activity of an andrographolide analogue functions through a GSK-3β-independent Wnt/β-catenin signaling pathway in colorectal cancer cells. Sci Rep 2018; 8(1): 7924. http://dx.doi.org/10.1038/s41598-018-26278-8 PMID: 29784906

[89] Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol 2014; 15(3): 178-96. http://dx.doi.org/10.1038/nrm3758 PMID: 24556840

[90] Luo H, Yang Y, Duan J, Wu P, Jiang Q, Xu C. PTEN-regulated AKT/FoxO3a/Bim signaling contributes to reactive oxygen species-mediated apoptosis in selenite-treated colorectal cancer cells. Cell Death Dis 2013; 4(2): e481.

[91] Liang X, Lan C, Jiao G, Fu W, Long X, An Y. Therapeutic inhibition of SGK1 suppresses colorectal cancer. Exp Mol Med 2017; 49(11): e399. http://dx.doi.org/10.1038/emm.2017.184

[92] Lang F, Perrotti N, Stournaras C. Colorectal carcinoma cells--regulation of survival and growth by SGK1. Int J Biochem Cell Biol 2010; 42(10): 1571-5. http://dx.doi.org/10.1016/j.biocel.2010.05.016 PMID: 20541034

[93] Pai SG, Carneiro BA, Mota JM, *et al.* Wnt/beta-catenin pathway: Modulating anticancer immune response. J Hematol Oncol 2017; 10(1): 101. http://dx.doi.org/10.1186/s13045-017-0471-6 PMID: 28476164

[94] Laissue P. The forkhead-box family of transcription factors: Key molecular players in colorectal cancer pathogenesis. Mol Cancer 2019; 18(1): 5. http://dx.doi.org/10.1186/s12943-019-0938-x PMID: 30621735

[95] Zhu R, Yang G, Cao Z, *et al.* The prospect of serum and glucocorticoid-inducible kinase 1 (SGK1) in cancer therapy: A rising star. Ther Adv Med Oncol 2020; 12: 1758835920940946. http://dx.doi.org/10.1177/1758835920940946 PMID: 32728395

[96] Schatoff EM, Leach BI, Dow LE. Wnt Signaling and Colorectal Cancer. Curr Colorectal Cancer Rep 2017; 13(2): 101-10. http://dx.doi.org/10.1007/s11888-017-0354-9 PMID: 28413363

[97] Polakis P. Wnt signaling in cancer. Cold Spring Harb Perspect Biol 2012; 4(5): a008052. http://dx.doi.org/10.1101/cshperspect.a008052 PMID: 22438566

[98] Wang W, Smits R, Hao H, He C. Wnt/β-catenin signaling in liver cancers. Cancers (Basel) 2019; 11(7): E926. http://dx.doi.org/10.3390/cancers11070926 PMID: 31269694

[99] Chiurillo MA. Role of the Wnt/β-catenin pathway in gastric cancer: An in-depth literature review. World J Exp Med 2015; 5(2): 84-102. http://dx.doi.org/10.5493/wjem.v5.i2.84 PMID: 25992323

[100] Oliveira LA, Oshima CTF, Soffner PA, *et al.* The canonical wnt pathway in gastric carcinoma. Arq Bras Cir Dig 2019; 32(1): e1414. http://dx.doi.org/10.1590/0102-672020180001e1414 PMID: 30624523

[101] Aguilera Ó, González-Sancho JM, Zazo S, *et al.* Nuclear DICKKOPF-1 as a biomarker of chemoresistance and poor clinical outcome in colorectal cancer. Oncotarget 2015; 6(8): 5903-17. http://dx.doi.org/10.18632/oncotarget.3464 PMID: 25788273

[102] Novellasdemunt L, Antas P, Li VSW. Targeting Wnt signaling in colorectal cancer. A Review in the Theme: Cell Signaling: Proteins, Pathways and Mechanisms. Am J Physiol Cell Physiol 2015; 309(8): C511-21. http://dx.doi.org/10.1152/ajpcell.00117.2015 PMID: 26289750