# FGF signaling network in the gastrointestinal tract (Review)

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**Abstract.** Fibroblast growth factor (FGF) signals are transduced through FGF receptors (FGFRs) and FRS2/FRS3-SHP2 (PTPN11)-GRB2 docking protein complex to SOS-RAS-RAF-MAPKK-MAPK signaling cascade and GAB1/GAB2-PI3K-PDK-AKT/aPKC signaling cascade. The RAS~MAPK signaling cascade is implicated in cell growth and differentiation, the PI3K~AKT signaling cascade in cell survival and cell fate determination, and the PI3K~aPKC signaling cascade in cell polarity control. FGF18, FGF20 and SPRY4 are potent targets of the canonical WNT signaling pathway in the gastrointestinal tract. SPRY4 is the FGF signaling inhibitor functioning as negative feedback apparatus for the WNT/FGF-dependent epithelial proliferation. Recombinant FGF7 and FGF20 proteins are applicable for treatment of chemotherapy/radiation-induced mucosal injury, while recombinant FGF2 protein and FGF4 expression vector are applicable for therapeutic angiogenesis. *Helicobacter pylori*, a causative pathogen for peptic ulcer diseases, chronic atrophic gastritis and gastric cancer, injects bacterial proteins into gastric epithelial cells by using Type IV secretion system, which leads to FGF signaling activation through FGF2 upregulation as well as CagA-dependent SHP2 activation. *FGFR2* gene is preferentially amplified and overexpressed in diffuse-type gastric cancer. PD173074 is a small-molecule inhibitor for FGFR, while RO4396686 and SU6668 are small-molecule inhibitors for FGFR and other tyrosine kinases. Cocktail therapy using multiple protein kinase inhibitors could enhance the therapeutic effects for gastrointestinal cancer through the reduction of recurrence associated with somatic mutations of drug-target genes. Single nucleotide polymorphism (SNP) and copy number polymorphism (CNP) of genes encoding FGF signaling molecules will be identified as novel risk factors of gastrointestinal cancer. Personalized prevention and personalized medicine based on the combination of genetic screening and novel therapeutic agents could dramatically improve the prognosis of cancer patients.

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**Contents**



## 1. Introduction

Fibroblast growth factor (FGF) family proteins play key roles in growth and survival of stem cells during embryogenesis, tissues regeneration, and carcinogenesis (1-4). FGF signals are transduced through FGF receptors (FGFRs) and FRS2/FRS3-SHP2-GRB2 docking protein complex to SOS-RAS-RAF-MAPKK-MAPK signaling cascade and GAB1/GAB2-PI3K-PDK-AKT/aPKC signaling cascade (Fig. 1). The RAS~MAPK signaling cascade is implicated in cell growth and differentiation, the PI3K~AKT signaling cascade in cell survival and cell fate determination, and the PI3K~aPKC signaling cascade in cell polarity control. Here, recent progress, especially in the fields of evolutionary developmental biology, signaling network and clinical applications on FGF research will be reviewed.

## 2. FGF family

FGF1 (aFGF), FGF2 (bFGF), FGF3 (INT2), FGF4, FGF5, FGF6, FGF7 (KGF), FGF8 (AIGF), FGF9, FGF10, FGF11, FGF12, FGF13, FGF14, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22 and FGF23 are human FGF members, while Fgf1, Fgf2, Fgf3, Fgf4, Fgf5, Fgf6, Fgf7, Fgf8, Fgf9, Fgf10, Fgf11, Fgf12, Fgf13, Fgf14, Fgf15, Fgf16, Fgf17, Fgf18, Fgf20, Fgf21, Fgf22 and Fgf23 are mouse Fgf family members (1). In 2003, we demonstrated mouse *Fgf15* as the ortholog of human *FGF19* based on the inter-species comparative genomics analyses on the *CCND1-ORAOV1-FGF19-FGF4* locus (5). Therefore, 22 FGF family orthologs are conserved between human and mouse genomes.

The zebrafish fgf family consists of fgf1, fgf2, fgf3, fgf4, fgf5, fgf6a, fgf6b, fgf7, fgf8, fgf9, fgf10, fgf11, fgf12, fgf13, fgf14, fgf16, fgf17a, fgf17b, fgf18a, fgf18b, fgf19, fgf20a, fgf20b, fgf21, fgf22, fgf23, fgf24 and fgf25. Zebrafish

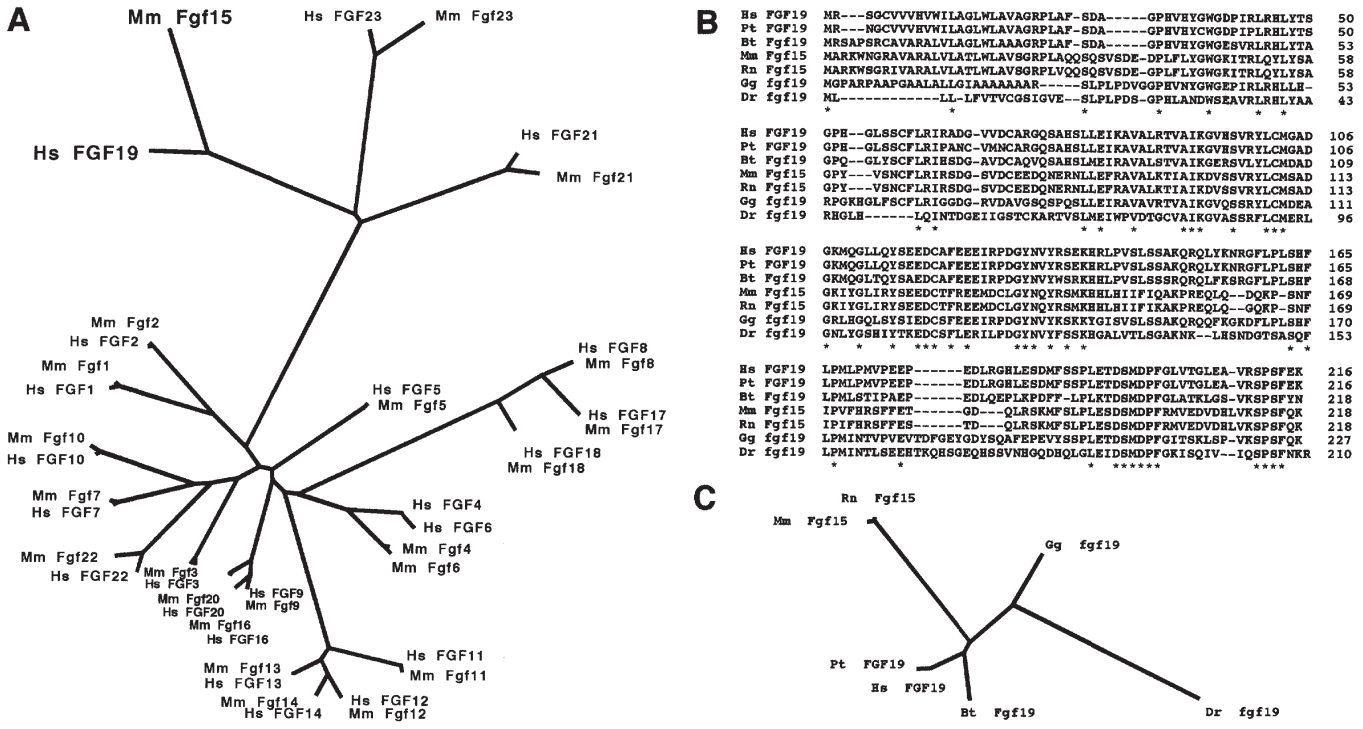


Figure 1. Comparative proteomics on the FGF family. Hs, human; Pt, chimpanzee; Bt, cow; Mm, mouse; Rn, rat; Gg, chicken; Dr, zebrafish. (A), Phylogenetic analysis on human and mouse FGF family members. Human FGF19 and mouse Fgf15 are orthologs; however, FGF19 and Fgf15 are significantly divergent. (B), Alignment of vertebrate FGF19 orthologs. (C), Phylogenetic analysis on vertebrate FGF19 orthologs.

fgf24 and fgf25 are homologs of human FGF8 and FGF10, respectively (6,7). At least 28 *fgf* family genes exist within the zebrafish genome. Zebrafish *fgf24* and *fgf25* genes are fish specific *fgf* family members generated due to fish-specific genome duplication.

Phylogenetic analyses on human and mouse FGF family members showed that human FGF19 (NP_005108.1) and mouse Fgf15 (NP_032029.1) were significantly divergent (Fig. 1A). We previously identified and characterized rat Fgf15 and zebrafish fgf19. In this study, we identified chimpanzee *FGF19* and cow *Fgf19* genes within NW_113926.1 and NW_930789.1 genome sequences, respectively. Complete CDS of chimpanzee FGF19 and cow Fgf19 were determined by assembling exonic regions to determine amino-acid sequence of chimpanzee FGF19 and cow Fgf19 (Fig. 1B). Phylogenetic analyses on vertebrate FGF19 orthologs next revealed that cow Fgf19 was more homologous to primate FGF19 and chicken fgf19 than to rodent Fgf15 (Fig. 1C). These facts indicate that significant nucleotide substitutions within the Fgf19 locus occurred specifically in the rodent lineages to induce functional divergence of rodent Fgf19 orthologs (Fgf15) from other mammalian FGF19 orthologs.

### 3. Regulation of FGF signaling by WNT

FGF signaling pathway networks with WNT signaling pathway during a variety of cellular processes, such as early embryogenesis, body-axis formation, limb-bud formation, neurogenesis, hematogenesis, hepatogenesis, gastrointestinal morphogenesis, MMTV-induced mammary carcinogenesis, and human colorectal carcinogenesis (1,2,8,9).

We have comprehensively cloned (or identified) and characterized WNT signaling molecules within the human genome, because WNT signaling molecules implicated in carcinogenesis and embryogenesis are pharmacogenomics targets in the field of oncology and regenerative medicine (http://www.esi-topics.com/fmf/2005/september05-Masaru Katoh.html). WNT signals are transcuced through Frizzled (FZD) seven-transmembrane-type receptors, LRP5, LRP6, ROR1, ROR2, and RKY. WNT1, WNT2, WNT2B, WNT3, WNT3A, WNT8A, WNT8B, WNT10A, and WNT10B are canonical WNTs to activate the ß-catenin pathway. Canonical WNT signals are transduced to the transcriptional complex consisting of TCF/LEF, ß-catenin, BCL9/BCL9L and PYGO1/PYGO2 to activate transcription of target genes (10-21). We have reported that *FGF16, FGF18* and *FGF20* genes are evolutionarily conserved targets of the canonical WNT signaling pathway based on the comparative genomics on the 5'-promoter regions of the *FGF* family genes (22-24).

Three TCF/LEF-binding sites were identified at about 1400 bp, 1250 bp and 200 bp upstream of the transcriptional start site of the human *FGF7* gene (Fig. 2A and B). Chimpanzee *FGF7* promoter, cow *Fgf7* promoter, mouse *Fgf7* promoter and rat *Fgf7* promoter were then identified within NW_116403.1, AC161632.2, AL845292.4 and AC130100.3 genome sequences, respectively, by using the BLAST programs as described previously (25-30). Phylogenetic analysis revealed that cow *Fgf7* promoter was more related to primate *FGF7* promoters than to rodent *Fgf7* promoters (Fig. 2C). Three TCF/LEF-binding sites within human *FGF7* promoter were conserved in the chimpanzee *FGF7* promoter (Fig. 2D). The most proximal TCF/LEF-binding site within human *FGF7*

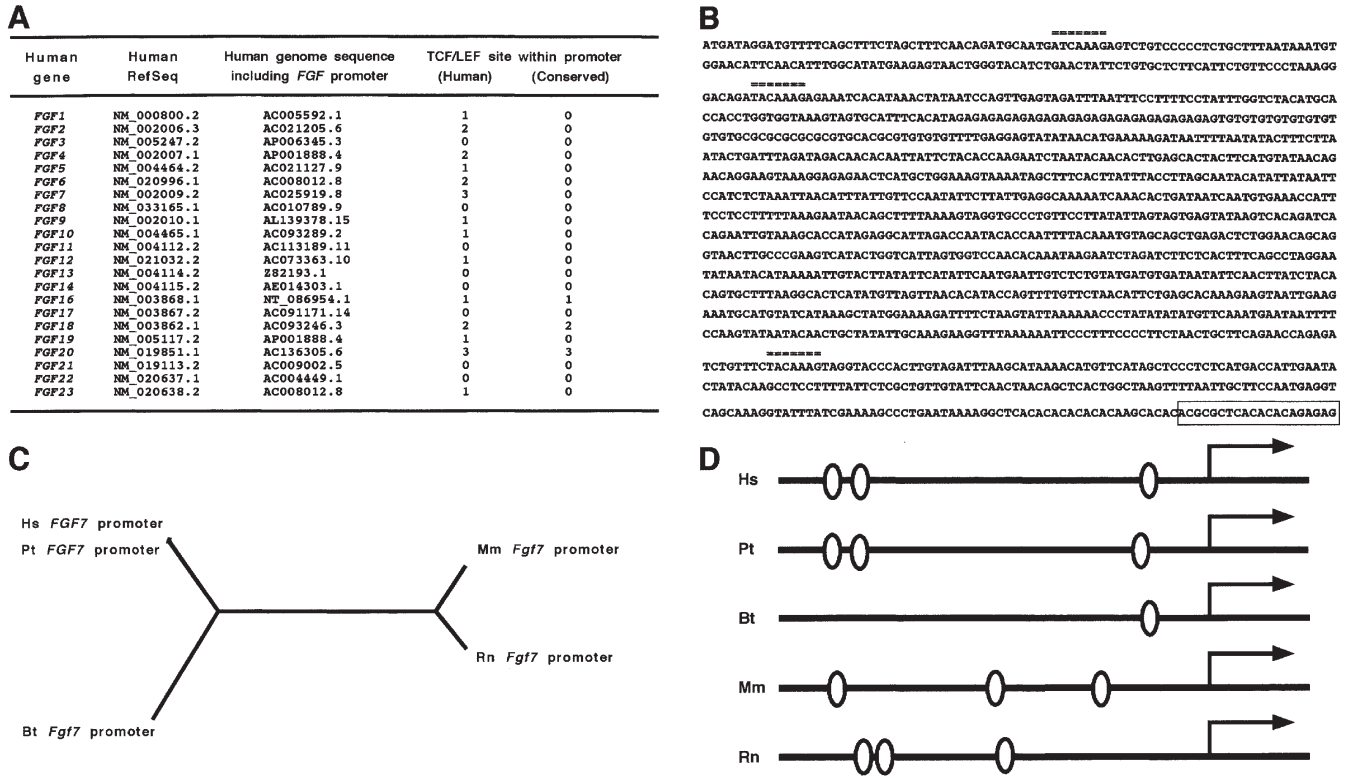


Figure 2. Comparative genomics on the *FGF* family. (A), Human *FGF* gene family. Gene symbol, RefSeq accession number, genome clone accession number, and TCF/LEF-binding sites within 5'-flanking promoter of *FGF* family genes are listed. (B), Nucleotide sequence of human *FGF7* promoter. Region corresponding to exon 1 of human *FGF7* gene is boxed. Three TCF/LEF-binding sites are shown by double over-lines. (C), Phylogenetic analysis on vertebrate *FGF7* promoters. Cow *Fgf7* promoter is more related to primate *FGF7* promoters than to rodent *Fgf7* promoters. (D), Schematic representation of vertebrate *FGF7* promoters. Three TCF/LEF-binding sites within human *FGF7* promoter are conserved in the chimpanzee FGF7 promoter, and the most proximal one in cow *Fgf7* promoter, but not in rodent *Fgf7* promoters.

promoter was conserved in the cow *Fgf7* promoter, but not in rodent *Fgf7* promoters (Fig. 2D). Because three TCF/LEF-binding sites within human *FGF7* promoter were not conserved among mammals, it remained unclear whether human *FGF7* is the target of the canonical WNT signaling pathway or not.

Expression analyses on *FGF16, FGF18* and *FGF20* genes revealed that *FGF18* and *FGF20* genes are expressed in epithelial cells or cancer cells derived from gastrointestinal tract. Therefore, FGF18 and FGF20 are targets of the canonical WNT signaling pathway in the gastrointestinal tract.

## 4. FGF signaling network in the stomach

FGF2 and FGF7 are major FGFs implicated in embryogenesis and tissue regeneration within the stomach (31-33). FGF2 is expressed in submucosal tissues to transduce signals through FGFR1 expressed mucosal tissues. FGF7 is expressed in mesynchymal fibroblast to transduce signals through FGFR2 expressed in epithelial cells.

*Helicobacter pylori* is a causative pathogen for peptic ulcer diseases, chronic atrophic gastritis and gastric cancer (34-37, and refs. therein). FGF2 is one of the pro-angiogenic factors inducing healing of gastric mucosal damage associated with *Helicobacter pylori* infection. CagA protein and peptideglycan of *Helicobacter pylori* are injected into human gastric epithelial cells by using the Type IV secretion system. CagA protein is phosphorylated by SRC family protein kinases to activate SHP2 phosphatase. Because SHP2 is a component of docking protein complex for FGF signaling, SHP2 activation leads to FGF signaling activation (Fig. 3A).

Gastric cancer arises from normal tissues based on genetic predisposition for *CDH1* gene, chronic *Helicoabcter pylori* infection, and salt over-uptake (34,38-40). Cancer cells are characterized by dysregulated proliferation, dysregulated adhesion, and also by resistance to apoptosis, senescence, and anti-cancer drugs. Cancer cells acquire malignant phenotypes mentioned above during multi-stage carcinogenesis due to the accumulation of multiple epigenetic changes and genetic alterations of cancer-associated genes. FGF7 secreted from mesenchymal fibroblasts stimulate the proliferation of gastric cancer, especially diffuse-type gastric cancer derived from fundic gland mucosa (41). *FGFR2* gene is preferentially amplified in diffuse-type gastric cancer to overexpress FGFR2 splicing variant encoding a high-affinity FGF7 receptor (42). These facts clearly indicate that the FGF7~FGFR2 signaling cascade plays a critical role for the development and progression of diffuse-type gastric cancer.

## 5. FGF signaling network in the colon

FGF2 and FGF20 are major FGFs implicated in embryogenesis and tissue regeneration within the colon (31,43,44).

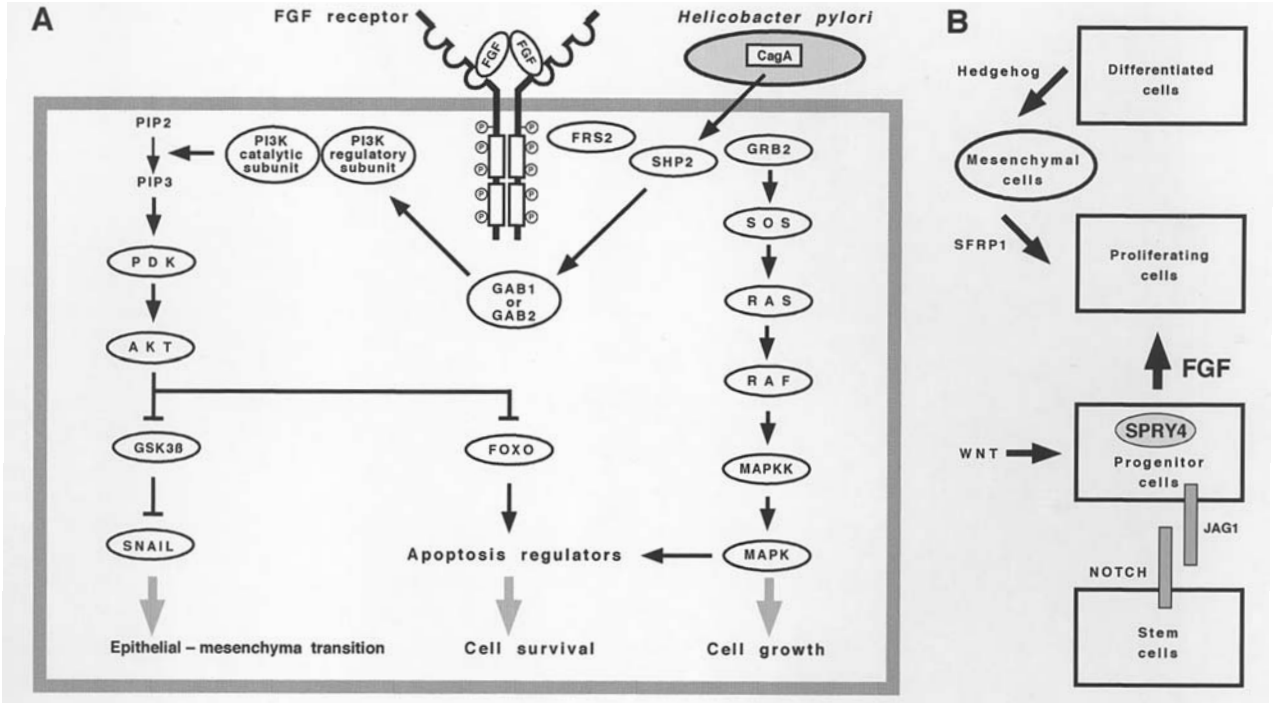


Figure 3. FGF signaling network in the gastrointestinal tract. (A), FGF signaling network during gastrocarcinogenesis. FGF7 secreted from mesenchymal fibroblasts activate FGF signaling through FGFR2 and FRS2-SHP2-GRB2 docking complex in gastric epithelial cells as well as in diffuse-type gastric cancer. *Helicobacter pylori* injects CagA protein and peptideglycan into human gastric epithelial cells by using Type IV secretion system. CagA phosphorylation by SRC family kinases leads to FGF signaling activation through SHP2 activation in precancerous lesion and early gastric cancer. *FGFR2* overexpression associated with *FGFR2* gene amplification leads to FGF signaling activation in advanced gastric cancer, especially in diffuse-type gastric cancer derived from fundic gland mucosa. (B), FGF signaling network in colorectal mucosa. Canonical WNT signaling activation in progenitor cells leads to transcriptional activation of *SPRY4* and *FGFs*, which results in FGF signaling down-regulation in progenitor cells themselves as well as FGF signaling activation in proliferating cells. Canonical WNT signaling pathway is activated in progenitor cells, and FGF signaling pathway is activated in proliferating cells.

FGF2 is expressed in submucosal tissues to induce angiogenesis, while FGF20 is expressed in epithelial progenitor cells to induce epithelial proliferation.

We reported molecular cloning and characterization of human *FGF20* in August, 2000 (43). Ohmachi *et al* claimed the same gene as a novel *FGF* family member in October, 2000 (45), and Jeffers *et al* in April, 2001 (46). *FGF20* mRNA is almost undetectable in normal human tissues by using Northern blot analyses, but is detected in SW480 colorectal cancer cells. *FGF20* is upregulated in human colorectal cancer with the canonical WNT signaling activation.

SPROUTY (SPRY) and SPRED family members function as inhibitors for FGF signaling cascades. Among *SPRY1, SPRY2, SPRY3, SPRY4, SPRED1, SPRED2*, and *SPRED3* genes, *SPRY4* gene is the evolutionarily conserved target of the canonical WNT signaling pathway (47). WNT signaling activation in progenitor cells leads to growth regulation of progenitor cells themselves through SPRY4 induction, and also to growth stimulation of proliferating cells through FGF secretion (Fig. 3B). SPRY4 is the FGF signaling inhibitor functioning as negative feedback apparatus for the WNT/FGF-dependent epithelial proliferation.

## 6. Clinical application of FGF

Recombinant human FGF7 (Palifermin) is clinically applied to decrease the incidence and duration of myelotoxic therapy-induced oral mucositis in cancer patient (48).

Recombinant human FGF20 (CG53135) is clinically applicable for mucosal restitution in patients with inflammatory bowel disease as well as for chemotherapy/radiation-induced oral mucositis in cancer patient (44,49); however, the benefits of recombinant human FGF20 remain to be demonstrated by clinical trials.

Recombinant human FGF2 is clinically applicable for wound healing in patients with peptic ulcer or burn as well as for therapeutic angiogenesis in patients with cardiovascular diseases (50); however, the benefit of recombinant human FGF2 is not significant in the general population.

Adenovirus containing human FGF4 (GENERX) developed by Collateral Therapeutics and Shering AG might be applicable for mucosal restitution in patients with inflammatory bowel disease or radiation-induced colitis as well as for therapeutic angiogenesis in patients with cardiovascular diseases (51); however, the benefits of adenovirus containing human FGF4 remain to be demonstrated by clinical trials.

## 7. Clinical application of FGF signaling inhibitors

Small-molecule inhibitors and antibody drugs targeted to growth factor signaling molecules appeared as novel therapeutic agents for cancer patients in the 21st century. Gefitinib (Iressa), Erlotinib (Tarceva) and Lapatinib (GW572016) are small molecule inhibitors for receptors of EGF family members, while Cetuximab (Erbitux), Pertuzumab (Omnitarg) and Trastuzumab (Herceptin) are monoclonal antibodies targeted to EGF family ligands or receptors (52-54).

*In silico* screening of ATP mimetic compounds, fitting into ATP-binding cassette of protein kinases, are performed in the post-genome era to facilitate the efficacy of high-throughput screening for protein kinase inhibitors by using three-dimensional structure of protein kinases and small-molecule compounds for docking simulation software. PD173074 is a small-molecule inhibitor for FGFR, while RO4396686 and SU6668 are small-molecule inhibitors for FGFR and other tyrosine kinases (55-57).

## 8. Perspectives

Epigenetic changes occur at the early stage during multi-stage carcinogenesis associated with chronic persistent inflammation and/or aging (58). *SFRP1* gene, encoding WNT antagonist, is silenced due to promoter CpG hypermethylation in gastrointestinal cancers. *HHIP1 (HHIP)* gene, encoding Hedgehog antagonist, is also silenced due to promoter CpG hypermethylation in gastrointestinal cancers. Because *SPRY* and *SPRED* family genes encode FGF signaling inhibitors, promoter CpG hypermethylation of *SPRY* and *SPRED* family genes in gastrointestinal cancers should be searched for in the future.

Small-molecule inhibitors for FGFR are promising anti-cancer drugs for certain patients with diffuse type gastric cancer. Single nucleotide polymorphisms (SNPs) or copy number polymorphism (CNP) analyses on FGF signaling genes as well as transcriptome or proteome analyses on FGF family ligands could lead to the establishment of criteria to predict which patients should be treated with small-molecule FGFR inhibitors.

Although small-molecule inhibitors are initially effective for some cancer patients, recurrence due to drug resistance associated with somatic mutations of drug-target genes occurs in most cases. Cocktail therapy using multiple protein kinase inhibitors could enhance the therapeutic effects for gastrointestinal cancer through the reduction of recurrence associated with somatic mutations.

Genetic predisposition, chronic persistent inflammation, life style and aging are causative factors for gastrointestinal cancers. Comprehensive characterization of host genome as well as bacterial genomes could promote the realization of personalized prevention and personalized medicine to improve the prognosis of cancer patients.

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