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SP and KLF Transcription Factors in Digestive Physiology and Diseases

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Abstract

Specificity proteins (SPs) and Krüppel-like factors (KLFs) belong to the family of transcription factors that contain conserved zinc finger domains involved in binding to target DNA sequences. Many of these proteins are expressed in different tissues and have distinct tissue-specific activities and functions. Studies demonstrate that SPs and KLFs regulate not only physiological processes such as growth, development, differentiation, proliferation, and embryogenesis, but pathogenesis of many diseases, including cancer and inflammatory disorders. Consistently, these proteins have been shown to regulate normal functions and pathobiology in the digestive system. We review recent findings on the tissue- and organ-specific functions of SPs and KLFs in the digestive system including the oral cavity, esophagus, stomach, small and large intestines, pancreas, and liver. We provide a list of agents under development to target these proteins.

Keywords

Specificity Protein; Krüppel-Like Factor; Digestive System; Cancer; Stem Cells; Proliferation; Differentiation; Development; Apoptosis; Cell Cycle

Specificity proteins (SPs) and Krüppel-like factors (KLFs) belong to the evolutionarily conserved family of zinc finger transcription factors (the SP/KLF family)[1]. SP and KLF proteins recognize and bind to high GC content DNA sequences and 5'-CACCC-3' elements via the zinc finger domains near the carboxyl terminus[2]. Despite similarities in the genomic DNA sequences they bind, SPs and KLFs regulate expression of numerous genes in tissues

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in a distinct and context-dependent manner. This characteristic is due to differences in their amino-terminal sequences (Figure 1) and their ability to interact with other co-factors, activators, or repressors (Figure 2)[2-6].

Since the identification of the first member of the SP/KLF family, SP1, in 1983, human genes encoding 17 KLFs and 9 SP proteins have been identified (Figure 1). Comprehensive evolutionary studies by Presnell et al confirmed the existence of SP/KLF family in 48 species within Eukaryota[1, 7]. The past 30 or so years of research demonstrated that these factors regulate cell proliferation, differentiation, metabolism, apoptosis, and migration and govern processes such as embryogenesis, development, and homeostasis, as well initiation, progression, and maintenance of tumorigenesis (reviewed in[2, 5, 8-10]). Numerous studies have elucidated the physiological and pathological functions of SP and KLFs in many systems. We review the latest discoveries on the SP and KLF transcription factors in the physiology and pathology of the digestive system (Figure 3 and Table 1).

Roles in the Digestive System and Diseases

Oral cavity and esophagus

Cancer of the oral cavity and lips is the 10th most prevalent type of cancer in the world. More than 90% of oral cancers are oral squamous cell carcinoma (OSCC)[11]. Several members of the SP/KLF family have been implicated in the pathogenesis of OSCC. Increased levels and interaction between SP1 and SP3 during tumorigenesis result in supra-basal aberrant expression of keratin 14 (*KRT14*) in early epithelial dysplasia and OSCC[12]. KLF2, 4, 5, 8, and 13 are believed to be involved in oncogenesis of OSCC[13-17]. KLF4 is expressed at a higher level in low-grade OSCC than high-grade OSCC, and its depletion promotes the development of cancer in both oncogene-mediated and chemically induced mouse models of OSCC[14, 18, 19]. Although overexpressing *KLF4* in human OSCC cell lines decreases their proliferation and induces apoptosis, it increases invasiveness through a matrix metallopeptidase 9 (MMP9)-dependent mechanism[14]. Together, those results indicate that KLF4 suppresses early tumorigenesis of OSCC but promotes invasion in later stages of tumor progression.

In squamous carcinoma of the esophagus, levels of SP1 are increased compared to adjacent non-tumor tissues; SP1 expression is associated with tumor metastasis to lymph nodes (LNM) and the extent of the tumor, extent of its spread to the lymph nodes, and the presence of metastasis (TNM stage)[20]. SP1 is implicated in the transcriptional regulation of potential prognostic markers ezrin and keratin 19 (KRT19), which have each been associated with malignant transformation[21, 22]. Interestingly, KLF4 also regulates the expression of KRT19 and has an overlapping binding site with SP1 in the *KRT19* promoter[22]. In adult esophagus, KLF4 is expressed in the supra-basal layer of the squamous epithelium, whereas KLF5 is expressed in the basal layer[23-25].

Conditional disruption of *Klf4* in the mouse esophageal epithelium results in basal cell proliferation and a delay in cellular maturation of the squamous epithelium[26]. In addition, KLF4 regulates transcription of *Klf5*, and *Klf4* disruption results in increased expression of *Klf5*[26]. Overexpression of *Klf5* in mouse esophageal epithelia results in increased

proliferation strictly within the basal layer[25]. In cultured primary esophageal keratinocytes, KLF5 directly upregulates transcription of the epidermal growth factor receptor gene (*Egfr*), creating a positive feedback loop via activation of MEK signaling to ERK to promote proliferation[27]. Furthermore, overexpression of *Klf5* in primary esophageal keratinocytes results in increased migration mediated by the increased expression and activation of integrin-linked kinase (ILK)[28]. Collectively, these studies indicate that KLF5 regulates cell proliferation and migration, whereas KLF4 regulates cell differentiation and maturation of esophageal squamous epithelium.

KLFs are involved in development of esophageal diseases. KLF4 is highly expressed in both rat and human Barrett's epithelium specimens[29]. This increase in expression is thought to result from bile acid-induced activation of nuclear factor-kappa B (NF-κB), which activates KLF4 and subsequent production of mucin 2 (MUC2)—a characteristic of metaplastic columnar epithelium. Additionally, inhibition of NOTCH signaling induces a switch from squamous to columnar gene expression and results in upregulation of *Klf4* expression, whereas *Klf4* knockdown in these cells reverses the Barrett's epithelium-like metaplasia[30].

Esophageal squamous carcinoma (ESCC) is the sixth leading cause of cancer death worldwide. KLF4 expression is decreased in 8 of 9 human ESCC cell lines[31]. Gene expression profiling of ESCCs shows that decreased KLF4 correlates with reduced expression of keratin 13 (*KRT13*)—an indicator of cell differentiation in ESCC. Furthermore, induced differentiation of human ESCC KYSE-150 using sodium butyrate results in increased expression of *KLF4* and *KRT13*[32].

Findings from a recent study indicated that KLF4 could have stage-specific functions as a tumor suppressor and an oncoprotein. Although KLF4 expression is decreased in early-stage tumors, increased expression is observed in advanced tumors, and restored expression of *KLF4* in human ESCC cells is important for tumor metastasis[31]. On the other hand, decreased expression of *KLF5* is observed in human ESCC[27, 28, 33]. In immortalized primary esophageal keratinocytes (EPCS-hTERT cells) containing the hotspot mutation $p53^{R175H}$, KLF5 inhibits the formation of invasive tumors by directly activating transcription of *NOTCH1*, a keratinocyte tumor suppressor[33]. Furthermore, in absence of functional p53, KLF5 functions as an anti-proliferative factor by activating transcription of *CDKN1A*, which encodes a tumor suppressor and mediator of p53-dependent cell cycle arrest[34]. Concurrent p53 mutation and KLF5 loss result in transformation and invasion of keratinocytes. KLF5 is also involved in regulation of apoptosis and cell viability. Upon its restoration to the human ESCC cell lines TE7 and TE15, KLF5 activates JNK signaling, leading to the release of BAX, an apoptosis regulator. KLF5 also upregulates *BAX* expression through direct biding to its promoter, indicated by increased *BAX* mRNA levels and findings from chromatin immunoprecipitation assays[35]. Collectively, these findings indicate that KLF5 is a tumor suppressor of esophageal carcinoma.

Stomach

Expression of SP1 increases in peptic cells of the gastric fundus in mouse pups at 3 weeks of age and continues until mice are fully grown [36, 37]. In addition to SP1, SP7 is expressed in the gastric epithelium, including parietal cells[37]. However, the functions of SPs in these cells

have not been determined[36, 37]. Hormonal signaling is critical for the secretory function of the stomach and involves SPs. For example, gastrin stimulates the production of chromogranin A (*CGA*) through the transcriptional activation by SP1 in AGS-B (human gastric adenocarcinoma cells)[38]. SP1 is overexpressed in human gastric cancer specimens and linked to cancer cell growth and invasion and its increase induces invasion of several human gastric adenocarcinoma cells[39-41]. Consistently, inhibition of *SP1* by microRNA-335 (MIR335) in several human adenocarcinoma cell lines suppresses cell migration and invasion[42]. Gastric tumors have been reported to have increased levels of SP2 and SP5; inhibition of *SP2* via MIR638 suppresses proliferation of AGS cells[43, 44]. SP3 is also expressed by GES-1 cells (an immortalized gastric epithelial cell line); SP3 knockdown in GES-1 cells inhibits their invasive activity[45].

KLF4 is expressed in the non-proliferative, differentiated mid- to upper portion of the gastric epithelium in humans and mice, and regulates proliferation and cell fate determination[46]. Transgenic mice with gastric epithelium-specific disruption of *Klf4*, via *Foxa3*-induced Cre recombinase, develop gastric hypertrophy and altered differentiation in gastric epithelium[47]. Furthermore, in AGS cells, KLF4 activates transcription of ghrelin (*GHRL*), an orexigenic hormone secreted from the stomach during fasting, and represses the expression of histidine decarboxylase (*HDC*), which is important for the conversion of histidine to histamine—a bioamine that stimulates gastric acid secretion[46, 48]. KLF4 functions as a tumor suppressor in gastric cancer—its level is decreased in the human gastric cancer tissue specimens compared to normal gastric epithelium and correlates with poor survival[49, 50].

Multiple mechanisms are implicated in the decrease or loss of *KLF4* expression in gastric cancer, including allelic loss, loss of heterozygosity, hypermethylation of the *KLF4* promoter, and targeting by MIR10b and MIR32[51-53]. Mice with conditional disruption of *Klf4* in the gastric epithelium spontaneously form tumors and have increased susceptibility to N-methyl-N-nitrosourea-induced gastric carcinogenesis[54]. Restoration of *KLF4* expression in human gastric cancer cell lines suppresses cell proliferation and induces apoptosis[49]. KLF4 suppresses gastric cancer progression by regulating the expression of *CDKN1A*, leading to p53-dependent G_1/S cell-cycle arrest[47]. KLF4 regulates cancer cell growth by inhibiting the expression of forkhead box M1 (*FOXM1*)—a proliferation-associated transcription factor involved in gastric tumorigenesis[54]. In addition, overexpression of *KLF4* in the MKN-45 gastric cancer cell line inhibits the expression of β-catenin and suppresses proliferation, colony formation, and metastatic properties[55]. These findings indicate that KLF4 is a suppressor of gastric carcinogenesis.

In contrast to KLF4, KLF5 activates proliferation of human gastric carcinoma cells. Its nuclear levels have been associated with higher tumor grades, higher clinical status, LNM, and lower rates of patient survival[56, 57]. *Helicobacter pylori* infection, a risk factor for intestinal metaplasia, has been reported to stimulate *KLF5* expression[58, 59]. KLF5 also collaboratively regulates an oncogenic transcriptional network with GATA4 and GATA5—transcription factors with significantly increased expression in KLF5-expressing human gastric carcinoma specimens[60]. Despite these findings, further mechanistic studies are warranted to better determine the functions of KLF5 in gastric tumorigenesis.

KLF6 expression is decreased in gastric cancers, due to loss of heterozygosity, mutations, and alternative splicing[61, 62]. This decrease is associated with poor cell differentiation, LNM, and TNM stage[63]. KLF6 functions as a tumor suppressor in gastric cancer by regulating transcription of *CDKN1A* and *MYC*, whose products regulate cell cycle progression and apoptosis[62]. A splice variant of KLF6 (KLF6-SV1) functions as a dominant negative regulator of wild-type KLF6, blocking its tumor-suppressor activities. Reducing *KLF6-SV1* expression with small interfering RNAs (siRNAs) causes caspase-dependent apoptosis, via regulation of PI3K signaling to AKT, and BCL2-related protein expression; this results in proliferation, colony formation, migration, and invasion in gastric cancer cell lines[64]. These findings indicate that KLF6 has a tumor suppressive function whereas the variant KLF6-SV1 has an oncogenic function and is a potential therapeutic target.

In addition to KLF6, KLF8 has been implicated in gastric carcinogenesis. Its levels are increased in nuclear and cytoplasmic compartments of gastric cancer tissues, compared with non-tumor gastric tissue; increased expression was associated with increased tumor size, tumor angiogenesis, local invasion, LNM, and TNM stage[65, 66]. siRNA-mediated knockdown of KLF8 expression inhibited proliferation of SGC7901 cancer cells and reversed hypoxia- and transforming growth factor beta 1 (TGFB1)-induced epithelial-to-mesenchymal transition (EMT)[67, 68]. KLF8 therefore appears to promote gastric oncogenesis, regulating cancer cell proliferation, invasion, and metastasis.

Small and large intestine

Several SP factors have physiological and pathophysiological effects in the intestinal epithelium. SP1 and SP3 positively regulate the expression of Na^+/H^+ exchangers (NHE2, NHE3, and NHE8) in rat intestinal epithelium and colon cancer cell lines[69-71]. In addition to NHEs, SP1 and SP3 are involved in transcriptional regulation of genes encoding other transporters: SP1 regulates expression of the sodium-glucose co-transporter (SGLT1) in the rabbit intestinal epithelium[72] and SP3 regulates expression of the epithelial sodium channel (SCNN1G) in rat distal colon[73]. SP1 also promotes expression of metabolism-related genes, including the ATPase copper transporting alpha (*ATP7A*)[74] and apolipoprotein A-1 (*APOA1*)[75]. SP1 and SP3 promote the expression of ethanolamine kinase 1 (EK1) and thereby stimulates biosynthesis of phosphatidylethanolamine, a component of the lipid bilayer[76]. SP1 also regulates expression of markers of differentiation in the intestinal epithelium, including expression of intestinal alkaline phosphatase (IAP) and MUC2 in HT29 colorectal cancer cells[77, 78].

SP3 promotes apoptosis and reducing SP3 levels increases expression of *BCL2*, decreases expression of *BAX*, and decreases expression and activities of caspase-3, -8, and 9 in IEC-6 cells[79]. Butyrate also induces apoptosis in HT29 and Caco2 cells, by inducing acetylation of SP1 and SP3. This activates transcription of *BAK1* (which promotes apoptosis) and the cell cycle inhibitor *CDKN1A*[80, 81]. In addition to SP1 and SP3, SP6, a regulator of iron absorption, is expressed at a low level in rat duodenum, with a diminishing gradient of expression from the crypts to the villi.

Increased expression and transcriptional activity of SP1 have been observed in colorectal cancer (CRC) tissues compared to normal tissues[82-84]. Knockdown of SP1, SP3, and SP4 by

RNA interference in SW480 cells blocks proliferation and reduces survival, migration, and invasion through down-regulation of *EGFR, VEGF, BCL-2*, and *BIRC5*[85]. Ulrich et al showed that SP1 regulates transcription of the cyclooxygenase-2 gene (*COX2*) and might therefore affect intestinal inflammation[86]. It had been shown that inhibition of COX2 prevents colon tumorigenesis[87]. COX2 inhibition decreases *SP1, SP3*, and *SP4* expression in several human CRC cell lines by inducing their degradation, which contributes to anti-cancer effects of COX2 inhibition[88, 89].

SP1 has been implicated in drug resistance, as it positively regulates the expression of ATP-binding cassette transporter (ABCB1), encoded by the multidrug resistance gene *MDR1* in Caco2 cells[90]. Cancer stem cells mediate tumor growth, resistance to chemotherapy, and metastasis; high levels of SP1 expression by these colorectal cancer stem cells might contribute to colorectal tumor drug resistance[84]. On the other hand, SP1 and SP3 promote apoptosis, so it might be possible to activate this activity in cancer cells. Histone deacetylase inhibitors induce growth arrest and apoptosis in CRC cells by specifically activating SP1 and SP3[91].

KLF4 and KLF5 are highly expressed in the intestinal epithelium, with distinct expression patterns[92, 93]. KLF4 is primarily expressed in differentiated villus cells, whereas KLF5 is highly expressed in proliferating crypt epithelial cells[24, 94]—these factors therefore appear to have opposing functions[92, 93]. During mouse fetal development, *Klf4* expression increases between E10 to E13 and peaks at E17[95], although intestinal epithelial-specific disruption of *Klf4* is not embryonic lethal[96]. Expression of KLF4 is induced by serum withdrawal or DNA damage, which in turn induces growth arrest [94, 96]. DNA damage activates p53, which activates transcription of KLF4, which in turn activates transcription of *CDKN1A*, resulting in arrest of the cell cycle at the G_1/S[97-99]. In addition, DNA damage-induced expression of KLF4 regulates mitotic entry and centrosome duplication by regulating transcription of *CCNB1* and *CCNE*[100, 101]. The role of KLF4 in regulating the cell cycle has been confirmed by cDNA microarray analysis[102].

KLF4 also has anti-apoptotic effects that are mediated through activation of $p21^{WAF1/CIP1}$ and inhibition of BAX; loss of KLF4 increases apoptosis[98, 103]. These results indicate that KLF4 functions as a nodal factor for cells to undergo either cell cycle arrest or apoptosis, depending on the extent of DNA damage. The anti-apoptotic functions of KLF4 were confirmed in studies of intestinal epithelial regeneration following γ radiation-induced injury. Mice with intestinal epithelium-specific deletion of *Klf4* (Villin-Cre; $Klf4^{fl/fl}$) have increased mortality after γ irradiation[104]. The post-irradiation epithelial regeneration was achieved by activation of reserve intestinal stem cells expressing *Bmi1*; disruption of *Klf4* in this cell population blocked this regenerative response[105].

KLF4 therefore modulates reserve stem cell functions during epithelial regeneration. In addition to regulating cell-cycle proteins, KLF4 inhibits WNT signaling by interacting directly with β-catenin, to inhibit β-catenin's transcriptional activity[106]. *In vitro* experiments indicated that KLF4 regulates expression of differentiation markers, including IAP and epithelial-specific keratin genes[96, 102, 107]. Mice with intestine-specific conditional or induced disruption of *Klf4* have significant reductions in colonic goblet cells and decreased

expression of differentiated markers, such as MUC2 and carbonic anhydrase 1 (CA1)[96, 108, 109].

Inhibition of NOTCH signaling by γ secretase inhibitors in mice increased expression of *Klf4* and the number of goblet cells[110, 111], although KLF4 inactivation in NOTCH-deficient mice did not inhibit goblet cell differentiation[112]. Recent studies showed that KLF4 forms complex with YAP–TAZ and upregulates expression of genes involved in regulation of metabolism, differentiation, and biosynthetic processes[113]. In addition to cellular differentiation, KLF4 regulates migration of differentiated cells. Deletion of KLF4 from the intestinal epithelium resulted in abnormal Paneth cell migration, possibly due to altered ephrin B signaling via its receptor, EPHB2[96, 109]. On the other hand, KLF4 is a potential therapeutic target for inflammatory bowel disease; conditional disruption of *Klf4* from mouse intestinal epithelium decreases susceptibility to dextran sodium sulfate (DSS)-induced colitis, by preventing activation of NF-kB signaling and inflammation[114].

During embryonic development, KLF5 is expressed in endodermal progenitors that become the lining of the gastrointestinal tract. Although proliferation of these cells is unaffected, *Klf5* disruption in cells that express sonic hedgehog inhibits villus formation and epithelial differentiation. This appears to be due to decreased expression of KLF5 target genes involved in intestinal epithelial differentiation, including *Elf3, Atoh1, Ascl2, Cdx1, Cdx2*, and *Pparγ*[115]. Conditional disruption of *Klf5* (Villin-Cre; $Klf5^{fl/fl}$) in the mouse intestinal epithelium is lethal to approximately two-thirds of the newborn mice[116]. Remaining mice survive due to variegated *Klf5* deletion in the intestinal epithelium, but die around 8 weeks of age; they have reduced epithelial proliferation and altered differentiation, migration, and barrier functions[116].

Although inducible, intestine-specific disruption of *Klf5* (Villin-$CreER^{T2}$; $Klf5^{fl/fl}$) in adult mice has similar consequences, proliferation and differentiation of epithelial cells are eventually restored, through increased expression of the HMG-box transcription factor SOX9 and regenerating proteins (REGs) [117, 118]. In addition, *Klf5* deletion results in reduced expression of stem cell markers, such as *Lgr5, Ascl2*, and *Olfm4*[117]. Recent studies support a role for KLF5 in regulating proliferation and survival of intestinal stem cells. *Lgr5*-expressing crypt-based columnar cells are rapid-cycling active intestinal stem cells that express KLF5; disruption of *Klf5* in these cells results prevents their proliferation[119, 120].

KLF5 is important for intestinal epithelial regeneration and wound healing. Infection of mice with *Citrobacter rodentium* results in transmissible murine colonic hyperplasia, mediated by increased KLF5 expression[121]. Furthermore, KLF5 protects mice from development of colitis in response to DSS by promoting epithelial proliferation and migration of cells adjacent to the sites of ulceration[122]. DSS-induced colitis is more severe in mice with heterozygous disruption of *Klf5*, compared to $Klf5^{+/+}$ mice, since KLF5 activates interleukin 22 signaling via JAK2 and STAT3, which leads to intestinal repair[122, 123].

KLF5 is also important for epithelial regeneration following γ irradiation[124, 125]. DNA damage in HCT116 cells induced by ultraviolet exposure and 5-fluorouracil activates

transcription of *KLF5* by a p53-independent mechanism[124]. Mice with heterozygous deletion of *Klf5* have more severe intestinal injury following radiation injury than *Klf5*$^{+/+}$ mice; level of injury correlated with decreased expression of genes involved in DNA damage repair[125]. KLF9, is expressed in smooth muscle cells of the small intestine and colon, where it regulates proliferation and intestinal morphogenesis. Deletion of KLF9 from smooth muscle cells results in shortening of villi in the jejunum, reduced proliferation, and altered cell differentiation[126].

Many studies have reported levels of KLF4 are lower in human colorectal neoplasia specimens than adjacent normal mucosa[127-130]. In addition, decreased expression of KLF4 correlates with CRC LNM and reduced survival times of patients[129, 130]. KLF4 expression can be reduced by loss of heterozygosity, accompanied by decreased activity of p21$^{WAF1/CIP1}$[127]. KLF4 also downregulates expression of genes whose products promote cell cycle progression, such as *CCND1* and *ODC*[131]. KLF4 is down-regulated in colon tumors from patients with familial adenomatous polyposis and intestinal adenomas of the *Apc*$^{Min/+}$ mice, which have a germline mutation in the *Apc* gene[132]. Moreover, haploinsufficiency of *Klf4* in *Apc*$^{Min/+}$ mice increases development of intestinal adenomas[133]. In contrast, overexpression of *KLF4* in human CRC cell lines reduces β-catenin activity, leading to growth arrest and reduced tumor formation in mice[134, 135]. Mutations in *APC* downregulate expression of KLF4, because APC mediates expression of CDX2, which regulates cell differentiation and cell cycle progression intestinal epithelial cells[136].

WNT signaling to β-catenin increases expression of *BMI1*, which is essential for proliferation of human CRC cell lines[137]. KLF4 trans-represses BMI1 expression by directly binding to the *BMI1* promoter and inhibiting BMI1-mediated histone ubiquitination[137]. These results indicate that KLF4 may prevent intestinal tumorigenesis in the absence of a functional APC. KLF4 also prevents colorectal carcinogenesis upon NOTCH inhibition. *Apc*$^{Min/+}$ mice given the NOTCH inhibitor dibenzazepine develop fewer adenoma, associated with upregulation of KLF4 expression[110].

In contrast to KLF4, KLF5 promotes colorectal carcinogenesis; its expression is often up-regulated in human CRC specimens compared to normal epithelium[138]. Overexpression of *KLF5* in intestinal epithelial cell lines IEC-6 and HCT116 increases proliferation[139-141]. Lysophosphatidic acid induces *KLF5* expression in CRC cells, which increases cell proliferation due to increased expression of *CCND1* and *CCNB1*[142, 143]. In LoVo and SW480 cells, KLF5 directly interacts with the β-catenin–TCF4 complex to increase its transcriptional activity[144]. Furthermore, *Klf5* disruption in *Apc*$^{Min/+}$ mice reduces intestinal tumor formation, by reducing β-catenin nuclear localization and transcriptional activity[145].

Formation of intestinal tumors from *Lgr5*-expressing crypt-based columnar cells, via expression of a constitutively active, oncogenic form of β-catenin (*Catnb*$^{lox(\Delta ex3)}$), is inhibited by disruption of *Klf5*, which reduces nuclear localization of β-catenin[138]. Furthermore, KLF5 expression is induced by oncogenic KRAS^{V12G} in intestinal epithelial cells, and KLF5 is overexpressed in human CRC specimens with KRAS^{V12G} mutations[146].

Consistently, haploinsufficiency of *Klf5* in the intestinal epithelium of $Apc^{Min/+}$ mice that express $KRAS^{V12G}$ reduces the number of tumors that form[147].

Both KLF6 and KLF9 suppress colorectal carcinogenesis. Expression of *KLF6* is either reduced or absent in CRC specimens, due to loss of heterozygosity or missense mutations, although the tumor suppressive function of KLF6 is not clear[148-150]. Levels of *KLF9* mRNA and protein are reduced in human CRC tissues, compared with non-tumor tissues, in microarray analyses[151]. In addition, disruption of *Klf9* in $Apc^{Min/+}$ mice slightly increases tumor formation[152]. These results suggest that KLF6 and KLF9 could be suppressors of colorectal carcinogenesis.

Pancreas

SP1 and SP3 are expressed in islet, acinar, and ductal epithelial cells in normal pancreatic tissues[153-157]. In pancreatic cancer cells, SP1, SP3, and SP4 regulate expression of genes involved in cell proliferation, differentiation, and migration[158]. SP1 also activates genes during the stress response[159-161]. In normal pancreas, SP1 maintains basal expression of pancreas-specific transcription factor 1 A (PTF1A) in acinar cells and vesicular glucose transporter 2 and pyruvate carboxylase in β cells[154, 156, 157]. SP1 interacts with muscle, intestine and stomach expression 1 (MIST1) to form a transcriptional complex that regulates acinar cell proliferation through CDKN1A[162]. Interaction between SP1 and SP3 regulates expression of genes such as the secretin receptor (*SCTR*) and pancreatic and duodenal homeobox 1 (*PDX1*)[153, 155]. SP1 and SP3 compete for the same GC boxes in the promoter of *SCTR*, although SP1 acts as activator whereas SP3 as a repressor[153]. SP1 binding to the *PDX1* promoter increases its activation by forkhead box A2 (FOXA2, also called HNF3B); whereas binding of SP3 to the same region reduces transactivation by HNF3B[155]. SP1 also mediates the response of β cells to lipotoxicity and acinar cells to chronic alcohol exposure[159-161].

SP1, SP3, and SP4 are overexpressed in pancreatic ductal adenocarcinoma (PDAC), compared with non-tumor pancreatic tissues, and might be therapeutic targets[85]. SP1 regulates mucin production in pancreatic cancer cell lines[163-165]. It also activates transcription of *KRT19*, binding to the same regulatory sequence as KLF4[22].

The best-studied member of KLF family in development of the exocrine pancreas is KLF11, also called TGFB-inducible early gene 2 or TIEG2. Transgenic mice that overexpress *Klf11* specifically in acinar cells, via elastase 1 promoter-driven Cre recombinase (*Ela1*-Cre), have smaller pancreases that are histologically reminiscent of primary pancreatic acinar atrophy[166]. The reduced acinar mass is due to reduced cell proliferation and increased apoptosis, although the residual acinar cells function normally. KLF11 represses transcription by binding to corepressor SIN3A[166, 167]. Removal of the SIN3A-interacting domain from KLF11 prevents it from blocking proliferation[107]. *KLF11* overexpression also renders acinar cells more susceptible to oxidative stress-mediated apoptosis, by repressing the expression of superoxide dismutase 1 (SOD1) and catalase 1[166].

In addition to repressing acinar cell growth, KLF11 suppresses neoplastic transformation induced by oncogenic KRAS[166, 168]. Normally, KLF11 represses TGFB-induced

transcription of *SMAD7* by binding to the promoter of *SMAD7* and recruiting SIN3A. This interaction disables the negative-feedback loop imposed on TGFB signaling by SMAD7. In PDAC cells with oncogenic *KRAS* mutations, phosphorylation of KLF11 disrupts its interaction with SIN3A, leading to negative regulation of TGFB signaling. Furthermore, KLF11 interacts with SMAD3 to inhibit expression of *MYC* in normal epithelium; this interaction is disrupted by phosphorylation of KLF11 in oncogenic KRAS-expressing PDAC cells and releasing them from TGFB-induced *MYC* repression[169]. KLF10 (also called TIEG), is another transcriptional repressor. When overexpressed in PDAC cell line PANC-1, KLF10 increases oxidative stress and inhibits cell proliferation and induces apoptosis[170].

KLF4 is also involved in development of PDAC. Unlike KLF10 and KLF11, KLF4 can either promote or inhibit tumor development, depending on the stage of the disease. *KLF4* overexpression in PDAC cell lines reduces cell proliferation *in vitro* and tumor growth in subcutaneous xenograft models *in viv*o. The mechanism lies in the ability of KLF4 to up-regulate *CDKN1B* expression, which leads to G_1/S cell cycle arrest[171].

There is a negative correlation between KLF4 expression, late-stage PDAC, and increased levels of lactate dehydrogenase A (LDHA) in patients. Overexpression of KLF4 in PDAC inhibits tumorigenicity by transcriptionally inhibiting *LDHA* expression[171]. Furthermore, KLF4 overexpression reduces metastasis of orthotopic xenograft tumors[171, 172]. KLF4 appears to prevent metastasis by regulating cancer cell stemness, by inhibiting expression of CD44, a marker of cancer stem cells[172]. Wei et al. identified 4 KLF4 splice variants (α, β, γ, and δ) and found levels of KLF4α to be increased in aggressive pancreatic cancer cells and pancreatic cancer human tissue[173].

Interestingly, KLF4 also activates transcription of *KRT19*, which encodes type 1 keratin differentially expressed in pancreatic ductal epithelial cells and PDAC[174, 175]. Overexpression of KLF4 and SP1 in acinar cells led to aberrant expression of KRT19—an observation also made in pancreatic cancer cells[22, 176]. Pancreas-specific knockout of *Klf4* in the oncogenic KRAS-mediated (KC) mouse model of PDAC reduced acinar to ductal metaplasia—a transformation process that gives rise to premalignant pancreatic lesions. KC mice with pancreas-specific knockout of *Klf4* develop fewer pancreatic intraepithelial neoplasia (PanINs)—the most common type of premalignant lesion that can lead to PDAC. Alternatively, overexpression of *Klf4* in KC mice increased acinar to ductal metaplasia and subsequent PanIN formation[177]. KLF4 is therefore required for early pancreatic carcinogenesis but becomes a tumor suppressor as the disease progresses. The changing role of KLF4 during the progression of the disease raises concerns about therapies to target KLF4 in treatment of pancreatic cancer[178].

Genome-wide association studies identified several single nucleotide polymorphisms (SNPs) near *KLF,5* gene at loci 13q22.1, associated with increased risk of pancreatic cancer[179, 180]. KLF5 promotes anchorage-independent growth and cell proliferation in human pancreatic cancer cell lines[181-183]. KLF5 activates genes specifically expressed in low-grade PDAC by recruiting other transcriptional activators to the enhancers of those genes and by inhibiting the expression of *ZEB1*, a transcriptional regulator in high-grade PDAC[183]. Knockout of *KLF5* from a human low-grade PDAC cell line causes cells to transform from an epithelial

to a mesenchymal morphology[183]. KLF5 cooperates with SOX4 to promote tumorigenesis and repress SOX4-mediated apoptosis during TGFB-induced lethal EMT[184]. In pancreatic cancer cells that express full-length *SMAD4*, TGFB induces expression of *SOX4* and *SNAIL*. The expression of *SNAIL* promotes the EMT and inhibits expression of *KLF5*, leading to the EMT followed by apoptosis. Cells with a loss of function mutation in *SMAD4* do not express *SNAIL* upon TGFB stimulation but do express *KLF5*[184].

In addition to their roles in the exocrine pancreas, KLF10 and KLF11 function in the endocrine pancreas. *Klf10* knockout mice have reduced numbers of islets of Langerhans and poor performance on oral glucose tolerance test and homeostatic model assessments[185]. KLF10 upregulates expression of SERTA domain containing 1 (SERTAD1, also called SEI1), which increases expression of *CDKN1A*[185]. It is not clear exactly how KLF10 determines β-cell mass.

KLF11 regulates transcription of insulin in β cells[186]. Mutations in *KLF11* have been associated with French mature-onset diabetes of the young[186, 187]. Some mutations reduce the ability of KLF11 to trans-regulate expression of *PDX1*, which is required for β cell functions[187]. A mutation in the insulin gene promoter is associated with neonatal diabetes mellitus and disrupts its interactions with multiple KLF transcription factors[188]. KLF11 is the strongest activator of the insulin gene promoter and the most abundant in human β cells.

Despite evidence showing that disruption of KLF11 function leads to human diabetes mellitus, *Klf11*-knockout mice do not develop diabetes[189]. *Klf11*-knockout mice have lower levels of insulin, but they also develop increased sensitivity to insulin and increased lipid metabolism[189]. These findings indicate that KLF11 regulates not only insulin production, but also metabolic homeostasis. KLF2 and KLF6 are expressed in the pancreas but little is known about their functions in this tissue[190, 191].

Liver

In normal liver, SP1 mediates the cellular response to oxidative stress by regulating expression of ZNF32; SP1 also regulates expression of protein S[192-194]. In liver diseases, SP1 and SP3 mediate leptin-induced liver fibrosis by activating expression of collagen type I, alpha 1 chain (COL1A1)[195]. In alcohol-induced liver injury, transglutaminase 2 cross-links SP1, which leads to SP1 inactivation and apoptosis of hepatocytes[196]. SP1 promotes migration and invasion of hepatocellular carcinoma (HCC) cells by upregulating expression of *MMP2*[197]; SP1 promotes liver cancer metastasis by transactivating *CD151*[198]. SP1 may be involved in aberrant histone acetylation in HCC cells[199]. SP1, SP3, and SP4 all upregulate expression of a long non-coding RNA (lnRNA) called HCC up-regulated long non-coding RNA (*HULC*), and promote HCC cell proliferation and survival[200].

During liver development, KLF6 is required for hematopoiesis, angiogenesis, and hepatic organogenesis[201]. Without *Klf6* expression, mouse embryos fail to develop a definable liver[201]. Studies that knocked out or overexpressed *Klf6* in mouse embryonic stem cells showed that KLF6 is required for development of endoderm-derived organs[191]. In normal liver, gluconeogenesis is regulated by KLF15, which is abundantly expressed and increases with fasting[202, 203]. Disruption of *Klf15* in mice leads to fasting hypoglycemia, due to

decreased gluconeogenesis[204]. KLF15-knockout mice have defects in use of amino acids as sources of gluconeogenic substrates and decreased expression of phosphoenolpyruvate carboxykinase (PCK1)[204, 205].

KLF15 is involved in the mechanism of action of metformin—a first-line drug for treatment of type 2 diabetes mellitus. Metformin decreases gluconeogenesis by increasing the ubiquitination and degradation of KLF15[205]. Expression of *Klf15* from an adenovirus in mice partially attenuates the effects of metformin on decreasing gluconeogenesis[205].

KLF9 and KLF14 also have physiological functions in the normal liver. KLF9 regulates expression of P450 enzymes such as *CYP1A1* and *CYP2D6* and might be involved in bile acid synthesis, via regulation of *CYP7A*[206-208]. KLF14 regulates generation of signaling lipids in the liver by transactivating expression of sphingosine kinase 1 (SK1)[209]. KLF14 also regulates expression of apolipoprotein A1 and increases high-density lipoprotein-C [210].

In addition to its role in development, KLF6 contributes to the pathogenesis of liver diseases. Since its cloning from fibrotic rat liver, KLF6 has been found to be upregulated during progression of non-alcoholic steatohepatitis to fibrosis in rats[211, 212]. Splice variants of KLF6 determine its function in steatosis and fibrosis of the liver. Levels of full-length KLF6 are increased in liver with advanced-stage steatosis, which is associated with increased levels of α-smooth muscle actin (α-SMA) and collagen I in hepatic stellate cells (HSCs)[213]. In contrast, in human liver, the SNP KLF6-IVS1-27G>A has been associated with increased levels of the SV1 splice variant of KLF6, compared to the full-length protein, and decreased levels of α-SMA and collagen I. Patients with the variant allele have been shown to have less advanced fibrosis[214].

Full-length and SV1 variants of KLF6 decrease the fibrogenic activity of HSCs in response to injury in rodents, by direct suppression of fibrogenic genes and induction of apoptosis[213]. Even though the exact role of KLF6 in hepatic fibrosis is not clear, the association between increased expression of KLF6 and steatosis and non-alcoholic fatty liver disease is well studied[215-217]. In transgenic mouse model, KLF6 regulates transcription of the glucokinase gene (*Gck*)[215]. The KLF6-IVS1-27G>A SNP has been associated with increased hepatic insulin sensitivity and glucose production via upregulation of GCK[215]. Furthermore, decreased KLF6 and GCK levels correlate with non-alcoholic fatty liver disease[215].

In addition to modulating hepatic insulin sensitivity, KLF6 regulates expression of peroxisome proliferator activated receptor alpha (PPARA). Expression of PPARA leads to gluconeogenesis and contributes to steatosis[216, 217]. KLF6 increases transcription of *PPARA* by repressing its negative regulator MIR10b[216]. Similarly, KLF11 promotes development of steatosis by increases expression of PPARA[218]. KLF5, KLF6, and KLF9 are believed to increase lipid accumulation during steatosis by direct transactivation of *PPARG*[217, 219]. KLF2 and KLF15 contribute to development of steatosis by promoting insulin resistance and lipid accumulation in response to endoplasmic reticulum stress and by activating CD36 expression[220, 221].

KLF2 protects both normal and cirrhotic liver. The vasoprotective action of KLF2 is mainly mediated through the activation of target genes such as endothelial nitric oxide synthase,

thrombomodulin, and c-type natriuretic peptide in liver sinusoid endothelial cells (LSECs)[222]. In acute liver injury, KLF2 protects LSECs through increased autophagy by upregulating *RAB7*[223]. KLF2 also improves microcirculation in rat liver tissues after cold storage and warm ischemia reperfusion[224, 225]. Simvastatin can provide vasoprotection by increasing expression of *KLF2*, by activating an isoprenoid pathway[222-226]. Upregulation of these genes in LSECs reduces the severity of portal hypertension in cirrhotic liver disease[222]. KLF2 also protects the liver from cirrhosis by inhibiting the activation of HSCs and decreasing subsequent fibrosis—either directly through activation of NF-E2-related factor 2 (NRF2) or indirectly, through a KLF2–NO–cGMP paracrine mechanism mediated by LSECs[226, 227]. KLF2 also induces heme oxygenase-1, which may be responsible for the inhibition of HCV replication by statins[228].

Other KLFs that are involved in liver fibrosis include KLF5 and KLF11[219, 229-231]. KLF11 directly regulates the expression of collagen type I, alpha 2 chain (COL1A2) and may contribute to fibrosis[231]. Reducing levels of KLF11 decreases the severity of liver fibrosis induced by tetrachloride, but increasing negative feedback of TGFB signaling via SMAD7[231].

KLF4 is a suppressor of HCC development. Lower levels of KLF4 in HCC tissues correlate with reduced overall survival time and higher-grade tumors[232-234]. KLF4 induces differentiation and reduces migration and invasion of HCC cells[232, 234-236]. It blocks HCC progression by reducing expression of *SLUG, TIMP1*, and *TIMP2* and by inducing expression of vitamin D receptor and hepatocyte nuclear factor-6 *(HNF6)*[232, 234-236]. Levels of KLF4 are reduced in cancer cells by miRNAs and increased protein degradation[237, 238].

KLF6 is also a suppressor of HCC[239-244]. HCCs have loss of heterozygosity at the *KLF6* gene loci, and express mutant forms of KLF6 that lack tumor suppressor activity[239]. However, KLF6 is not frequently mutated in HCC samples patients[245]. Instead, the ratio of the KLF6 splice variants determines its tumor suppressor function[242, 244]. Full-length KLF6 acts as a tumor suppressor by inducing *CDKN1A* expression independent of p53—this transactivation of *CDKN1A* increases when KLF6 is phosphorylated by glycogen synthase kinase 3 beta (GSK3B)[240, 243, 246]. In HCC, the SV1 splice variant of KLF6 antagonizes the tumor suppressor activity of the full-length KLF6[242, 244, 247]. The SV1 variant does not affect transcription of the *KLF6* gene itself[242]. Instead, SV1 variant increases the degradation of full-length variant by direct binding[244]. Differential splicing of *KLF6* mRNA in HCCs increases via several mechanisms. Increased HRAS increases splicing and the amount of SV1 variant by inducing PI3K pathway, which in turn induces the activity of ASP and SF2 splice regulatory proteins[242]. Hepatocyte growth factor can also promote alternative splicing of KLF6 through a PI3K–AKT–SRSF3 pathway[247].

Activities of KLF8, KLF9, KLF10, and KLF17 have been associated with HCC. KLF8 increases the invasive activity of HCC cell lines[248]. In surgically resected HCC samples, levels of KLF8 correlate with levels of FAK and MMP9, and correlate inversely with level of E-cadherin[249]. KLF8 promotes cell proliferation and survival by activating *CCND1* and *BCL2L1*, respectively[248]. In HCC cell lines, KLF8 expression is upregulated in response to WNT signaling via β-catenin; KLF8 recruits p300 to β-catenin–TCF4 transcription

complex, leading to transactivation of genes[250]. Levels of KLF9 are decreased in human HCC tissues, compared to non-tumor tissues; restoring KLF9 expression to human HCC cell lines inhibits proliferation and induces apoptosis, possibly by increasing expression of p53 and stabilizing this protein[251].

KLF10 mediates the TGFB-induced apoptosis in HCC cell lines through generation of reactive oxygen species and loss of mitochondria membrane potential[252]. *KLF17* expression is downregulated in patient HCC samples; reducing *KLF17* expression in an HCC cell line increased the migration and invasiveness of the cell line with concurrent increase in expression of genes associated with EMT[253, 254].

Future Directions

Members of the SP/KLF family of transcription factors are important regulators of homeostasis and pathophysiology of the digestive system. These factors control multiple processes and are indispensable for proper function of the digestive system. Levels of SP and KLF factors are altered in diseases such as cancer and inflammatory bowel disease, and might therefore serve as therapeutic targets. Table 2 provides examples of many of the novel small molecular compounds capable of modifying expression and activities of SP/KLF family.

Significant progress has been achieved in understanding the mechanisms by which SP and KLFs function. Nevertheless, many important questions remain. For example, these factors bind to similar DNA sequences, allowing them to interact. However, it is not clear how they interact among one another to influence transcription of their target genes. Many of these factors are expressed in the same tissues but their temporal and spatial relationships have not been well defined. In addition to their functions as transcriptional regulators, SP and KLF regulate epigenetic and post-transcriptional modification of genes, which represent areas also under-examined. There are therefore abundant opportunities for further investigation in elucidating many of their undefined functions.

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Abbreviations

SP	Specificity protein
KLF	Krüppel-Like Factor
OSCC	oral squamous cell carcinoma
ESCC	Esophageal squamous carcinoma
CRC	Colorectal cancer
EMT	Epithelial-to-Mesenchymal Transition
AKT	Protein kinase B

APC	Adenomatous polyposis coli
BCL-2	B-cell lymphoma 2
BAX	BCL-2-like protein 4
EGFR	Epidermal growth factor receptor
VEGF	Vascular endothelial growth factor
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
MUC2	Mucin-2
NOTCH1	Neurogenic locus notch homolog protein 1
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
TCF	T-Cell-Specific transcription factor
TGFB	transforming growth factor beta
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
TCF	T-cell Factor
MicroRNA	Mi-RNA
DSS	Dextran sodium sulfate
TNM	TNM Classification of malignant tumors
LNM	lymph node metastasis

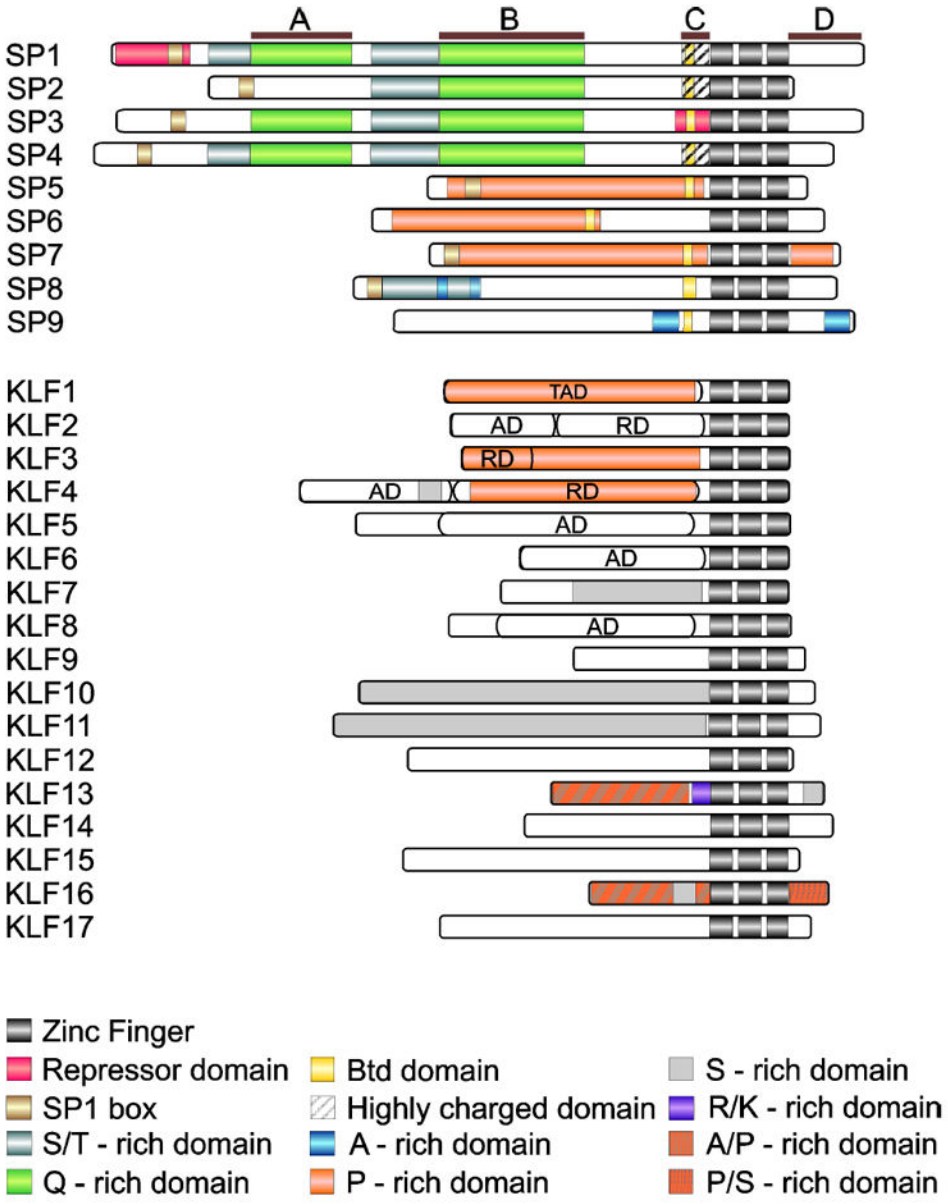

Figure 1. Structure of Human SP and KLF Proteins

The A, B, C, and D define the modules of SP1, TAD – transactivation, AD – activation, and RD – repression domain (reviewed in[2-6]). The accession numbers of proteins used for this figure are listed per UniProtKB database as follows: SP1 (P08047), SP2 (Q02086), SP3 (Q02447), SP4 (Q02446), SP5 (Q6BEB4), SP6 (Q3SY56), SP7 (Q87DD2), SP8 (Q8IXZ3), SP9 (P0CG40), KLF1 (Q13351), KLF2 (Q9Y5W3), KLF3 (P57682), KLF4 (Q43474), KLF5 (Q13887), KLF6 (Q99612), KLF7 (O75840), KLF8 (O95600), KLF9 (Q13886), KLF10 (Q13118), KLF11 (O14901), KLF12 (Q9Y4X4), KLF13 (Q9Y2Y9), KLF14 (Q8TD49), KLF15 (Q9UIH9), KLF16 (Q9BXK1), and KLF17 (Q5JT82).

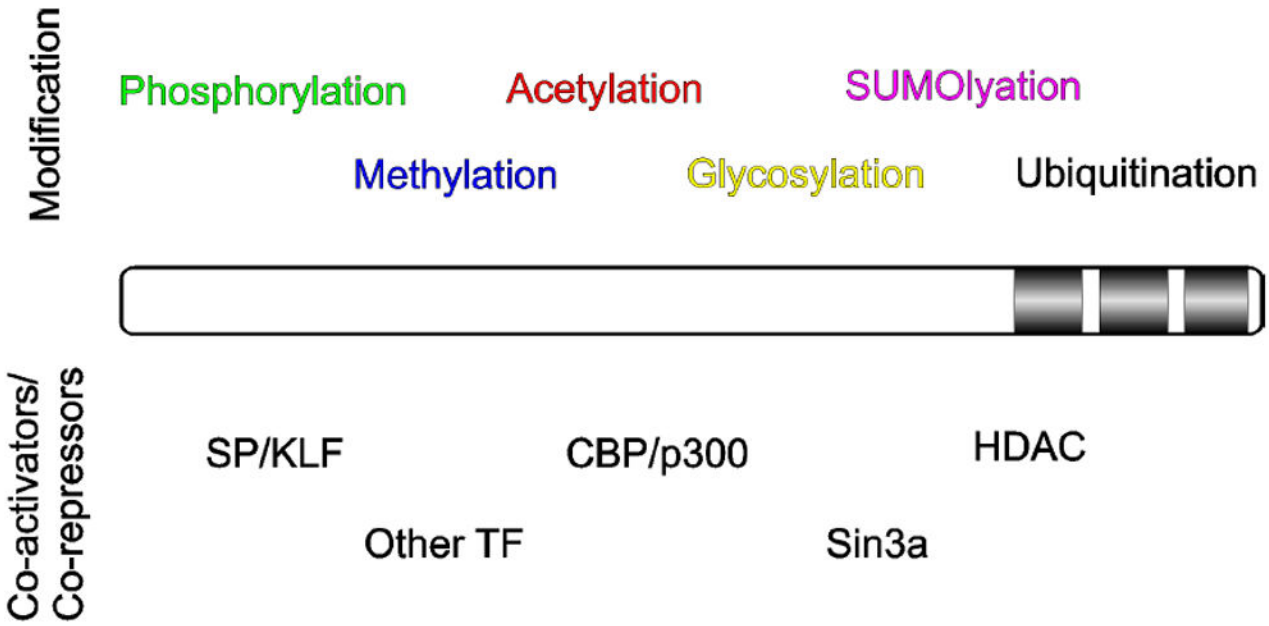

Figure 2. Post-translational Modifications and Co-factors That Interact With SP and KLF Proteins

SP/KLF protein is illustrated as a bar with the three zinc fingers identified near the carboxyl terminus. The various post-translational modifications are described above the protein and the various co-activators or co-repressors that interact with the protein below.

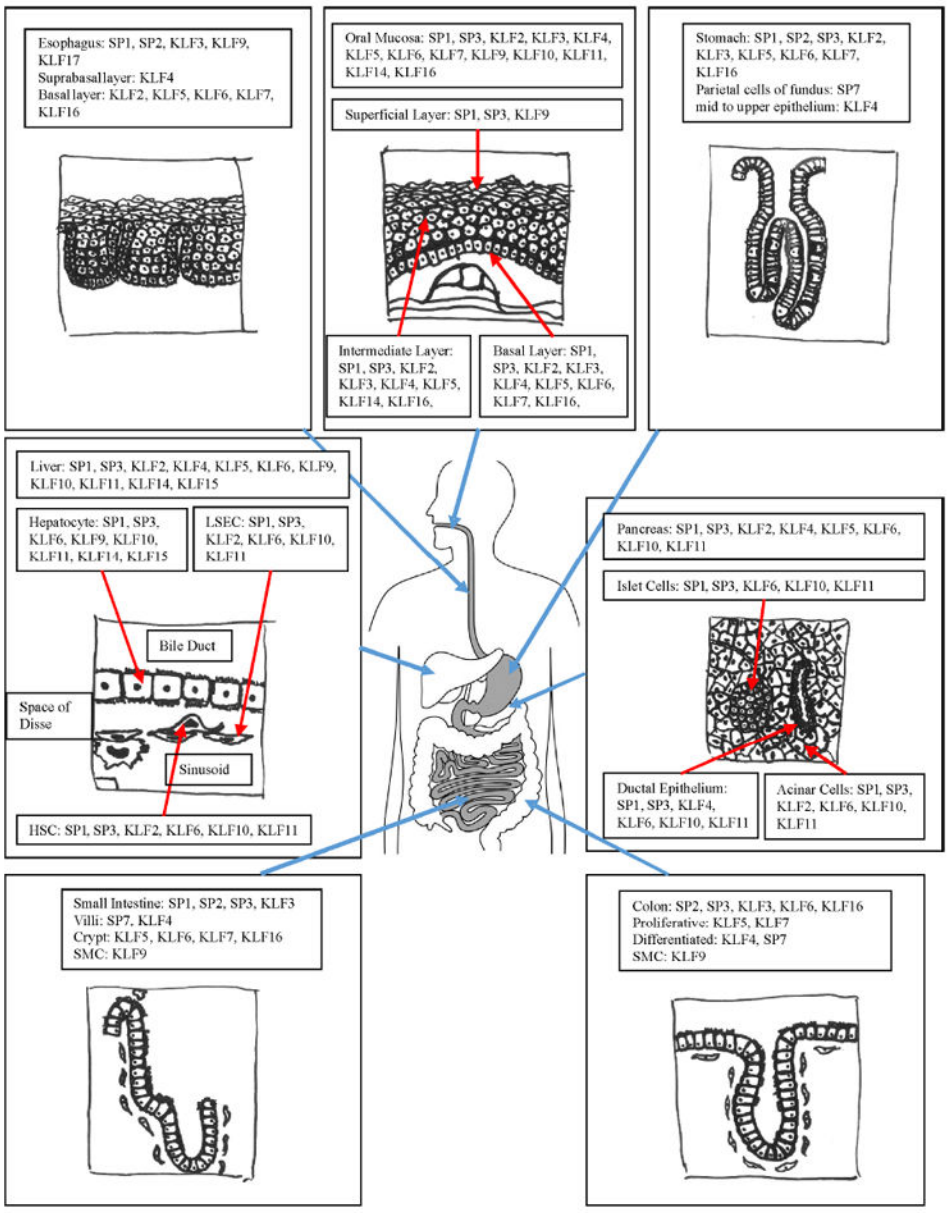

Figure 3. Expression Patterns of SP and KLF Proteins Under Physiologic Conditions in the Digestive System

The diagram illustrates the various organs or tissues in the digestive system, including the oral mucosa, esophagus, stomach, small intestine, colon, liver, and pancreas. Various members of SP and KLF proteins found in the given tissues or cells types are included in the figure.

TABLE 1

SP/KLF Family Members in the Digestive System

	Adult GI system		GI Disorder	
Name	**Expression**	**Function**	**Expression**	**Function**
SP1			ESCC: Upregulated[20]	ESCC: Expression associated with LNM and TNM staging[20]
	Stomach: Peptic cells of the stomach fundus[36]	Stomach: Promotes production of REG1 under stress-induced damage[255]; Stimulates the production of chromogranin A (CgA)[38]	Gastric cancer: Upregulated[40, 41]	Gastric cancer: Promotes cell invasion[42]
	Pancreas: Acinar cells[154, 162]	Maintains acinar cell function by promoting expression of *PTF1A*[154]; Inhibits acinar cell proliferation by interacting with MIST1[162]	PDAC: Upregulated[85]	Regulates mucin production[163-165]; Regulates expression of *KRT19* with KLF4[22]
	Pancreas: Beta cells[155-157]	Regulates expression of vesicular glucose transporter 2[156] and pyruvate carboxylase[157], and regulates expression of *PDX1* with SP3[155]	Mild fasting hyperglycemia: mutation to the cis-regulatory region in *Gck* promoter[156]	Mutations cause loss of binding from SP1 to the cis-regulatory element[156]
	Pancreas: Ductal epithelial cells[153]	Regulates expression of secretin receptor gene with SP3[153]		
	Liver[192-194]	Mediates response to oxidative stress[192]; Maintains expression of protein S[193, 194]	Cirrhotic Liver: Upregulated[195]	Increases fibrosis by increasing *COL1AI* expression[195]
			Alcohol-induced liver injury: crosslinking[196]	Cross-linked by tranglutaminase 2 leading to loss of transcription factor function and induction of apoptosis[196]
			HCC: Upregulated[85]	Promotes tumor invasion and migration through expression of matrix metalloproteinase 2[197] and transactivation of CD151[198]; involved in aberrant histone acetylation[199]; Promotes proliferation[256]; Promotes expression of

	Adult GI system		GI Disorder	
Name	**Expression**	**Function**	**Expression**	**Function**
				HULC lnRNA, which induces cell proliferation and survival[200]
SP2			Gastric cancer: Upregulated[43]	Gastric cancer: Promotes cell proliferation[43]
SP3	The Gastric epithelium	Stomach: Promotes production of REG1 under stress-induced damage[255]	Gastric cancer: Expressed but no differential expression pattern noted	Gastric cancer: Promotes cell invasion[45]
	Intestinal epithelium	Promotes apoptosis [79, 80]; Promotes expression of Na+/H+ exchangers NHEs[69-71]; Promotes expression of *EKI*[76]	CRC: Expression pattern not noted	CRC: Promotes cell proliferation, survival, and invasion[85]; Promotes apoptosis [91]
	Pancreas: beta cell[155]	Regulate expression of *PDX1* with SP1[155]	PDAC: Upregulated[85]	
	Pancreas: ductal epithelial cell[153]	Regulates expression of *SCTR*, secretin receptor gene with SP1[153]		
			HCC: Upregulated[85]	Promotes expression of *HULC* lnRNA, which increases cell proliferation and survival[200]
SP4			CRC: Expression pattern not noted	CRC: promotes cell proliferation, survival, and invasion[85]
			PDAC: Upregulated[85]	
			HCC: Upregulated[85]	Promotes expression of *HULC* lnRNA, which increases cell proliferation and survival[200]
SP5			Gastric cancer: Upregulated[44]	
			CRC: Upregulated[44]	
SP6	Low expression in the crypts of the duodenum[257]			
SP7	Stomach: Parietal cells[37]			
	Intestines: Differentiated cells[37]			

	Adult GI system		GI Disorder	
Name	**Expression**	**Function**	**Expression**	**Function**
SP8	ND (not determined)		ND	
SP9	ND		ND	
KLF1	ND		ND	
KLF2	Pancreas[190]		PDAC: Downregulated[258]	Inhibits cell proliferation and migration[258]
	Liver[222]		Acute Liver Injury: Downregulated[223]	Vasoprotective, promotes autophagy in liver sinusoid endothelial cells[223]
			Cirrhotic Liver: Downregulated[222, 226, 227]	Protects against endothelial damage, reduce portal hypertension[222]; Inhibits the activation of HSCs [226, 227]
KLF3	ND		ND	
KLF4	Oral Mucosa[18]		OSCC: Downregulated in high grade cancer[14, 18, 19]	Has tumor suppressor function[18, 19] and has higher expression in low grade OSCC[14]
	Esophagus: Suprabasal layer[26]	Esophagus: Cell differentiation and maturation[26]	Barrett's esophagus: Overexpressed in BE specimens;	Barrett's esophagus: Involved in the metaplasia of squamous epithelium to columnar epithelium[29, 30];
			Esophageal squamous carcinoma: Loss of expression in human ESCC specimens[32]; increased expression observed in advanced stage ESCC[31]	ESCC: Context-dependent functions as an oncoprotein or tumor-suppressor depending on the stage. At early stage, functions as a tumor suppressor and induces cell differentiation [32, 259]. At later stage, increased expression was observed[31]
	Stomach: Differentiated mid- to upper part of the epithelium[46]	Stomach: Cell proliferation and cell fate determination[47]; ghrelin and histamine production[46, 48]	Gastric cancer: Loss of *KLF4* expression[49, 50]	Gastric cancer: Functions as a tumor suppressor by inhibiting cell proliferation and

	Adult GI system		GI Disorder	
Name	**Expression**	**Function**	**Expression**	**Function**
				inducing apoptosis[49, 54]
	Small and large intestines: Differentiated cells of the small intestinal villi or luminal surface of the colonic epithelium[100-103]	Small and large intestines: Cell cycle regulation[100-102]; Anti-apoptotic factor[97, 98, 103, 104]; Cell differentiation[96, 99, 107, 112]	Colorectal cancer: Loss of *KLF4* exprssion[127-130]	IBD: protects against DSS-induced colitis; CRC: Functions as a tumor suppressor; Associated with LNM and poor survival[129, 130]; Regulates cell cycle[127, 131]; Inhibits cell invasion[135]; Functions as an oncogenic factor by promoting anti-apoptotic effects in cells with mutant $KRAS^{V12}$ [260]
	Pancreas: Ductal Epithelial Cells[22, 176]	Transactivates *KRT19* expression[174, 175]	PDAC: Required for precursor lesion formation during early tumorigenesis; Downregulated in later stages of tumorigenesis[171, 172, 177]	Cell cycle arrest via upregulate p27Kip1 expression[171]; Inhibits *LDHA* expression[171]; Suppresses metastasis[171, 172]; Required for acinar-to-ductal metaplasia and PanIN formation[177]
	Liver[232]		HCC: Downregulated[232, 234-236]	Tumor suppressor by inhibiting migration and invasion[232, 234-236]
KLF5	Oral Mucosa[15]		OSCC: Upregulated[15]	Promotes cancer growth and survival[15]
	Esophagus: Basal (proliferative) layer[25]	Esophagus: Cell proliferation[25]; cell migration[28]	ESCC: Downregulated[33-35]	ESCC: Inhibits tumor invasion[33]; Anti-proliferative factor[34]; Pro-apoptotic factor[35]
	Gastric epithelium[56, 57]		Gastric cancer: Upregulated[56, 57]	Gastric cancer: Associated with higher tumor grade LMN, and lower survival rate[57]; Involved in *H pylori*-infection mediated gastric-to-intestinal trans-differentiation[58, 59]
	The intestinal epithelium: Expressed in proliferating cells of the crypts[24]	Regulates cell proliferation[117, 261]; Regulates cell cycle progression[139, 146, 262];	IBD: Intestinal epithelial regeneration[121-123]	CRC: Increased cell proliferation[139-141]; Promotes nuclear translocation of β-

	Adult GI system		GI Disorder	
Name	**Expression**	**Function**	**Expression**	**Function**
		Promotes cell differentiation and barrier function[116]; Maintains stem cell markers and functions[117, 119, 120]; Involved in intestinal epithelial regeneration[124, 125]; DNA damage repair[125]		catenin and transcriptional functions[144, 145]; Promotes oncogenic transformation of *Lgr5*-expressing stem cells[138]; Mediates the oncogenic functions of KRAS^{V12G}[146, 147]
	Pancreas[183]		PDAC: Upregulated[179-181, 183, 184]	Promotes cancer cell growth[179-181] and cell survival[184]; Promotes epithelial phenotype[183]
	Liver[219]		Non-alcoholic steatohepatitis: Upregulated[219]	Promote triglyceride synthesis by activating PPARG expression[219]
KLF6			Gastric cancer: downregulated[61, 62]; Variant form of KLF6 (KLF6-SV1) expressed[64]	Gastric cancer: Functions as a tumor suppressor by transcriptionally regulating *CDKN1A, c-MYC*[62]; Associated with poor cell differentiation, LMN and TNM stage[63]; KLF6-SV1 functions as an oncogenic factor and dominant negative regulator of full-length KLF6[64]
			CRC: Downregulated or lost[148-150]	
	Liver[201]	Required for organogenesis of liver[191, 201]	Non-alcoholic steatohepatitis: Upregulated[214, 215, 217]	KLF6-IVS1-27G>A single nucleotide polymorphism is associated with increased SV1 spliced variant, increased steatosis[215] and decreased fibrosis[214]; Increase steatosis by expression of PPARA and PPARG[217]
			HCC: Full length variant downregulated; SV1 spliced variant upregulated[244]	Full length variant act as a tumor suppressor[239240-244]; SV1 variant inhibits

	Adult GI system		GI Disorder	
Name	**Expression**	**Function**	**Expression**	**Function**
				tumor suppressor function of full length variant[244]
KLF7	ND		ND	
KLF8			Gastric cancer: Upregulated[65, 66]	GC: Associated with poor prognosis, LNM and TNM staging[65, 66]; Promotes cell proliferation and EMT[67, 68]
			HCC: Upregulated[248]	Increases tumor invasion[248, 249]; Promotes cancer cell proliferation and survival[248]
KLF9	Esophagus[263]		ESCC: Downregulated[263]	ESCC: Tumor suppressor; Forced expression inhibits growth, migration, and metastasis[263]
	Small and large intestines: smooth muscle cells[126]	Regulates proliferation and intestinal morphogenesis[126]	CRC: Downregulated[152]	CRC: Prevents tumor formation[152]
	Liver: Hepatocytes[206-208]	Regulates the expression of P450 enzymes important for detoxification[207, 208]; Has a role in regulating CYP7A in bile acid synthesis[206]	Non-alcoholic steatohepatitis: Upregulated[217]	Activates expression of PPARG, as does KLF6[217]
			HCC: Downregulated[251]	Tumor suppressor functions through increasing expression of *TP53*[251]
KLF10	Pancreas[185]	Islet Cell: Important for maintaining beta-cell mass and function[185]	PDAC: Downregulated[170, 252]	Inhibits cell growth and induces apoptosis in response to TGFB[170, 252]
			HCC: Downregulated[252]	Mediates the TGFB induced apoptosis[252]
KLF11	Pancreas: Acinar cells[166]	Promotes acinar cell differentiation and senescence and suppresses oxidative stress response genes[166]	PDAC: Downregulated[166, 168, 169]	Inhibits cell proliferation; induces apoptosis in response to TGFB[166, 168, 169]

	Adult GI system		GI Disorder	
Name	**Expression**	**Function**	**Expression**	**Function**
	Pancreas: Islet cells[187]	Maintains normal beta-cell function[187]	French mature-onset diabetes of the young; mutations in *KLF11* gene[187]	Loss of ability to transactivate *PDX1*, required for beta-cell function[187]
			Neonatal diabetes mellitus: Mutation in cis-regulatory element in insulin promoter[189]	Mutation in insulin promoter prevents KLF11 transactivation of the insulin gene[189]
	Liver[264]		Non-alcoholic steatohepatitis: Upregulated[218]	Activates expression of PPARA and promotes steatosis[218]
			Cirrhotic Liver: Upregulated[231]	Directly activates expression of collagen 1a2 and induce fibrosis[231]
KLF12	ND		ND	
KLF13	ND		ND	
KLF14	Liver: Hepatocytes[209, 210]	Increases signaling lipid production by activating *SK1*[209]; Regulates expression of *APOAI* gene[210]		
KLF15	Liver: Hepatocytes[204, 205]	Regulates gluconeogenesis by regulating amino acid utilization[204] and *PEPCK* expression[205]	Non-alcoholic steatohepatitis: Upregulated[220]	Promotes steatosis by promoting insulin resistance and lipid accumulation[220]
KLF16	ND		ND	
KLF17	Esophagus[265]		ESCC: Downregulated[265]	ESCC: Decreased expression correlated with metastasis[265]
			Gastric cancer: Downregulated[266]	Gastric cancer: Associated with tumor size, LMN, and poor survival[266]
			HCC: Downregulated[253, 254]	Inhibits tumor invasion and migration[253, 254]

TABLE 2

Agents That Target SP and KLF Proteins in the GI Tract

Cancer or disease type	Compound	Affected SP/KLF family members	Mode of action	References
Oral	Coffee-specific deterpene (Kahweol)	SP1	Decreases cell viability and increases nuclear condensation and sub-G1 population, Suppresses SP1 factor, which leads to apoptosis; Tested in vitro	267
	Manumycin A (Manu A)	SP1	Reduces SP1 levels and affects its target genes (p27, p21, MCL1 and survivin), Causes nuclear fragmentation and cell death; tsted in vitro	268
	6,7-dihydroxycoumarin (Esculetin)	SP1	Decreases SP1 protein levels with reduction of proliferation and increase in apoptosis; tested in vitro,	269
	Dibenzylideneacetone (DBA), an analogue of curcumin	SP1	Decreases SP1 protein levels by inducing its degradation; inhibits cell proliferation, induces apoptosis and nuclear condensation; tested in vitro,	270
	Licochalcone A, a cholconoid derived from root of Glycyrrhiza inflata	SP1	Decreases SP1 and affects its downstream targets (p27, p21, Cyclin D1, MCL1, and survivin), Causes increase in Sub-G1 population and nuclear condensation, which increase caspase activity and apoptotic regulatory proteins to induce apoptosis; tested in vitro,	271
	2,4-bis (p-hydroxyphenyl)-2-butenal (HPB242)	SP1	Decreases SP1 and affects its downstream targets (p27, cyclin D1, MCL1, and survivin), Reduces cell viability; tested in vitro,	272
	Panobinostat (LBH589)	SP1	Induces apoptosis via downregulation of SP1, affects targets of SP1 factor (p21, p27, cyclin D1, MCL1, and survivin), Increases activity of apoptotic pathway by increase of BAX and reduction of BID and BCL-XL expression, Induces cleavage of caspase-3 and PARP; tested in vitro,	273
	β-lapachone (β-lap)	SP1	Suppresses activation of SP1 followed by downregulation of cell cycle regulatory proteins and upregulation of apoptosis-related proteins that are known as SP1 target genes; tested in vitro	274
	4-O-methylhonokiol (MH)	SP1	Inhibits SP1 protein synthesis and induction of SP1 proteasome-dependent protein degradation that results in decrease of cell growth and increase of apoptosis, inhibits tumor growth in xenografts model using HN22 cells in nude mice, tested in vitro and in xenografts	275
Esophageal	Tolfenamic acid (TA)	SP1, SP3, and SP4	Increases degradation of SP1, SP3, and SP4 and inhibits cell proliferation and tumor growth (incidence and multiplicity); tested in rats in NMBA-induced murine tumor model; TA reported to decrease SP TF and SP-regulated genes (Cyclin D1, VEGF, Survivin, c-MET) and decreases tumor	276, 277

Cancer or disease type	Compound	Affected SP/KLF family members	Mode of action	References
			growth in xenograft model in nude mice; tested in vitro and in xenografts	
Gastric	Methyl jasmonate (MJ)	SP1	Decreases SP1 expression and its binding capacity to the MMP-14 promoter; attenuates migration, invasion, and angiogenesis, but not cell viability or proliferation; tested in vitro	278
	Arsenic sulfide (As4S4)	SP1	Inhibits migration and invasion of cells, Upregulation of E-cadherin and KLF4, Downregulation of β-catenin, VEGF, and SP1, suppression of activity of MMP2 and MMP9, inhibits tumor growth and invasion in xenografts	279
Colorectal	Ethyl 2-((2,3-bis(nitrooxy)propyl)disulf anyl)benzoate (GT-094)	SP1, SP3, and SP4	Repression of SP and SP-regulated genes (cyclin D1, c-MET, EGFR, Survivin, VEGF and VEGFR1 and VEGFR2) was mediated by downregulation of MIR27a and induction of ZBTB1, an SP repressor and led to inhibition of proliferation, induction of apoptosis, decrease in mitochondrial membrane potential and induction of ROS; tested in vitro	280
	Ascorbic acid (Vitamin C)	SP1, SP3, and SP4	Induction of apoptosis and necrosis accompanied by downregulation of SP1, SP3, and SP4, and their targets (c-MET, EGR, cyclin D1, Survivin, BCl-2, VEGF, VEGFR1, and VEGFR2); tested in vitro	281
	Acetylsalicylic acid (Aspirin)	SP1, SP3, and SP4	Decrease in SP1, SP3, and SP4 and SP-regulated genes (Bcl2, survivin, VEGF, VEGFR1, cyclin D1, MET, and p65), which induces apoptosis and decreases proliferation and inhibits tumor growth in nude mice; aspirin induces nuclear caspase-dependent cleavage of SP1, SP3, and SP4; tested in vitro and in xenografts	89
	2,3-Dihydro-5-methyl-3-([morpholinyl]methyl)pyr ollo(1,2,3-de)-1,4-benzoxazinyl]-[1-naphthaleny]methanone [WIN 55,212-2, (WIN)] (Synthetic cannabinoid - WIN)	SP1, SP3, and SP4	Decrease in SP1, SP3, and SP4 and SP-regulated genes (survivin, VEGF, VEGFR1, cyclin D1, and EGFR), Inhibition of SP proteins was due to PP2A-dependent downregulation of MIR27a and induction of ZBTB10, inhibited proliferation and induced apoptosis; tested in vitro,	282
	Sulindac, Sulindac sulfone, and Sulindac sulfide	SP1, SP3, and SP4	Decrease in SP1, SP3, and SP4 and SP-regulated genes (survivin, BCL2, VEGF, EGFR, cyclin D1, and p65), Sulindac sulfide downregulated MIR27a and induced ZBTB10, inhibiting cell proliferation; tested in vitro	283
	JW67 and JW74	SP5	Reduction in active β-catenin levels with a subsequent downregulation of Wnt target genes, including AXIN2, SP5, and NKD1; JW74 inhibited tumor cell proliferation in CRC xenografts and in $Apc^{Min/+}$ mice; tested in vitro and in vivo	284
	Monensin, a polyether ionophore antibiotic	SP5	Inhibits Wnt signaling and activation of target genes (cyclin D1 and SP5); decreases proliferation, reduces progression of intestinal tumors in $Apc^{Min/+}$ mice; tested in vitro and in vivo	285

Cancer or disease type	Compound	Affected SP/KLF family members	Mode of action	References
	Celecoxib, Nimesulfide, and NS; N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide (NS-398)	SP1 and SP4	Decreases expression of SP1 and SP4 proteins via ubiquitination; inhibits expression of *VEGF*; tested in vitro,	88
	Tolfenamic acid (TA)	SP1, SP3, and SP4	Decreased expression of SP1, SP3, and SP4 and SP-regulated genes (cyclin D1, hepatocyte growth factor receptor, VEGF, VEGRF1, survivin, BCL2, and NFκB p65 and p50 subunits). Mechanism of TA-mediated effects on SP proteins involved activation of caspases, tested in vitro and in xenografts	286
	Norcantharidin (NCTD), a cantharidin derivative,	SP1	Inhibits SP1 expression, DNA-binding capacity, and downregulates its target gene (*MMP9*), tested in vitro	287
	Methyl 2-cyano-3,11-dioxo-18beta-olean-1,12-dien-30-oate (beta-CDODA-Me) and methyl 2-cyano-3,11-dioxo-18alpha-olean-1,12-dien-30-oate (alpha-CDODA-Me)	KLF4	beta-CDODA-Me but not alpha-CDODA-Me induces caveolin-1 in SW480 colon cancer cells, whereas caveolin-1 is induced by both compounds in HT-29 and HCT-15 colon cancer cells. The CDODA-Me isomers increase levels of *KLF4* mRNA in HT-29 and SW480 cells but had minimal effects in HCT-15 cells; tested in vitro	288
	ML-133	KLF4	Activates KLF4, which displaces SP1 from the cyclin D1 promoter, negatively regulating expression of cyclin D1 and promoting the G(1)-S phase arrest of cell proliferation, Anti-proliferative effect on cells and in xenografts	289
	CIDs: 439501 and 5951923	KLF5	Reduces endogenous levels of KLF5 protein and decreases viability of colorectal cancer cell lines without affecting IEC-6 cells; tested in vitro	290
	ML264	KLF5	Inhibits proliferation of colorectal cancer cells DLD-1 and HCT116 through modifications of the cell-cycle profile. In mice with xenograft tumors grown from human colon cancer cells (DLD-1), ML264 inhibits growth of the tumors within 5 days, reducing tumor cells proliferation and expression of KLF5 and EGR1; tested in vitro and in xenografts	291, 292
	15-hydroxy-eicosatetraenoic acid (15S-HETE)	KLF10	Increases levels of KLF10 and a decreases levels of Bcl2; incubation of colon cancer cells with 15S-HETE inhibits cell proliferation and induces apoptosis; tested in vitro	293
	1-Methylpropyl 2-imidazolyl disulfide (PX-12)	KLF17	Inhibits proliferation of DLD-1 and SW620 colorectal cancer cells in a dose- and time-dependent manner. Reduces colony formation, induces a G2/M phase arrest and apoptosis, and increases activation of caspase-3. A low dose of PX-12 inhibits colorectal cancer cell migration and invasion. Incubation of cancer cells with PX-12 reduces *NOX1, CDH17*, and *S100A4* mRNA and increases *KLF17* mRNA	294
	Mithramycin A (MIT), Bevacizumab (BVZ)	SP1	MIT suppresses expression of SP1 and its downstream targets in vitro and in xenografts model, accompanied by	295

Cancer or disease type	Compound	Affected SP/KLF family members	Mode of action	References
			reduction in tumor angiogenesis, growth, and metastasis. BVZ upregulates SP1 expression and its downstream targets in in vivo but not in vitro. Combination of MIT and BVZ has synergistic effect and suppresses expression of SP1 and its downstream targets; tested in vitro and in xenografts	
	Betulinic acid (BA)	SP1, SP3, and SP4	BA induces proteasome-dependent and –independent downregulation of SP1, SP3, and SP4 and the pathway is cell context dependent; in RKO induces reactive species - mediated repression of MIR27a and induction of ZBTB10 repressor of SP1, SP3, and SP4; leads to downregulation of cyclin D1, survivin, VEGF, EGFR, p65, and PTT1; tested in vitro and in xenografts	296
	5,5'-dihydroxy, 5,5'-dimethyl, 5,5'-dibromo, 5,5'-dinitro and 5,5'-dimethoxyindole ring-substituted analogs of DIM-C-pPhC(6)H(5)	KLF4	Activates P21 in Panc28 cells and induces caveolin-1 and KLF4 in colon cancer cells; structure- and cell context-dependent; tested in vitro	297
Pancreatic	2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) and its methyl ester (CDDO-Me)	SP1, SP3, and SP4	Reduces expression of all 3 SP factors; reduces expression of cyclin D1, survivin, VEGF, and VEGFR2; inhibits proliferation and induces apoptosis; tested in vitro and in orthotopic tumors	298
	Diferuloylmethane (Curcumin), Synthetic Cyclohexanome and Piperidine analog – RL197,	SP1, SP3, and SP4	Reduces expression of all 3 SP factors; reduces expression of cyclin D1, survivin, VEGF; Reduces tumor necrosis factor activation of NF-κB, inhibits tumor growth and angiogenesis, induces apoptosis; reduces mitochondrial membrane potential and induces reactive species formation, Induction of SP repressors ZBTB10 and ZBTB4 and downregulation of MIR27a, MIR20a, MIR17-5p, and MIR199a and upregulation of MIR22; tested in vitro and in xenografts	299, 300
	Metformin	SP1, SP3, and SP4	Reduces expression of SP1, SP3, and SP4 and several SP-regulated genes (BCL2, survivin, cyclin D1, VEGF, VEGFR1, and fatty acid synthase); inhibits proliferation and tumor growth; tested in vitro and in vivo in orthotopic tumors. Metformin inhibited SP TF and SP-regulated insulin-like growth factor 1R and EGFR, which in turn negatively regulated mTOR and RAS signaling; tested in vitro and in orthotopic tumors	301, 302
	Tolfenamic acid (TA) and structurally related biaryl derivatives	SP1, SP3, and SP4	Induces degradation of SP1, SP3, and SP4, inhibits *VEGF* mRNA and protein expression; reduces tumor weight and volumes and incidence of liver metastasis; tested in vitro and in orthotopic tumors	303
	Celecoxib	SP1	Reduces phosphorylation, protein levels, DNA binding and transactivation activities of SP1; reduces expression of VEGF; ; inhibits tumor growth and metastasis; tested in vitro and in orthotopic tumors	304

Cancer or disease type	Compound	Affected SP/KLF family members	Mode of action	References
	Triptolide	SP1	Inhibits hexosamine biosynthesis pathway to inhibit glycosylation of SP1; prevents SP1 nuclear localization and affects its DNA binding; reduces cell survival; inhibits NFκB, HSF1, and HSP70 to induce cell death; negatively affects tumor growth; tested in vitro and in orthotopic tumors	305
	MCC-555	KLF4	Reduces levels of cyclin D1 by activating PPARG; increases expression of KLF4 and reduces expression of targets (p21 and NAG1); reduces proliferation; tested in vitro	306
Liver	Resveratrol	SP1	Inhibits cell migration and invasion; inhibits signaling via JNK1 and JNK2 and transcriptional activity of SP1; tested in vitro	307