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Title

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Journal

World Journal of Gastroenterology, 16(18)

ISSN

1007-9327

Author

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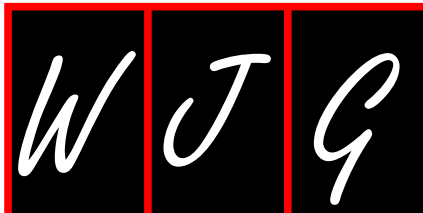
Publication Date

2010

DOI

10.3748/wjg.v16.i18.2195

Peer reviewed



Serum response factor: Look into the gut

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Received: January 26, 2010 Revised: February 27, 2010

Accepted: March 6, 2010

Published online: May 14, 2010

Abstract

Serum response factor (SRF) is a transcription factor that regulates many genes involved in cellular activities such as proliferation, migration, differentiation, angiogenesis, and apoptosis. Although it has only been known for about two decades, SRF has been studied extensively. To date, over a thousand SRF studies have been published, but it still remains a hot topic. Due to its critical role in mesoderm-derived tissues, most of the SRF studies focused on muscle structure/function, cardiovascular development/maintenance, and smooth muscle generation/repair. Recently, SRF has received more attention in the digestive field and several important discoveries have been made. This review will summarize what we have learned about SRF in the gastrointestinal tract and provide insights into possible future directions in this area.

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Key words: Angiogenesis; Cell invasion; Myofibroblast differentiation; Smooth muscle contraction; Serum response factor; Wound healing

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Modak C, Chai J. Serum response factor: Look into the gut. *World J Gastroenterol* 2010; 16(18): 2195-2201 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v16/i18/2195.htm>
DOI: <http://dx.doi.org/10.3748/wjg.v16.i18.2195>

INTRODUCTION

Although serum response factor (SRF) has only 25-year history, its studies have been exponentially grown in several fields including smooth muscle structures, cardiac functions, cellular stress responses and cell motility. SRF is a ubiquitously expressed transcription factor, therefore, its role should be far beyond these areas. When the new millennial dawn broke, we opened a new field for SRF research-digestive system. Several important discoveries have been made in different parts of the system ever since, which foresee a bright and fruitful future for this area. This article is to provide you an update in this line of study and hopefully point you to the right direction.

HISTORY OF SRF

SRF was first identified by Treisman^[1] in 1986 based on a previous observation in Greenberg's lab that resting cells responded to serum addition with a rapid activation of *c-fos*^[2]. He discovered that it is SRF that initiates the immediate response of *c-fos* to serum or any other growth factors by binding to a short DNA sequence-serum response element (SRE), which is located about 300 bp upstream of the *c-fos* gene transcription initiation site. Since then, SRE has been identified in as many as 300 human genes, accounting for 1% of our entire genome^[3,4]. Although it has only been known for a little over two decades, studies on SRF have been populated exponentially. Last year, more than a hundred SRF studies were documented in PubMed; and ten papers have already been published within the first 3 wk of this

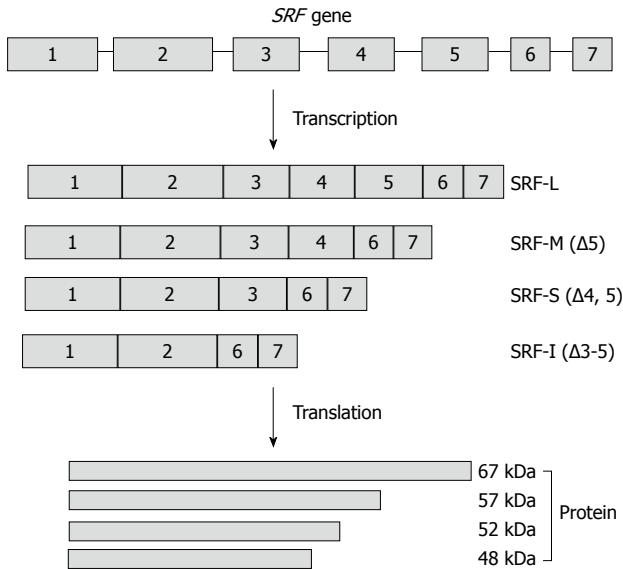


Figure 1 Serum response factor (SRF) splice variants (adapted from Chai and Tarnawski 2002).

year. Most of the published SRF studies deal with its functions in muscle structures or in the regulation of immediate early genes. However, SRF is a ubiquitously expressed protein and thus its role must be far beyond these areas. A few years ago, we started to look for SRF in the gastrointestinal (GI) tract^[5,6]. After that, several other groups have expanded our mission. Today, there have been over 20 studies published dealing with SRF in the digestive system.

BIOCHEMISTRY OF SRF

The human SRF gene was mapped to chromosome 6p21.1. It is 10607 bp long and contains 7 exons. In both humans and mice, SRF can be expressed in different isoforms due to alternative splicing and some of them appear to display tissue specificity^[7]. For instance, SRF-S, which lacks both exon 4 and 5 ($\Delta 4, 5$), has only been detected in the aorta, while SRF-I, which is the shortest isoform (missing exon 3, 4 and 5), is specific to embryonic tissues. On the other hand, SRF-M, which lacks only exon 5, has been shown to be a dominant negative mutant (Figure 1).

Full length SRF protein, which is approximately 67 kDa, was shown to contain three distinct domains: a SRE DNA binding domain, a transactivation domain and multiple phosphorylation sites^[8]. The DNA binding domain, which also serves for dimerization and interaction with accessory factors, has been highly conserved throughout evolution, showing a 93% homology between fruit flies and humans^[9]. Phosphorylation at Serine 103, which is immediately adjacent to the DNA binding domain, was shown to greatly enhance SRF activity^[10]. Since its initial discovery in response to serum, SRF has also been shown to be activated by several other agents, including mitogens, cytokines, specific oncogenes and extracellular stimuli, such as antioxidants, UV light and microgravity, to name a few^[7].

FUNCTIONS OF SRF

SRF is a master regulator of many cellular activities including cell growth and differentiation, cell migration, and apoptosis. To date, approximately 300 human genes have been estimated to contain an SRE element and be activated by SRF, accounting for 1% of our entire genome^[3,4]. Early transgenic data provided important clues to some of the biological functions of SRF, best elucidated through its role in the myocardium, which is of mesodermal origin, and to the different optimal expression requirements during embryogenesis and adulthood^[7]. More specifically, mice with complete SRF knockout (*srf*^{-/-}) failed to develop the mesoderm and died in the uterus between E8.5 and E12.5^[11], indicating that SRF is required for early embryonic development. For this reason, we generated a mouse model with overexpression of a dominant mutant SRF in cardiac-specific tissue and found that SRF is required for myofiber generation as the transgenic mice died within the first week after birth due to heart dysfunction^[12]. For comparison, we also developed a mouse model with overexpression of functional SRF in the heart and demonstrated that too much SRF can cause hypertrophic cardiomyopathy as the mice died of heart failure within 6 mo^[13]. From these initial studies, SRF emerged as a key factor in muscle development and maintenance. In addition, modulation of SRF expression levels seems to play an important role in its different functions, where high expression levels of SRF are required for proper embryonic development, while lower levels may be more beneficial in adulthood^[7].

IMPLICATIONS IN GI

Even though SRF had been studied extensively in other tissues since its discovery, its role in the GI system was not examined for at least another decade. The earliest record that can be found was in 1997, and this study showed that SRF binding activity is elevated in the liver of Long-Evans Cinnamon rats (animal model of Wilson's disease) compared to Wistar rats^[14]. In addition, several other studies used GI-derived cell lines purely as tools to investigate the molecular properties of SRF^[15-17]. However, the role of SRF in the GI system was not studied directly until eight years ago, when our group found that SRF is not only expressed in smooth muscle structures, such as muscularis mucosa and muscularis propria, which are of mesoderm origin, but it is also found at intermediate expression levels in the mucosal epithelium, which is of endoderm origin^[5]. Since then, work from our group and others has provided important information about the role of SRF in both normal and pathological processes in the digestive system (Table 1).

Esophagus

Esophageal ulcers occur with a great geographical variation, from 5%-10% in the United States to approximately 80% in some Iranian regions. Its causes are also different with locations. While gastroesophageal reflux is its main cause in

Table 1 Identified roles of SRF in the GI tract

GI system	Process involved	Molecules associated	GI disorder associated
Esophagus	Myofibroblast differentiation ^[19]	TGF β , ILK	Ulcer
Stomach	Angiogenesis ^[20]	VEGF, Rho-actin, MEK-ERK	Ulcer
Stomach	Re-epithelialization, muscular structure restoration ^[6]	Actin, immediate-early genes	Ulcer
Stomach	<i>H. pylori</i> activates SRF ^[21,22]	CagA, villin	Intestinal metaplasia
Intestine	Smooth muscle contraction ^[23,24]	Smooth muscle actin, smooth muscle myosin, smoothelin, F/G actin	Intestinal obstruction, CIPO
Colon	Alternative splicing, cell survival ^[26]	SRF Δ 5, K-ras	Colon cancer
Liver	Cell cycle; hepatocyte proliferation/survival ^[29,30]	IGF-1	Liver injury
Liver	Cell proliferation, cell cycle, apoptosis ^[33]	E2F1	Hepatocellular carcinoma
Liver	Cell invasion ^[31]	E-cadherin, β -catenin	Liver metastasis
Pancreas	Cell proliferation ^[32]	Pro-inflammatory cytokines	Pancreatitis

SRF: Serum response factor; GI: Gastrointestinal; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor; MEK: Mitogen-activated protein kinase kinase; ERK: Extracellular regulated kinase; *H. pylori*: *Helicobacter pylori*; IGF: Insulin-like growth factors; CIPO: Chronic intestinal pseudo-obstruction.

the United States, in Europe it is alcohol consumption and in the Middle East it is the diet^[18]. Healing of esophageal ulcers proceeds *via* a series of overlapping events^[19], and among them myofibroblasts make a significant contribution to the wound closure. Our study^[20] showed that when the connective tissue has been damaged and denuded of its epithelium during gastrointestinal ulceration, fibroblasts next to the ulcer area are activated to become myofibroblasts and participate in restoration of new epithelial continuity and extracellular matrix. Over-expression of SRF promotes myofibroblast differentiation both *in vitro* and *in vivo*, and knockdown of SRF was sufficient to prevent TGF β -induced myofibroblast differentiation.

Stomach

While there are nearly 50 thousand publications dealing with stomach ulcers, we are the only researchers to have investigated the role of SRF in this common gastric disorder. SRF is a master regulator of cytoskeleton dynamics and cell motility. We showed that injury-activated SRF is critical to gastric ulcer healing, as local knockdown of SRF severely impairs angiogenesis^[21], an essential process for any wound healing. Without SRF, VEGF, the most powerful activator of angiogenesis, loses its power. Since angiogenesis is a key step in tumor progression by providing growing tumors with oxygen and nutrient supplies through generation of new blood vessels, these findings may have potentially important therapeutic implications for blocking cancer progression. We also demonstrated^[6] that over-expression of SRF in gastric epithelial cells or in smooth muscle cells (*in vitro*) as well as in gastric tissue (*in vivo*) can promote cell proliferation/migration, and thereby promotes re-epithelialization and restoration of smooth muscle structures damaged by ulcers. These findings show great potential for therapeutic applications of SRF.

While the normal processes of angiogenesis and wound healing have been indirectly associated with promoting cancer when inappropriately activated, therefore making SRF a potential oncogenic factor through its regulation of these processes and a promising target for cancer therapy as elucidated before, more direct evidence that SRF can indeed promote cancer progression has come

from different sources. First, two different groups linked SRF to *Helicobacter pylori* (*H. pylori*), a gram-negative bacterium that colonizes the human gastric mucosa, resulting in stomach disorders such as chronic gastritis, peptic ulcers and gastric adenocarcinoma. Of the two *H. pylori* strains, the type one strain contains the cag pathogenicity island (PAI), which confers greater virulence compared to the type two strain lacking PAI. Hirata *et al.*^[22] showed that transfection of the *CagA* gene into gastric epithelial cells greatly increases *in vitro* binding activity of SRF to SRE. Up to that point, CagA protein had only been linked to cellular cytoskeletal rearrangements, after activation through tyrosine phosphorylation. Therefore, aside from linking SRE and SRF to *H. pylori* pathogenesis, their findings are important for understanding *H. pylori* infection mechanisms by identifying a novel, phospho-tyrosine-independent, mode of action of CagA protein. Rieder and co-workers later built on the story by identifying villin as a new target of SRF and showing that SRF mediates *Helicobacter*-induced intestinal metaplasia in the stomach through villin^[23]. Intestinal metaplasia is a premalignant precursor lesion to several organs of the GI tract, including stomach, gall bladder and pancreas, and it is defined by the presence of intestine-like cells expressing enterocyte-specific markers, such as villin.

Intestine

The importance of SRF in the GI tract was further strengthened by the work from Angstenberger and collaborators on smooth muscle contraction^[24], which is a key feature of proper GI function. They developed an inducible mouse model where SRF was conditionally knocked out only in the smooth muscle cells of adult mice. The mutant mice developed symptoms of ileus paralyticus due to impaired contraction of intestinal smooth muscle and died 2 wk after the induction. Through more detailed phenotypic and gene expression analysis of the same model system in collaboration with Feil, Mericskay and co-workers confirmed^[25] that SRF plays a central role in maintaining proper smooth muscle function and they provide an inducible mouse model that could have potential implications for studying chronic intestinal pseudo-obstruction

(CIPO). The mutant mice displayed cachexia and autopsy showed severe dilation of the intestinal tract associated with food stasis, indicating impairment of GI motility due to smooth muscle deficiency. Defects in GI contractile function can lead to a variety of different disorders, from common and relatively benign, to more rare but potentially life-threatening. CIPO falls in the latter category, sharing similarities with chronic heart failure in the way that the “intestinal pump” is no longer able to effectively maintain tone and coordinate transit of intestinal contents through the luminal cavity, resulting in intestinal pseudo-obstruction^[26]. Several different mechanisms have been associated with CIPO, with both genetic and environmental causes, surely making CIPO a multifactorial condition. Nonetheless, these two studies clearly show that SRF plays a central role in proper smooth muscle contraction and that it could be an important model system to shed new light on CIPO. In their editorial commentary, De Giorgio *et al.*^[26] propose three different models by which SRF ablation could affect intestinal contractility: “(1) loss of smooth muscle cell (SMC) contractile phenotype due to an impairment of the contractile apparatus; (2) degeneration of SMCs with synthetic phenotype; and (3) derangements of pathways (including neuronal ones) implicated in smooth muscle contraction”^[26]. Even though results from Angstenberger and Merickskay made it possible to define these models of potential SRF involvement in CIPO, there is definitely room for additional work, especially in regard to the latter model, which is only briefly touched upon by Merickskay and co-workers.

Colon

As we mentioned earlier, SRF can be expressed in different isoforms in a tissue-specific manner due to alternative splicing of mRNA. Patten and co-workers^[27] found that the predominant SRF isoform expressed in colon cancer cell lines derived from poorly differentiated tumors (WiDr, HCT116, LoVo, and SW480) is SRF Δ 5, the dominant negative isoform lacking the transactivation domain (Figure 1). SRF Δ 5 is normally expressed at high levels in terminally differentiated tissues, such as brain, heart, skeletal muscle, testes and liver. However, aberrant elevated expression of SRF Δ 5 in other tissues has been associated with medical conditions. For instance, while normal lungs express very low levels of SRF Δ 5, hypoplastic lungs, in which stretching is compromised, express elevated levels of this isoform^[28]. Similarly, over-expression of another isoform (SRF Δ 4,5), which was shown to inhibit transcription of SRF-dependent cardiac muscle genes, was detected in failing hearts^[29]. Patten and co-workers also showed that stable expression of SRF Δ 5 in rat intestinal epithelial cells (IEC-6) significantly increased cell survival rates, possibly by preventing apoptosis, as cell proliferation was improved only after day 11 and mRNA levels of pro-apoptotic caspase 3 and Fas were significantly reduced.

Liver

It is known that the liver has a remarkable capacity to regenerate after injury. Latasa *et al.*^[30] found that SRF and

its targeted immediate early genes are rapidly activated after partial hepatectomy in rodents. When they knocked down SRF in the liver, this regeneration capacity was severely damaged. Following up on this idea, Sun and co-workers showed that liver-specific SRF knockout in mice led to a lower survival rate, where surviving animals were generally smaller with smaller and poorly functioning livers^[31]. Through gene array analysis of SRF deficient liver fragments, they also showed that loss of SRF prevents activation of a wide array of genes, particularly those involved in IGF-1-mediated cell cycle control, consistent with impaired normal growth, as well as several genes specific to hepatocyte function, suggesting that adequate amounts of SRF are indispensable for proper liver development and function. These findings highlight the different expression requirements for SRF in tissue development and proper function/maintenance, stressing the importance of optimal SRF expression. While cell culture and animal models on the mechanistic action of SRF are quite informative, correlation with cancer progression in patients is often determined based on differential expression between normal and tumor tissue, which implies that up- or down-regulation of a particular gene (or aberrant expression of a different variant of the gene) confers more tumorigenic potential to the cell and is therefore maintained. In this respect, Choi *et al.*^[32] recently reported that nuclear SRF staining, which was not detected in normal colon tissue, was found in 37% of primary colon cancers and 60% of metastatic liver cancer. A similar trend was observed with loss of E-cadherin expression (14% and 33%, respectively), while nuclear expression of β -catenin was significantly higher in primary tumors (56%) compared to normal tissue but did not change much in metastatic tumors. Loss of E-cadherin expression and translocation of β -catenin from the membrane to the nucleus are fundamental steps in disruption of epithelial cell junctions and acquisition of more migratory potential, which are at the basis of tumor metastasis. Therefore, to follow up on these observations, Choi and co-workers showed that over-expression of SRF in colorectal carcinoma cells enhanced cell motility and invasiveness, paralleled by loss of E-cadherin protein expression and increase in non-phosphorylated (nuclear) β -catenin expression, suggesting that SRF promotes liver metastasis through its action on membrane E-cadherin and β -catenin^[32]. The oncogenic potential of SRF over-expression in the liver was further confirmed a few weeks ago by Farra and co-workers. Building on recent advances in the field mentioned above, they decided to test the effectiveness of SRF depletion in highly and poorly differentiated hepatocellular carcinoma (HCC) cell lines^[33]. Their studies, which highlight differences in response to SRF depletion among different grades, also support a therapeutic role for SRF depletion against HCC, for which there are currently no effective treatment options^[33].

Pancreas

The importance of SRF to the early phase of liver regeneration is well established by the studies above, however, they also noticed that the liver without SRF can still

Table 2 Tools and models available to study SRF functions in GI

Tool	Purpose	Model
SRF in pcDNA3.1, His ^[6,21]	SRF over-expression	Gene therapy
SRF antisense sequence ^[21,33]	SRF down-regulation (siRNA)	Gene depletion
Srf Flex1 mice ^[35]	Conditional <i>in vivo</i> SRF deletion	Gene depletion
Srf loxP mice ^[30]	Conditional <i>in vivo</i> SRF deletion	Gene depletion
CreER T2 mice ^[36]	SMS tissue expression	CIPO
AlfpCre mice ^[31]	Hepatocyte tissue expression	Liver function
K5-Cre mice ^[37]	Squamous epithelial expression	Esophagus, foregut
Fabp/Cre mice ^[38]	Conditional gut tissue expression	Small/large intestine
<i>H. pylori</i> ^[23]	<i>H. pylori</i> infection in human cell lines (<i>in vitro</i>) or mice (<i>in vivo</i>)	<i>H. pylori</i> gastric diseases

develop. A similar situation was also observed in the pancreas. Miralles and co-workers^[34] found that mice with conditional inactivation of SRF in the pancreas had normal development of both the exocrine and endocrine pancreas. However, after weaning, these mice developed profound morphological alterations of the exocrine pancreas, which were reminiscent of severe pancreatitis. In these mice, massive acinar injury and pro-inflammatory cytokines release led to complete destruction of the exocrine pancreas and its replacement by adipose tissue.

SRF-related tools and models

Over the last decade, work on SRF in GI tissues has been very productive not only in establishing that SRF plays very important roles in both normal and pathological processes, but also in generating good *in vivo* model systems and validated tools to further study the role of SRF in both normal development and function as well as in related pathologies of the GI tract. Here we provide a detailed list of SRF-related models and tools (Table 2), which will be very useful for further exploration of the role of SRF in the GI tract. These include His-tagged SRF cDNA in the pcDNA3.1 mammalian expression vector under the control of the cytomegalovirus (CMV) promoter^[6,21] for SRF over-expression in cell culture and gene therapy *in vivo*; validated antisense SRF oligonucleotide sequences to knock down SRF protein expression^[21,33]. Two different conditional SRF knockout mice^[30,35], are also available to generate temporally and spatially controlled SRF deletion in any desired tissue through the use of tissue-specific Cre mice. Currently, these have been combined with SMS^[36]- and hepatocyte^[31]-specific Cre mice to generate the CIPO model^[24] and the liver model^[30] of SRF, respectively. However, they hold unlimited potential for selectively knocking out SRF in any desired tissue or subpopulation of the GI tract to further study the role of SRF in GI. For instance, crossing either the SRF knockout line to the previously described K5-Cre transgenic mice^[37] would allow SRF deletion in the basal cell layers of various squamous epithelial cells, including esophagus and foregut. Moreover, the Gordon group also generated two different Cre model systems (Fabp), which allow for intestinal-specific deletion, which could also be temporally controlled in a doxycycline inducible manner by combining Fabp-rtTA and tetO-Cre with the desired gene knockout^[38].

FUTURE DIRECTIONS IN GI

Results summarized here clearly show that SRF is an important factor in mediating both normal and pathological conditions in the GI tract and that different optimal expression levels are associated with its various functions, while deviations from those levels can result in more or less severe pathological conditions. The flip side of that is that SRF could also lend itself to favorable manipulation, if we only know what it is. While providing initial clues and identifying several factors involved in SRF-mediated functions (Table 1), the findings above still leave the door wide open for additional exciting work in these areas of research, with particular focus on the finer details of SRF signaling in the individual processes, which would also help us understand how and when SRF could be a good therapeutic target.

Role of SRF in gastrointestinal ulcers

For instance, we show that SRF is critical for mediating the wound healing process in both gastric^[6] and esophageal^[21] ulcers, primarily through its role in VEGF-induced angiogenesis in a Rho A/actin- and ERK pathway-dependent manner^[21]. However, while both Rho A and ERK have been linked to SRF induction^[6], little is known about how they may interact with each other, and more studies along those lines would be extremely helpful in defining the role of SRF in this process and its potential as a therapeutic agent.

Role of SRF in gastrointestinal motility disorders

Similarly, preliminary work by Angstenberger and Merickskay established a very useful model for studying CIPO and trying to find possible treatment options for this very serious condition. Insights for new avenues into this area of research can be found in the three models proposed by de Giorgio^[26]. In addition, given the emerging central role of SRF in the contractile function of the intestine, findings in this area of research may also be useful for less severe but more common dysfunctions of the intestine, with wider applications.

Role of SRF in *H. pylori* and related pathologies

H. pylori infection appears to be another major new area of research for SRF function in GI pathogenesis, which definitely deserves more attention. Here too, Hirata^[22] and

Rieder^[23] outline initial important connections between SRF and *H. pylori* infection and premalignant transformation, however, more work is needed to fill in the gaps. For instance, SRF activation appears to be involved in a new mode of CagA-mediated infection, which, given its more virulent nature, deserves more attention. In addition, work from Rieder and co-workers provide a preliminary molecular framework to further study the signaling components involved in SRF-mediated metaplasia^[23]. A better understanding of the signaling cascades downstream and upstream of SRF in this process would be very useful for both diagnosis and more informed development of therapeutic options. For this purpose, the different *H. pylori* strains optimized for either *in vivo* mouse studies or human cell culture studies^[23] (Table 2) will be particularly useful.

Role of SRF in gastrointestinal cancers

Overall, several lines of evidence seem to point to a positive role of SRF in various GI cancers, such as its role in driving angiogenesis^[21], in mediating *H. pylori* infection^[22] and metaplasia^[23], which is strongly associated with gastric cancer, and in promoting cell proliferation in HCC^[33] and liver metastasis by weakening cell adhesion^[32]. Findings by Patten and co-workers that an SRF variant is also over-expressed in colon cancer in response to a very prevalent colon cancer mutation^[27] further highlight the potential importance of SRF in cancer. However, the fact that the variant is a known dominant negative form of SRF makes its role in cancer progression not as straight forward. This is particularly true given findings by Choi and co-workers, which clearly correlate SRF over-expression with colon cancer progression^[32]. However, since Patten and co-workers never examined actual tumor tissues and, while SRF Δ 5 expression was indeed elevated in response to K-ras activation, full-length SRF was also elevated and generally showed much stronger expression than SRF Δ 5 itself, more work may be required to better understand the actual prevalence of this variant in colon cancer and, most importantly, its role in cancer progression. More solid evidence to support the conclusions by Patten and co-workers could have important implications for diagnosis, identifying the SRF Δ 5 variant as a possible marker for colon cancer. Since it is much easier to routinely collect small biopsies from colon tissue than from some other tissues, this could potentially be an effective way for better risk assessment.

Role of SRF in normal and abnormal liver function

Recent findings reported here suggest an interesting role for SRF in liver function. While Sun and co-workers show that not enough SRF is bad for proper liver function and regeneration after injury^[31], studies from Ferrà and co-workers raise hopes for effective HCC therapy through SRF depletion^[33]. Clearly, this is just the tip of the iceberg and more data is needed in this area of research, where SRF is once again taking a leading role.

CONCLUSION

The last decade has been very prolific in shifting the focus

of SRF from its role in the myocardium to a central role in the gastrointestinal tract as well. As summarized here, SRF is critical for proper development and function of most GI tissues in what appears to be a dose-dependent manner, as changes in its expression pattern have been implicated in various GI pathologies from intestinal motility disorders to cancer. In addition, both SRF gene therapy and SRF antisense expression to either elevate or inhibit normal SRF expression have been shown to hold great promise as potential therapeutic agents to either promote ulcer healing or inhibit cancer-related angiogenesis, respectively. Therefore, while great advances have already been made in this field, more in depth studies are warranted to fully understand its various roles and optimal expression requirements in all these processes, with particular attention to the potential therapeutic efficacy of SRF gene therapy and antisense expression where modulation of SRF expression may prove beneficial. For instance, SRF gene therapy could promote wound healing and liver regeneration, while its antisense expression could be more beneficial in slowing down cancer progression, where its effect on VEGF-mediated angiogenesis may play a central role in its dual applications.

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