Serum response factor: Look into the gut

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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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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
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 SRF element and be activated by SRF, accounting for 1% of our entire genome. 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. More specifically, mice with complete SRF knockout (srfrf-/-) failed to develop the mesoderm and died in the uterus between E8.5 and E12.5, 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. 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. 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.

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. In addition, several other studies used GI-derived cell lines purely as tools to investigate the molecular properties of SRF. 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. 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 gastroesophageal reflux disease, other factors may play a role in specific populations. Increased expression of SRF was observed in the esophageal mucosa of patients with gastroesophageal reflux disease compared to control subjects. Additionally, SRF expression was increased in the esophageal mucosa of patients with eosinophilic esophagitis compared to healthy controls. These findings suggest that SRF may play a role in the pathogenesis of esophageal disorders, particularly gastroesophageal reflux disease and eosinophilic esophagitis.
the United States, in Europe it is alcohol consumption and in the Middle East it is the diet[24]. Healing of esophageal ulcers proceeds via a series of overlapping events[19,20], 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 demuced 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 TGFβ-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[9] 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[25] 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 SRF and SRE 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.

**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[19] 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.

### Table 1 Identified roles of SRF in the GI tract

| GI system | Process involved | Molecules associated | GI disorder associated |
|-----------|-----------------|---------------------|------------------------|
| Esophagus | Myofibroblast differentiation[20] | TGFβ, ILK | Ulcer |
| Stomach  | Angiogenesis[21] | VEGF, Rho-actin, MEK-ERK | Ulcer |
| Stomach  | Re-epithelialization, muscular structure restoration[21] | Actin, immediate-early genes | Ulcer |
| Stomach  | H pylori activates SRF[22] | CagA, villin | Intestinal metastasis |
| Intestine| Smooth muscle contraction[23,24] | Smooth muscle actin, smooth muscle myosin, smoothelin, F/G actin | Intestinal obstruction, CIPO |
| Colon    | Alternative splicing, cell survival[25] | SRFΔ5, K-ras | Colon cancer |
| Liver    | Cell cycle; hepatocyte proliferation/survival[26,27] | IGF-1 | Liver injury |
| Liver    | Cell proliferation, cell cycle, apoptosis[27] | E2F1 | Hepatocellular carcinoma |
| Liver    | Cell invasion[28] | E-cadherin, β-catenin | Liver metastasis |
| Pancreas | Cell proliferation[29] | 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 factor; CIPO: Chronic intestinal pseudo-obstruction.
Regenerate after injury. Latasa

It is known that the liver has a remarkable capacity to regenerate after injury. Latasa et al. 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. 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. 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 translocation of β-catenin. The oncogenic potential of SRF overexpression 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. 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.

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 found that the predominant SRF isoform expressed in colon cancer cell lines derived from poorly differentiated tumors (WiDr, HCT116, LoVo, and SW480) is SRFΔ5, the dominant negative isoform lacking the transactivation domain (Figure 1). SRFΔ5 is normally expressed at high levels in terminally differentiated tissues, such as brain, heart, skeletal muscle, testes and liver. However, aberrant elevated expression of SRFΔ5 in other tissues has been associated with medical conditions. For instance, while normal lungs express very low levels of SRFΔ5, hypoplastic lungs, in which stretching is compromised, express elevated levels of this isoform. Similarly, over-expression of another isoform (SRFΔ4,5), which was shown to inhibit transcription of SRF-dependent cardiac muscle genes, was detected in failing hearts.

Patten and co-workers also showed that stable cardiac muscle genes, was detected in failing hearts. For instance, while normal lungs express very low levels of SRFΔ5, hypoplastic lungs, in which stretching is compromised, express elevated levels of this isoform. Similarly, over-expression of another isoform (SRFΔ4,5), which was shown to inhibit transcription of SRF-dependent cardiac muscle genes, was detected in failing hearts. For instance, while normal lungs express very low levels of SRFΔ5, hypoplastic lungs, in which stretching is compromised, express elevated levels of this isoform. Similarly, over-expression of another isoform (SRFΔ4,5), which was shown to inhibit transcription of SRF-dependent cardiac muscle genes, was detected in failing hearts.

Liver

It is known that the liver has a remarkable capacity to regenerate after injury. Latasa et al. found that SRF and
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 pCDA3.1 mammalian expression vector under the control of the cytomegalovirus (CMV) promoter[^31,32] 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[^34]-specific Cre mice to generate the CIPO model[^34] and the liver model[^35] 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. In fact, crossing either the SRF knockout line to the previously described K5-Cre transgenic mice[^31] 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].

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

| Tool | Purpose | Model |
|------|---------|-------|
| SRF in pcDNA3.1, His[^31] | SRF over-expression | Gene therapy |
| SRF antisense sequence[^23,28] | SRF down-regulation (siRNA) | Gene depletion |
| Srf Flex1 mice[^28] | Conditional in vivo SRF deletion | Gene depletion |
| Srf loxP mice[^24] | Conditional in vivo SRF deletion | CIPO |
| CreER T2 mice[^26] | SMS tissue expression | Liver function |
| AlfpCre mice[^20] | Hepatocyte tissue expression | Esophagus, foregut |
| K5-Cre mice[^27] | Squamous epithelial gene expression | Small/large intestine |
| Fabp/Cre mice[^29] | Conditional gut tissue expression | |
| H. pylori Cre mice[^30] | H. pylori infection in human cell lines (in vitro) or mice (in vivo) | H. pylori gastric diseases |

### 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[^8] and esophageal[^21] ulcers, primarily through its role in VEGF-induced angiogenesis in a Rho A/actin- and ERK pathway-dependent manner[^21,31]. However, while both Rho A and ERK have been linked to SRF induction[^9], 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 Merki-skay 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[^30]. 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

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[^10]: Modak C et al. (2010) *World Journal of Gastroenterology*. 16: 2199–2210.
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, in mediating H. pylori infection, and metastasis, which is strongly associated with gastric cancer, and in promoting cell proliferation in HCC and liver metastasis by weakening cell adhesion. 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 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 straightforward. This is particularly true given findings by Choi and co-workers, which clearly correlate SRF over-expression with colon cancer progression. However, since Patten and co-workers never examined actual tumor tissues and, while SRFΔ5 expression was indeed elevated in response to K-ras activation, full-length SRF was also elevated and generally showed much stronger expression than SRFΔ5 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 SRFΔ5 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 of SRF in liver function. While Sun and co-workers show much stronger expression than SRFΔ5 itself, more work may be required to better understand the actual prevalence of this variant in colon cancer and, most importantly, its 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.

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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