

## Scatter Factor and the *c-Met* Receptor: A Paradigm for Mesenchymal/Epithelial Interaction

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**Abstract.** Epithelia and mesenchyme interact during various physiologic and pathologic processes. Scatter factor is a mesenchyme-derived cytokine that stimulates motility, proliferation, and morphogenesis of epithelia. Recent studies suggest that scatter factor and

its receptor (*c-met*) mediate mesenchyme/epithelia signaling and even interconversion. In this mini-review, we will discuss how scatter factor and *c-met* may mediate interactions between mesenchyme and epithelia during embryogenesis, organ repair, and neoplasia.

**E**PITHELIA and mesenchyme are morphologically and functionally distinct tissue types. Epithelial cells are usually immobile, form ordered structures (e.g., ducts, skin, alveoli), and perform specialized functions. In contrast, mesenchymal cells are more mobile, form loose aggregations within the extracellular matrices (ECMs)<sup>1</sup> of most organs, and usually perform supportive functions. Epithelia and mesenchyme interact by direct cell contact and by secreted proteins that convey a signal from one cell type to the other. One such protein is scatter factor (SF) (42). SF appears to play major roles in normal development, regeneration, and carcinogenesis. The emerging SF story raises intriguing questions concerning the parallels between these processes.

### Scatter Factor and *c-Met*

SF was identified as a mesenchymal cell-derived cytokine that dissociates ("scatters") cohesive colonies of epithelium into individual cells (42). Hepatocyte growth factor (HGF) was discovered as a mitogen for adult hepatocytes (17, 21). Later studies revealed that SF and HGF are identical (1, 47). SF is a heparin-binding glycoprotein consisting of a 60-kD  $\alpha$ -chain and 30-kD  $\beta$ -chain linked by disulfide bonds (6, 28).

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1. **Abbreviations used in this paper:** ECM, extracellular matrix; HGF, hepatocyte growth factor; HSPG, heparan sulfate proteoglycans; KS, Kaposi's sarcoma; PI3K, phosphatidylinositol-3'-kinase; SF, scatter factor; SH2, src-homology region 2; uPA, urokinase.

SF belongs to the family of kringle proteins (21), characterized by triple disulfide loop structures (kringles) that mediate protein/protein and protein/cell interactions. Although SF exhibits 38% sequence identity to the proenzyme plasminogen, it lacks protease activity due to two amino acid substitutions at the catalytic center of the  $\beta$ -chain (21). SF is synthesized as a 728-amino acid precursor (preproSF) and is cleaved intracellularly to its secreted single-chain form (proSF), which is inactive. Extracellular cleavage of proSF at <sup>494</sup>arg-<sup>495</sup>val, yields active two-chain SF (21). One enzyme capable of activating proSF is HGF activator, a serine protease related to coagulation factor XII (16). This enzyme is secreted in zymogen form, and may be activated by a proteolytic cascade triggered by tissue injury (18).

The SF receptor is the *c-met* proto-oncogene product (3), a transmembrane tyrosine kinase that is expressed predominantly on epithelial cells (8). The *c-met* receptor is a 190-kD glycoprotein consisting of a 145-kD membrane-spanning  $\beta$ -chain and a 50-kD  $\alpha$ -chain. The extracellular binding, membrane, and tyrosine kinase domains are located on the  $\beta$ -chain. Two receptor tyrosine kinases closely related to *c-met*, *c-sea*, and *Ron*, have been described (10, 27), but ligands for these receptors have not been identified. Macrophage-stimulating protein, a serum protein that induces the motility and phagocytic activity of macrophages (51), is structurally related to SF and may be the ligand for one of these receptors.

### Biologic Activities of SF

SF dissociates sheets of epithelia into individual cells, which often exhibit characteristics of mesenchymal cells, such as

spindle-shape and increased motility. SF also stimulates directed cell migration and invasion (1, 28, 30, 31, 42). SF up-regulates gene and protein expression of urokinase (uPA) and uPA receptor (9, 24, 31). The net effect is to put more uPA on the cell surface, where it may mediate focal degradation of ECM to clear a path for invading cells. Thus, SF may "switch on" a program of cell activities for invasion. SF is mitogenic for various normal cell types, including mammary, epidermal, and bronchial epithelium (33). SF is also a potent morphogen. In the absence of SF, kidney epithelial cells incubated in collagen type I gels aggregate into cysts. In the presence of SF, these cells form a network of branching tubules that exhibit correct apical-basolateral polarity (19, 35). Similarly, SF induces mammary epithelial cells to form duct-like structures (45). The morphogenic activity of SF may be modulated by the extracellular environment and by cell-specific programs of differentiation (see below).

### Regulation of SF Expression and Activity

In vitro, the major SF-producing cell types are mesenchymal cells, including fibroblasts, vascular smooth muscle cells, glial cells, macrophages, and activated T lymphocytes (20, 28, 32, 42). SF production by some human fibroblast strains is stimulated by IL-1 and TNF $\alpha$  (43), cytokines that up-regulate the inflammatory response. On the other hand, TGF $\beta$ , which generally down-regulates the inflammatory response, inhibits SF production (7). Since IL-1, TNF $\alpha$ , and TGF $\beta$  each exhibit a wide array of activities, the existence of a more specific class of SF regulators seems likely. Recent studies indicate that mammary carcinoma cells, which do not produce SF, produce soluble factors distinct from IL-1 and TNF that stimulate SF gene and protein expression by fibroblasts (31, 32, 38). At least two factors are produced, a high molecular weight (>30 kD) heat-labile protein and a low molecular weight (<30 kD) heat-stable protein. A 12-kD SF-inducing protein with properties similar to the <30-kD factor secreted by breast carcinoma cells was recently purified and characterized (32).

Direct co-culture of fibroblasts and epithelia leads to down-regulation of SF gene expression by the fibroblasts (11, 38). This phenomenon may reflect a homeostatic mechanism to allow the stable coexistence of epithelia and mesenchyme in adult tissues. SF production is also down-regulated by culturing fibroblasts and carcinoma cells in a Millipore well chamber so that there is no direct cell contact (38). Thus, a soluble inhibitor may be released as a result of interaction between the two cell types. The promoter region of the murine SF gene is very large and complex (14). This region contains IL-6 response elements, binding sites for NF-IL6 (consistent with the sensitivity of fibroblasts to IL-1 and TNF), a TGF $\beta$  inhibitory element, a cAMP response element, estrogen response elements, cell type-specific transcription factor binding sites, and multiple positive and negative regulatory elements for which transcription factors have not been identified. The identification of SF regulators, their receptors, and the relevant transcription factors will undoubtedly enhance the understanding of mesenchyme/epithelia communication.

Some fibroblast lines produce a truncated form of SF consisting of the NH<sub>2</sub>-terminal region and the first two kringle domains (NK2) (4). NK2, which is generated by alternative mRNA splicing, binds to *c-met* receptor with high affinity

and blocks SF mitogenic activity. It is not known if NK2 can serve as a physiologic regulator of SF. An epithelial junction-promoting activity has been detected in medium from Nil8 hamster fibroblasts (41). This activity causes scattered colonies of mammary epithelia to revert to a cohesive morphology. A similar activity is found in extracts of mouse tissues that lack SF activity (31). These studies suggest the existence of active mechanisms for down-modulation of SF biologic action.

### *c-Met* Signal Transduction

Under different conditions, SF may direct cells toward motility, proliferation, or morphogenesis. These activities are not mutually exclusive. Branching morphogenesis in a collagen matrix involves motility, invasion, expression of proteases that mediate cell invasion (e.g., uPA), and tubule formation. Studies using chimeric receptors containing the extracellular and membrane domains of other ligands fused to the intracellular portion of *c-met* demonstrate that the *c-met* receptor tyrosine kinase can transduce multiple biologic functions (48). The activation of distinct pathways for motility, growth, and/or morphogenesis may be determined at the receptor level or more distally.

Specificity at the receptor level may be achieved by differential binding of phosphotyrosines of the activated receptor with cytoplasmic signaling proteins. These proteins recognize specific tyrosine-phosphorylated regions of a receptor via their *src*-homology region 2 (SH2) domains (13). The specificity of this interaction is determined, in part, by the three amino acids that immediately follow the receptor phosphotyrosines. A multifunctional site involving two YV(H/N)V motifs mediates the binding of *c-met* to phosphatidylinositol-3'-kinase (PI3K), protein tyrosine phosphatase 2, phospholipase C- $\gamma$ , pp60<sup>*c-src*</sup> and *grb2/hSos1* (25). Homologous sequences are found in *met*-related receptors, but not in EGF, PDGF, or other growth factor receptors (25). The binding of signaling proteins to this site may vary as a function of the binding affinity of specific SH2 domains, local concentration of signaling molecule, and level of *c-met* receptor phosphorylation. Although PI3K binds to the YV(H/N)V site, this site does not contain known consensus sequences for binding of COOH- or NH<sub>2</sub>-terminal SH2 domains of PI3K. *c-Met* contains four other potential phosphorylation sites, none of which contain known SH2 binding consensus sequences. By analogy, these sites may mediate binding to known or as yet undiscovered signaling proteins.

The ECM may play a major role in directing *c-met* signaling. SF-induced tubule formation by MDCK cells is facilitated by some ECM molecules (collagen I, laminin) and inhibited by others (heparan sulfate proteoglycans [HSPGs], collagen IV) (34). TGF $\beta$ , which is often found in basement membrane, inhibits branching morphogenesis. Morphogenesis is a vectorial process, and may depend upon the local concentrations of ECM proteins, SF, and other growth factors. Collagen I or laminin at the leading edge of a tubule may promote forward extension, while inhibitory molecules (e.g., collagen IV) may promote branching. These events may be modified by cell surface and ECM HSPGs, which bind SF and alter its bioavailability. The binding of ECM proteins to integrins is known to activate intracellular signaling events, including tyrosine phosphorylation (37). SF up-regulates adhesion of EMT6 mouse mammary tumor cells to

collagen I and laminin, but not to collagen IV or fibronectin (31). Thus, SF may induce expression of a particular set of integrins that allows the ECM to modulate intracellular signaling. Studies using pharmacologic agents that alter signal transduction suggest that the scattering and morphogenetic responses of MDCK cells are modulated by multiple phosphorylation pathways, including those involving protein kinases A and C (29, 35). *c-Met* itself contains a consensus phosphorylation sequence of PKC, and *c-met* activation is inhibited by phosphorylation of this site (5). Thus, the ECM may regulate *c-met* signaling by inducing phosphorylation of sites on *c-met* or other signalling molecules (Fig. 1).

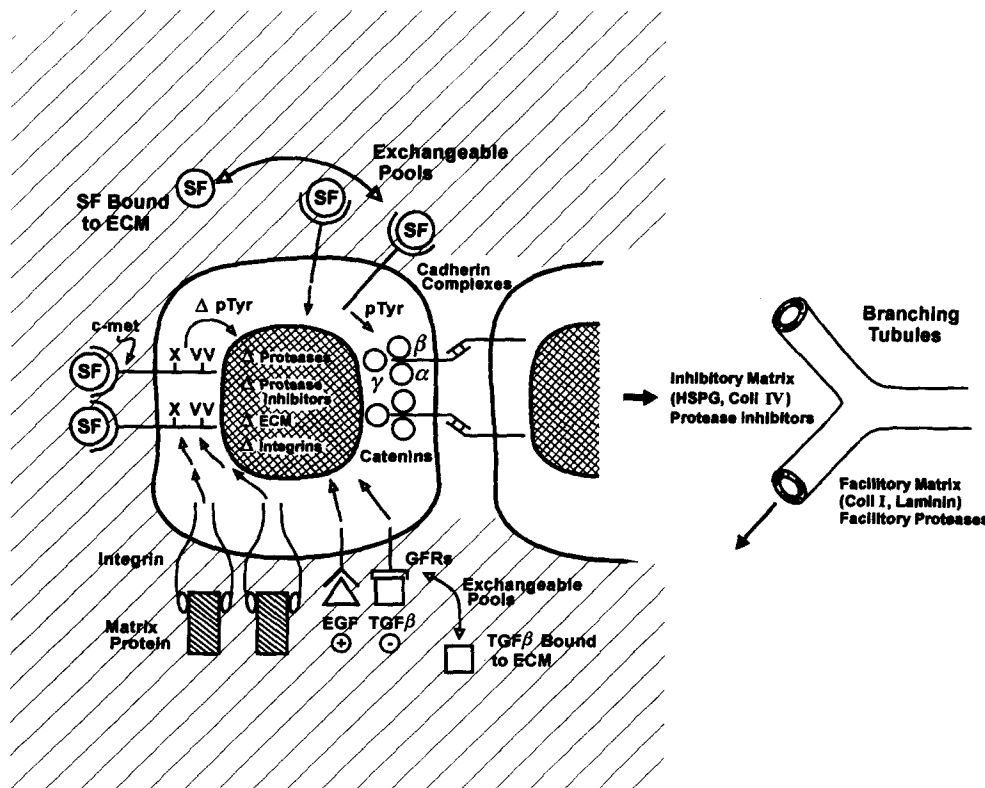
The ability of SF to dissociate epithelia has focused attention on its effects on adhesion molecules, including cadherins. Cadherin function is modulated by catenins and other proteins that bind to the cytoplasmic domain of cadherin molecules and link them to the cytoskeleton (23). SF may inhibit the function of cadherins by altering the phosphorylation of cadherin-associated proteins. SF induces tyrosine phosphorylation of  $\beta$ -catenin, which may down-regulate cadherin-mediated cell adhesion (39). Specific *src* family tyrosine kinases are known to be localized at adherens junctions (46), raising the possibility that scattering is due, in part, to phosphorylation of junctional proteins by the SF-activated *c-met* receptor. Cadherin adhesive function is impaired in carcinomas, especially, in poorly differentiated, highly invasive tumors (2). The biologic effects of SF may be influenced by the number, type, and quality of intercellular junctions. Thus, SF might promote dissociation and invasion in poorly differentiated tumors (see below), but might

induce glandular formation in well-differentiated tumors with intact adhesive mechanisms.

### SF/*c-Met* in Mesenchymal/Epithelial Interaction during Physiologic and Pathologic Processes

**Embryogenesis.** Epithelia/mesenchyme interconversion is an important theme in early embryogenesis. As described earlier, SF mediates conversion of sheets of epithelium into individual, fibroblast-like cells and, under other conditions, mediates organization of epithelial cells into ordered, tubular structures. When 3T3 mouse fibroblasts are transfected with human SF and *c-met* cDNAs and induced to express high levels of SF and *c-met* protein, these cells form duct-like structures, express cytokeratins, and form epithelial-like intercellular junctions (44). During mouse development, *c-met* mRNA is expressed in epithelial cells of various organs, while SF mRNA is expressed in mesenchymal cells in close proximity to these epithelial cells (40). In the developing kidney, SF and *c-met* are highly expressed at day 11.5, corresponding to the onset of tubulogenesis and branching morphogenesis (36). Moreover, an antiserum against SF inhibits kidney development in organ culture (36). Thus, the SF/*c-met* ligand-receptor pathway may transduce mesenchyme/epithelial signaling and conversion during embryogenesis. Misfunctioning of this pathway may contribute to cystic diseases of epithelia, such as polycystic kidney disease.

**Organ Regeneration.** SF has been studied as a potential organotropic factor for regeneration of injured liver and kidney (12, 15). When two-thirds of the rat liver is resected, the



**Figure 1.** Possible mechanism(s) of SF-induced morphogenesis. If *c-met* signaling occurs primarily through the multifunctional site (VV) (see text), then environmental context is likely to be critical in determining the cell response. In the model shown, morphogenesis is activated by SF/*c-met* only when specific matrix-integrin interactions occur. These interactions are presumed to modify the PTyr state of *c-met*, either at the VV site or at a different site (X), leading to coordinated changes in protease, protease inhibitor, ECM, and integrin expression. The *c-met* receptor also modifies cadherin-mediated intercellular adhesion through phosphorylation of  $\beta$ -catenin. Accessory growth factors may exert stimulatory (+) or inhibitory (-) influences on morphogenesis through their receptors (GFRs), by altering *c-met* signaling or by independent pathways. Cell/matrix interactions control

branching vs. forward extension of tubules (right half of figure), as described in the text. Additional modulation might occur through regulation of exchangeable pools of growth factors bound to ECM and to the cell surface.

remaining hepatocytes proliferate to restore the liver mass within 10 d. After resection, SF mRNA expression is up-regulated and peaks by 24 h, followed by a wave of hepatocyte DNA synthesis and cell division. High levels of SF appear in the blood  $\leq 6$  h after surgery, too early to be explained solely by synthesis in the liver. The early appearance of SF may be due to release of SF stored bound to heparin-like residues in the ECM and to synthesis of SF in distant uninjured organs (e.g., lung, kidney, spleen). While these studies implicate SF in organ regeneration, a definitive role for SF as an "instigator" rather than a "bystander" is not proven.

In situ hybridization studies suggest that the major SF-producing cells in the liver are mesenchymal cells, including Kupffer (macrophage-like) cells and sinusoidal endothelium (22). Following liver injury, pulmonary alveolar macrophages and endothelial cells are stimulated to produce SF (50). Mesenchyme/epithelia interactions contributing to liver regeneration might be of two types: (a) SF produced by local or distant mesenchymal cells induces proliferation of hepatocytes and biliary epithelium; and (b) SF inducers secreted by injured liver epithelium stimulate SF production by hepatic or distant mesenchymal cells. Although SF is produced at injured and distant sites, only epithelia of the injured organ are stimulated to proliferate. Mechanisms that prevent epithelial proliferation in uninjured organs are not well characterized, but could involve junction promoting proteins, as described above.

**Angiogenesis.** Recent studies indicate that SF is a powerful inducer of angiogenesis (9, 20), a process required for both embryogenesis and organ regeneration. Moreover, SF may contribute to the genesis of AIDS Kaposi's sarcoma (KS) (20), a cytokine-dependent neoplasm characterized by a major component of neovascularization. SF induces conversion of normal human endothelial cells to a KS tumor cell-like phenotype and functions as an autocrine growth factor for cultured KS tumor cells. Both SF and the *c-met* receptor are expressed by KS tumor cells and other cell types within KS lesions in vivo. Moreover, SF appears to be a major angiogenic and growth-stimulatory molecule present in conditioned medium from retrovirus-infected T lymphocytes, which is required for long-term cultivation of KS tumor cells.

**Neoplasia.** A role for SF as a mediator of neoplastic progression is suggested by the observations that: SF stimulates the motility and invasiveness of carcinoma cells (30, 31); SF induces angiogenesis (9), which is necessary for the growth and metastasis of solid tumors; and the SF receptor is encoded by a proto-oncogene (3). This role is further supported by several experimental and clinical studies. Mouse 3T3 cells induced to overexpress *c-met* become tumorigenic; and constitutive overexpression of both *c-met* and SF confers increased tumorigenicity via an autocrine loop (26). SF enhances the metastatic phenotype of mammary carcinoma cells in an in vivo murine model (31). SF is overexpressed in tumors, and a high level of SF in primary breast cancers is a strong, independent predictor of relapse and death (49). Overproduction of SF in tumors may be due to an abnormal mesenchymal/epithelial interaction in which tumor cells overexpress factors that induce SF production by stromal cells (31, 32, 38). The putative contributions of SF, *c-met*,

and SF inducers to tumor progression is a fertile area for future research.

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