



Review

The Role of Hepatocyte Growth Factor/*c-met* Interactions in the Immune System

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Abstract. Hepatocyte growth factor (HGF) is a pleiotropic cytokine with mitogenic, motogenic and morphogenic activity for mainly epithelial and endothelial target cells. All the different effects of HGF are mediated through its specific receptor *met*, a heterodimeric transmembrane tyrosine kinase. The broad activity of HGF and its impact on many physiologic and pathologic processes are reflected by *met* expression in a variety of organs and cell types. This paper discusses expression of HGF and *c-met* within the immune system and their interactions in the control of immune cell functions.

Key words: hepatocyte growth factor; *c-met*; immune system cell functions.

Hepatocyte Growth Factor – Structural and Functional Characteristics

In the early 1980's, hepatocyte growth factor (HGF) was detected as a hormone-like substance in the plasma of partially hepatectomized rats, based on its ability to stimulate mitogenesis in hepatocytes in primary culture^{16, 19}. Within a few years, however, it became quite clear that HGF's biological activities are not limited to stimulating DNA replication and cell growth, nor are they limited to a single cell type³⁵. Purification and characterization of HGF, including its cDNA, revealed that this factor is particularly large (~80 kDa in the unprocessed form). HGF is synthesized and secreted by stromal cells such as fibroblasts as a single-chained precursor that is biologically inert. It must be processed into a mature, active form by proteases, such as urokinase-type plasminogen activator or a factor XII-like

enzyme called HGF activator¹⁸. Culture supernatants of stromal cells contain biologically active HGF due to the presence of appropriate enzymes in fetal calf serum used to supplement tissue culture media. The mature form of HGF has two subunits, α and β , secured with a single interchain disulfide bond. The α chain is ~65 kDa, and the smaller β chain is ~35 kDa. Study of its amino acid sequence showed that HGF resembles factors of the clotting and fibrinolysis cascades, such as prothrombin and plasminogen, because it contains four kringle domains in the larger subunit and a modified, apparently non-functional, serine protease domain in the smaller subunit. HGF does not appear, however, to act as a pro- or anti-coagulant²⁰. Analysis of the HGF gene demonstrated that it is approximately 70 kb in size, resides on human chromosome 7 as a single copy, and consists of 18 exons and 17 introns. The major transcript encoding HGF is 6 kb in size, although

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naturally occurring variants of HGF have been identified which arise by alternative splicing of the HGF primary transcript. These variants are C-terminally truncated (i.e. they lack the entire β chain and half of the α chain), retain receptor-binding ability and, as shown by *in vitro* studies, have both agonistic and antagonistic effects on the full-length HGF molecule²⁴.

The Cellular Origins of HGF

Hepatocyte growth factor is produced by cells of mesenchymal origin in a number of organs³⁵. Stromal cells isolated from different primary (thymus, bone marrow) and secondary (tonsil, spleen, lymph node) lymphoid organs have been shown to constitutively secrete HGF *in vitro*^{25, 29, 30, 32}. It was shown that this secretion can be modulated by the addition of exogenous cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)- α and transforming growth factor β ²⁹. Direct stromal cell contact with activated T cells *in vitro* also results in increased HGF secretion. Detailed analysis showed that the enhanced HGF secretion was due to T cell membrane-associated IL-1 and CD40 ligand, suggesting the role of HGF in immune processes²⁵.

HGF Receptor

To stimulate a cell, HGF in its dimeric form binds to a specific cell-surface receptor identified as *met*⁵. *Met* was first cloned as an oncogene (called *tpo-met*) from a human osteosarcoma cell line in 1985, based on transformation assays. The product of the *met* protooncogene is a tyrosine kinase-containing, transmembrane protein which, like its ligand, possesses two subunits, α and β , that result from proteolysis of a single-chained molecule. The α subunit of *met* is ~50 kDa and is entirely extracellular, while the β subunit is larger (~145 kDa), spans the plasma membrane and harbors the tyrosine kinase in the intracellular portion^{12, 13}. All biological activities of HGF are mediated through *met*, and some of the signaling molecules down-stream of the HGF receptor have been identified⁹. Like other growth factors, HGF binds to cell-surface heparin sulphate proteoglycans that serve as low-affinity receptors and modulate the interaction between HGF and the *c-met* receptor^{22, 23}.

The unique structural features of HGF and *met* have led to their assignment as the prototypes of new growth factor and receptor families, respectively. Additional

members of these families are HGF-like protein (HLP), also known as macrophage-stimulating protein, and Ron. The HLP unique cell-surface receptor has recently been cloned and characterized. HLP and Ron not only resemble HGF and *met* structurally, they also exhibit similar biological activities on target cells¹¹.

Biological Activities of HGF

Clues to HGF and *met*'s list of biological activities and cellular targets mounted in the early 1990's. A research group who studied cell motility isolated a protein from fetal lung fibroblasts which they called scatter factor because it dispersed contiguous epithelial cells when added to cultures. Another group, meanwhile, isolated and cloned a factor having cytotoxic activity toward carcinoma and sarcoma cell lines *in vitro*. Comparison of the cDNA sequences of these other factors with that of HGF yielded nearly perfect matches and thus linked new biological activities to HGF³⁵.

Further studies into the functions of HGF and *met* proved that HGF induces tissue-specific morphogenic programs in several types of epithelial cells. Addition of HGF to kidney, mammary, lung and colon epithelial cells, and hepatocytes, cultured in three-dimensional gels, led them to the formation of tubules, ducts, alveoli, crypts, and cords, respectively^{3, 6}. Moreover, knock-out and knock-in studies in mice targeting the HGF and *met* genes showed that, without functional copies of these genes, the animals die *in utero* at day 15 of gestation with major defects in the placenta, liver and muscle³¹. Results from these studies and various experimental models of organ regeneration in combination with data from immuno- and *in situ* histochemical studies helped to demonstrate that HGF and *met* are critical mediators of epithelial-mesenchymal interactions and organ morphogenesis, particularly during embryogenesis. Also, the role has been partially explained for HGF and *met* in the formation and maintenance of some epithelialized organs, such as the intestine, liver, kidney, and lung. In other biological processes, such as muscle migration and growth, neuron outgrowth and regeneration, hematopoiesis, lymphocyte adhesion and migration, and angiogenesis, the role played by HGF and its specific receptor remains ill-defined.

HGF and the Immune System

It has now become clear that HGF, traditionally considered as an epithelial-specific growth factor, also acts as a regulator of immune cell functions.

Monocytes and macrophages

c-met expression becomes selectively induced and functionally active in monocytes. Analysis of the expressions of nearly 600 genes using cDNA expression array showed that the expression of 13% of genes, was changed when isolated monocytes were stimulated with HGF. The modulation of expression predominantly affected monocyte-related genes, especially those involved in cell motility. Accordingly, the expression of four chemokines (MIP-1b, MIP2-a, MCP-1 and IL-8) was stimulated. Other cytokines, such as IL-4, IL-1 β , M-CSF and GM-CSF, were also up-regulated, suggesting an important pro-inflammatory role for HGF stimulation of monocytes. In a functional experiment, recombinant HGF induced directional migration and cytokine secretion in human monocytes. Monocyte activation by endotoxin and IL-1 β resulted in up-regulation of the HGF-receptor expression and in the induction of cell-associated pro-HGF convertase activity, thus enhancing responsiveness to the factor. Secretion of biologically active HGF by activated monocytes was also detected. This implies that monocyte function can be modulated by HGF in a paracrine/autocrine manner and provides a new link between stromal environment and mononuclear phagocytes^{2, 10, 23}.

Dendritic cells

Dendritic cells (DC) are professional antigen-presenting cells that possess both migratory properties and potent T cell-stimulatory activity that allow the uptake of antigenic material in peripheral tissue and its subsequent presentation in the T cell areas of lymphoid organs. Thus motility represents an important property required for DC to function. The HGF receptor *c-met* is expressed in DC and is signaling competent, since it is effectively tyrosine phosphorylated in response to HGF. It has been demonstrated that HGF-activated *c-met* regulates DC adhesion to the extracellular matrix component laminin. The antigen-presenting function is, however, unaffected. It is suggested that, for example in the case of skin injury, DC are activated by TNF and IL-1 to produce HGF. Tissue injury also induces serine protease HGF activate, which processes pro-HGF into active HGF. Additionally, HGF is sequestered in the proximity of HGF-producing cells by binding to heparan sulfate proteoglycans, ensuring a local mode of HGF action. All this induces a microenvironment which induces DC to emigrate and to enter the lymphatic system¹⁵.

Neutrophils

Recruitment of neutrophils into tissue occurs in several pathologic processes, such as inflammation, atherosclerosis, thrombosis, and ischemia. In inflammation, the adherence of neutrophils to the endothelium depends on neutrophil integrins. Integrin-mediated adhesion is tightly regulated, i.e. integrins do not function if neutrophils are not triggered by certain activation stimuli. Detailed studies into the role of HGF in the adhesion of neutrophils to endothelial cells in inflammation showed that HGF induced not only lymphocyte function-associated antigen (LFA)-1-mediated adhesion of neutrophils to endothelial cells, but also transmigration of neutrophils in a concentration-dependent manner. Secondly, HGF functionally transformed neutrophil integrin LFA-1 to active form and reduced surface L-selectin expression level. HGF also induced F-actin polymerization and cytoskeletal rearrangement within seconds. Substances such as genistein, a tyrosine kinase inhibitor, as well as wortmannin, a phosphoinositide (PI)3-kinase inhibitor, inhibited both F-actin polymerization and LFA-1-mediated adhesion of neutrophils to endothelial cells. In studies carried out *in vivo* in cutaneous inflamed tissue, highly expressed HGF and elevated serum levels of HGF were found in patients with Behcet's disease, which is associated with neutrophilic vasculitis and marked neutrophil accumulation. These results indicate that HGF plays a pivotal role in integrin-mediated adhesion and transmigration of neutrophils to sites of acute inflammation through cytoskeletal rearrangement activated by tyrosine kinase and PI 3-kinase signaling¹⁷. A recent report showing that neutrophils isolated from bronchoalveolar lavage of patients with lung injury produce HGF suggests an important role of HGF in pro-inflammatory response^{14, 28}. Understanding the mechanisms by which HGF and *met* contribute to these processes will require additional experimentation.

T cells

mRNA transcripts encoding *c-met* are expressed in the mouse thymus. The *c-met* transcripts are expressed at higher levels in fetal and neonatal thymus than in adult thymus and are mostly expressed by lymphoid cells rather than by stromal cells. Interestingly, the addition of HGF to fetal thymus organ cultures increased the generation of mature T cells expressing high levels of T cell antigen receptors, indicating that *c-met*/HGF signals can promote T cell development³⁰. For mature T cells, ADAMS et al.¹ reported that HGF stimulated

adhesion and migration of memory subset. However, these target cells appeared not to express *c-met*. The possibility of involvement of a low-affinity receptor, such as heparan sulphate, seems logical and awaits experimental confirmation. Recently, DI NICOLA et al.⁸ studied the effect of bone marrow stromal cells on T cell proliferation induced by various mitogenic stimuli. They found that inhibition of T cell proliferation was mediated by HGF and TNF- β in synergistic fashion. The involvement of *c-met* receptor in the observed phenomena has not yet been established.

B cells

The first report drawing attention to the possible role of HGF in the immune system was that by DELANEY et al.⁷, who demonstrated that HGF enhances immunoglobulin production by murine B lymphocytes. However, *c-met* expression was not studied and indirect effects of HGF on T cells have not been ruled out. A few years later, VANDER VOORT et al.³² showed functional *c-met* expression on tonsillar B lymphocytes activated by different stimuli, including the physiologically important concurrent CD40 and anti- μ ligation. This is further stressed by the fact that *c-met* is expressed *in vivo* on a subset of tonsillar centroblasts (CD38⁺ CD77⁺). Centroblasts derive from B cells that have been activated at extrafollicular sites by antigen plus accessory signals provided by antigen-specific T cells. These signals critically involve CD40/CD40 ligand interactions. These findings were further extended by the demonstration of *c-met* expression in activated B cells from the human spleen²⁵. This study also showed that HGF is secreted by stromal cells from secondary lymphoid organs, such as the spleen and lymph nodes, and hence is readily available in the microenvironment of the lymphoid tissue in general. HGF secretion from stromal cells can also be up-regulated by activated T cells and this up-regulation is mediated by CD40 ligand and membrane-associated IL-1. Co-culture of activated B cells with stromal cells from the spleen leads to enhanced immunoglobulin secretion²⁵. This can be partially inhibited by introduction of anti-HGF antibodies to the culture system. Substitution of stromal cells with recombinant HGF did not produce enhancement of immunoglobulin secretion. On the other hand, stimulation of the *c-met* receptor with HGF leads to enhanced integrin-mediated adhesion of activated B cells to vascular cell adhesion molecule and fibronectin^{25,33}. On the basis of these experiments it can be concluded that HGF production by fibroblast-like stromal cells can be modulated by activated T cells,

thus providing signals for the regulation of adhesion of *c-met*-expressing B cells to extracellular matrix proteins. In this way, HGF may indirectly influence immunoglobulin secretion.

HGF/*met* Pathway in B Cell Neoplasia

Since HGF and *met* appear to be essential for the formation and maintenance of organ/structure, aberrant expression of either of these proteins could lead to cell transformation and cancer. Indeed, an active role for HGF and *met* in tumor growth and invasion has been documented by a variety of *in vitro* and *in vivo* studies.

c-met is constitutively expressed by several Burkitt's lymphoma cell lines including Raji, BJAB and EB4B^{32, 34} as well as by a subset of native Burkitt's lymphomas³⁵. On these tumor cells, which are counterparts of centroblasts, HGF induces *c-met* phosphorylation^{26, 32}. Furthermore, HGF stimulation of *c-met*-positive Burkitt's lymphoma cell lines enhances integrin-mediated adhesion to fibronectin and promotes their invasion into fibroblasts monolayers³⁴. Since HGF is produced by stromal cells and follicular DC, paracrine stimulation of Burkitt's lymphoma cells by HGF may take place within the lymphoid tissue microenvironment, promoting tumor growth and/or survival. Indeed, *in vitro* pre-treatment of *c-met*-expressing cell lines such as EB4 or Raji with HGF protects them from death induced by DNA-damaging agents commonly used in tumor therapy²⁶. HGF has also been identified as a potential growth factor for multiple myeloma cell lines and cells isolated from patients' bone marrow⁴.

Concluding Remarks

The past decade has shown that HGF is a physiologically essential cytokine which, in a diverse range of target cells, elicits a multitude of responses, including DNA replication and cell division, cell motility, adhesion, morphogenesis, cell differentiation and tumor cell cytostasis. Over the years, the mystery of how HGF elicits some of these responses is unfolding; however, it remains a mystery for many others. It has become clear that HGF plays an important role within the immune system in health and disease and may ultimately have therapeutic potential. The use of HGF competitors or inhibitors to interfere with tumor metastases is also a crucial issue deserving intensive research.

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