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Review article

Hepatocyte growth factor in physiology and infectious diseases

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ABSTRACT

Hepatocyte growth factor (HGF) is a pleiotropic cytokine composed of an α-chain and a β-chain, and these chains contain four kringle domains and a serine protease-like structure, respectively. The receptor for HGF was identified as the c-met proto-oncogene product of transmembrane receptor tyrosine kinase. HGF-induced signaling through the receptor Met provokes dynamic biological responses that support morphogenesis, regeneration, and the survival of various cells and tissues, which includes hepatocytes, renal tubular cells, and neurons. Characterization of tissue-specific *Met* knockout mice has further indicated that the HGF–Met system modulates immune cell functions and also plays an inhibitory role in the progression of chronic inflammation and fibrosis. However, the biological actions that are driven by the HGF–Met pathway all play a role in the acquisition of the malignant characteristics in tumor cells, such as invasion, metastasis, and drug resistance in the tumor microenvironment. Even though oncogenic Met signaling remains the major research focus, the HGF–Met axis has also been implicated in infectious diseases. Many pathogens try to utilize host HGF–Met system to establish comfortable environment for infection. Their strategies are not only simply change the expression level of HGF or Met, but also actively hijack HGF–Met system and deregulating Met signaling using their pathogenic factors. Consequently, the monitoring of HGF and Met expression, along with real-time detection of Met activation, can be a beneficial biomarker of these infectious diseases. Preclinical studies designed to address the therapeutic significance of HGF have been performed on injury/disease models, including acute tissue injury, chronic fibrosis, and cardiovascular and neurodegenerative diseases. Likewise, manipulating the HGF–Met system with complete control will lead to a tailor made treatment for those infectious diseases.

Contents

1. The HGF-Met signaling pathway

Hepatocyte growth factor (HGF) was originally identified and molecularly cloned as a mitogenic protein for hepatocytes in culture [1,2]. HGF is identical to the scatter factor, a fibroblast-derived factor that promotes the dispersal of sheets of epithelial cells [3,4], and a fibroblast-derived epithelial morphogen that induces the branching tubulogenesis of epithelia grown in three-dimensional cultures [5]. Thus, HGF is a unique growth factor that elicits multiple cellular responses including mitogenesis, cell motility and morphogenesis. These early findings implicated biological and pathophysiological roles for HGF in epithelial wound healing, tissue regeneration, tumorigenesis, and cancer invasion.

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The receptor for HGF was identified as the c-met proto-oncogene product of transmembrane receptor tyrosine kinase (RTK) in 1991 [6,7]. Historically, Met was first identified as the product of a human oncogene, Tpr-Met [8,9]. Tpr-Met was generated following a chromosomal rearrangement induced by the treatment of a human osteogenic sarcoma cell line with the carcinogen N-methyl-N′-nitronitrosoguanidine. This genomic rearrangement fuses two genetic loci. These include the *translocated promoter region* from chromosome 1q25, which encodes a dimerization leucine zipper motif, and *MET* from chromosome 7q31, which contributes the kinase domain and C terminus of the Met. Tpr-Met is a prototype for RTK-derived oncogenes generated following chromosomal translocation.

Mice lacking HGF die in utero 13.5–15.5 days after post-gestation, and this is characterized by the impaired development of the placenta in many epithelial organs, particularly the liver [10]. Mice lacking the *Met* gene also show embryonic lethality and liver pathology [11]. Moreover, HGF provides spatially defined chemoattractant-like motogenic signals for myogenic precursor cells. The migration of myogenic precursor cells from the dermomyotome in the somite to the limb buds and diaphragm is impaired in $Met^{-/-}$ mice. With this condition, the skeletal muscles of the limbs and diaphragm are not formed in mutant mice [11].

Moreover, the definitive roles of the HGF–Met pathway in tissue protection and repair have been demonstrated using a conditional ablation of the *Met* gene in mice (Table 1). Characterization of these tissue-specific *Met* knockout mice has indicated that the HGF-Met system plays a promoting role in the regeneration, protection, and homeostasis of tissues, but it also plays an inhibitory role in the progression of chronic inflammation and fibrosis. However, the biological actions that are driven by the HGF–Met pathway all play a role in the acquisition of the malignant characteristics in tumor cells—invasion, metastasis, and drug resistance in the tumor microenvironment (Fig. 1).

Contrary to the relationship between many cytokines and their receptors, the relationship between HGF and Met is considered bi-unique; HGF is the only ligand for Met, and Met is the only receptor for HGF. Exceptionally and interestingly, *Listeria monocytogenes*

Table 1
Physiological roles of HGF deduced from conditional knockout mice

$Met^{-/-}$ tissue/cell types	Characteristics	Ref.
Liver		
Hepatocytes	Highly susceptible to apoptosis after liver injury	[12]
	Impairment in recovery from liver necrosis after liver injury	
	Impairment in Erk1/2 activation and G2/M transition after liver injury	[13]
Hepatocytes	Steatotic change of the liver in aged mice	[14]
	Decrease in mitotic hepatocytes after partial hepatectomy	
	Delayed regeneration after partial hepatectomy	
Hepatocytes	Promoted liver fibrosis after liver injury	[15]
	Extensive necrosis and lower proliferation of hepatocytes after bile-duct ligation	[16]
	Enhanced susceptibility to liver fibrosis	
Oval cells	Decrease in oval cell viability and more prone to apoptosis	[17]
	Reduction in oval cell pool	[18]
	Impairment in migration and differentiation into hepatocytes	
Kidney		
Tubular cells	No appreciable defect in kidney morphology and function	[19]
	Aggravated renal injury and inflammation after acute kidney injury	
Podocytes	Neither albuminuria nor overt pathologic lesions	[20]
	Severe podocyte injury and apoptosis, and albuminuria after toxic injury	
Collecting duct	Increased fibrosis and tubular necrosis after unilateral ureteral obstruction	[21]
	Reduced capacity in regeneration after release of the obstruction	
Ureteric bud	Double knockout of *Met* and *EGF* receptor in ureteric bud	[22]
	Decrease in branching and a reduction in final glomerular number	
Skin		
Keratinocytes	Lack of keratinocyte migration after skin wound	[23]
	Severe impairment epidermal wound closure	
Pancreas		
β-Cell	Mild hyperglycemia, and decreased serum insulin levels at 6 months	[24]
	Loss of acute-phase insulin secretion in response to glucose, and impaired glucose tolerance	
	Diminished glucose tolerance and reduced plasma insulin after a glucose challenge	[25]
	Normal glucose and β-cell homeostasis	[26]
	Susceptible to streptozotocin-induced diabetes	
Nervous system		
Ganglionic eminence	Increased numbers of striatal GABAergic interneurons in the lateral sensorimotor	[27]
	Areas with distinct behavioral deficits	
	Delayed procedural learning	
Cerebral cortex and hippocampus	Larger size in the rostral cortex, caudal hippocampus, dorsal striatum, thalamus, and corpus callosum	[28]
Dorsal pallial	Increases proximal and reduces distal apical dendritic branching of neocortical pyramidal neurons in post-pubertal period	[29]
Forebrain neurons	Reduced volume of cortical tissue	[30]
	Increase in spine head volume, but no change in density of spines	
	Hyperconnectivity in circuit-specific intracortical neurons	
Heart		
Cardiomyocytes	Normal heart development	[31]
	Cardiomyocyte hypertrophy and interstitial fibrosis by 6 months	
	Systolic cardiac dysfunction by 9 months	
Immune system		
Dendritic cells	Impaired emigration toward draining lymph nodes upon inflammation-induced activation	[32]
	Impaired contact hypersensitivity reaction to contact allergens	

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