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The role of endosomal signaling triggered by metastatic growth factors in tumor progression



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ABSTRACT

Within tumor microenvironment, a lot of growth factors such as hepatocyte growth factor and epidermal growth factor may induce similar signal cascade downstream of receptor tyrosine kinase (RTK) and trigger tumor metastasis synergistically. In the past decades, the intimate relationship of RTK-mediated receptor endocytosis with signal transduction was well established. In general, most RTK undergoes clathrin-dependent endocytosis and/ or clathrin-independent endocytosis. The internalized receptors may sustain the signaling within early endosome, recycling to plasma membrane for subsequent ligand engagement or sorting to late endosomes/lysosome for receptor degradation. Moreover, receptor endocytosis influences signal transduction in a temporal and spatial manner for periodical and polarized cellular processes such as cell migration. The endosomal signalings triggered by various metastatic factors are quite similar in some critical points, which are essential for triggering cell migration and tumor progression. There are common regulators for receptor endocytosis including dynamin, Rab4, Rab5, Rab11 and Cbl. Moreover, many critical regulators within the RTK signal pathway such as Grb2, p38, PKC and Src were also modulators of endocytosis. In the future, these may constitute a new category of targets for prevention of tumor metastasis.

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Contents

1.	Intro	duction	40
	1.1.	Metastatic factors within the tumor microenvironment	40
	1.2.	Signal transduction mediating tumor progression triggered by the metastatic growth factors	40
		1.2.1. Similarity in signal cascade induced by metastatic growth factors	40
		1.2.2. Signal cross talk of growth factors with each other and integrin	40
		1.2.3. Target therapy against the metastatic growth factors: The challenge and perspective	40
2.	The re	ole of endocytosis in receptor-mediated signal transduction	40
	2.1.	Endocytosis and signal transduction as a molecular network	40
	2.2.	The pathophysiological process regulated by endosomal signaling	41
	2.3.	Recentor endocytosis and cell migration 15-	41
	2.4.	Receptor endocytosis and tumor progression	41
3	Endos	somal signaling induced by metastatic factor-implication in tumor progression 15-	41
5.	3.1	HGF 15-	41
	3.2	FGF 15.	42
	33	PDCF 15.	42
	3.4	FCF FCF 15/	12
	3.5	TGELA 15	12
	2.5.	Тапр	12 12
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4. Targeting the common endocytic pathway for prevention of tumor progression: A promising perspective	1542
Conflict of interest	1543
Acknowledgment	1543
References	1543

1. Introduction

1.1. Metastatic factors within the tumor microenvironment

Metastasis is one of the most complicated pathological processes which causes most cancer deaths [1]. Recent studies highlighted that the tumor microenvironment plays critical role in triggering tumor metastasis. The tumor microenvironment comprises the primary tumors themselves which may recruit and interact with stromal cells. A variety of cell types populate the stromal compartment including myofibroblasts, vascular cells and immune cells [2]. The interactions between tumor cells and stromal cells lead to secretion of growth factors and cytokines for not only supporting the growth and survival of tumor cells but also triggering tumor metastasis [3]. Among the growth factors, hepatocyte growth factor (HGF) [4–8], epidermal growth factor (EGF) [9-11], transforming growth factor (TGF)- β [12–16], platelet-derived growth factor (PDGF) [17–20], basic fibroblast growth factor (bFGF) [21,22] and vascular endothelial growth factor (VEGF) [23] are capable of triggering metastatic changes including epithelial mesenchymal transition (EMT) and enhancement of motility and invasiveness of a variety of tumor cells, thus may be collectively called as the "metastatic growth factors".

1.2. Signal transduction mediating tumor progression triggered by the metastatic growth factors

1.2.1. Similarity in signal cascade induced by metastatic growth factors In the past decades, signal transductions triggered by the metastatic growth factors were well established. Interestingly, all of them except TGF β activate receptor tyrosine kinase (RTK) triggering similar signal cascades. Engagement of the growth factors such as HGF, EGF, PDGF and FGF with their RTK receptors recruits common adaptor proteins such as Grb2 [24–28], Gab1 [29–32] and Shc [33–37]. These adaptor proteins serve as scaffold for activation of two major downstream signal cascades, Ras/Raf/MEK/ERK [38–45] and PI3K/AKT [38,46–55] (summarized in Table 1). In addition, TGFβ (acting via receptor serine threonine kinase) induces Smad pathways which frequently integrated with MEK/ERK [56,57] and/or AKT [58] cascades (summarized in Table 1).

1.2.2. Signal cross talk of growth factors with each other and integrin

Due to the similarity in signal transduction, it is not surprising that these growth factors may cooperate to enhance tumor progression. For example, couples of EGF and HGF [59,60], FGF-2 and VEGF [61], TGF-beta1 and HGF [62] may synergistically trigger migration, invasion and metastasis, via collaborative activation of downstream signaling such as ERK. Moreover, HGF [63,64], EGF [65,66], PDGF [67,68], FGF [69] and TGF β [70] can also cross talk with integrininitiated signal cascade for enhancing tumor progression (summarized in Table 1). For example, HGF may cross talk with integrin leading to activation of Ras–Rac1/Cdc42-PAK [63] and Shp2–Src [64] cascades. Also, EGF may cooperate with β 4 integrin to amplify ErbB2 signaling and promote mammary tumorigenesis [65].

1.2.3. Target therapy against the metastatic growth factors: The challenge and perspective

Since these metastatic factors play an essential role in malignant cell growth, proliferation, and motility, target therapy aiming at signal pathway induced by them is promising in prevention of tumor progression. The most frequently used inhibitors for blocking RTK pathway are the tyrosine kinase inhibitors (TKIs), most of which are adenosine triphosphate (ATP) analogs competing with ATP-binding pockets on the intracellular catalytic kinase domain of RTKs, thereby preventing their autophosphorylation. For example, the effectiveness of synthetic TKIs including JNJ-38877605 [71], BMS-777607 [72] and ARQ-197 [73] against HGF/c-Met and Gefitinib against EGF [74] for tumor preventions was demonstrated. Also, TKI258, sorafenib, sunitinib and cediranib were used for targeting FGFR/PDFGR/VEGFR in prevention of pancreatic cancer [75] and NSCLC [76], some of which were under phase II studies (summarized in Table 1). There are, however, several common problems and main challenges in RTK-targeting approach. One of them is the non-specificity that causes side effects on normal tissues. For example, the use of EGFR inhibitors (as a single agent or in combination therapy) results in cutaneous toxicities (rashes) such as acneiform eruptions, hyperpigmentation, xerosis, trichomegaly, paronychia etc. [77]. The other problem is that the point mutation of the RTK (pre-existing or de novo) or other unidentified factors can lead to drug resistance [78,79]. To address this issue, it is worthy of exploring more detailed mechanisms of RTK signaling for devising more effective and safe targeting strategy. Recently, receptor endocytosis was highlighted to be critical for RTK-mediated signal transduction. A lot of regulators for endosomal signaling of RTK are emerging to be more suitable targets for therapeutic intervention of tumor progression.

2. The role of endocytosis in receptor-mediated signal transduction

2.1. Endocytosis and signal transduction as a molecular network

In the past decade, endocytosis is well known to be an intriguing cellular process, which integrates with signal transduction thereby

Table 1

Similarity in signal	transduction	induced b	oy various	metastatic	growth	factors.
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Growth	Signal transd	TKI ^a used		
factor	Adaptor activation	Downstream signal	Cross talk with other ligands	for therapy
HGF	GrB2 [24] Gab1 [29]	MAPK [38–41] PI3–AKT [38,46–48]	EGF [59,60] TGFb [62]	JNJ ^b [71] BMS ^c [72]
EGF	Shc [33,34] GrB2 [25,26] Gab1 [30,43] Shc [35]	MAPK [42,43] PI3-AKT [49,50]	Integrin [63,64] HGF [59,60] Integrin [65,66]	ARQ-197 [73] Gefitinib [74]
PDGF	GrB2 [27] Gab1 [31]	MAPK [44] PI3-AKT [51-53]	Integrin [67,68]	TKI258 [75] Sorafenib [76]
FGF	GrB2 [28] Gab1 [32]	MAPK [45] PI3-AKT [54,55]	VEGF [61] Integrin [69]	TKI258 [75] Sorafenib [76]
TGFβ	ND ^d	MAPK [56,57]	HGF [62]	ND
VEGF	ND	ND	FGF [61]	TKI258 [75] Sunitinib [76]

The numbers in parenthesis represent the numbers of references cited in the text. TKI^a: tyrosine kinase inhibitor; JNJ^b: JNJ-38877605; BMS^c: BMS-777607; ND^d: the information is not available in the literature for relevant growth factor.

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