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Editorial Open Access

LRP1: A Tumor and Metastasis Promoter or Suppressor?

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Editorial

The low density Lipoprotein Receptor-related Protein 1 (LRP1) is a multifunctional cell surface receptor, which belongs to the Low Density Lipoprotein Receptor (LDLR) family. LRP1 is composed of a large 515-kDa N-terminal subunit linked to a smaller C-terminal 85-kDa subunit. The 515-kDa subunit contains most of the LRP1 extracellular portion with all the putative ligand-binding domains, while the smaller 85-kDa subunit contains the transmembrane and cytoplasmic tail. The LRP1 cytoplasmic tail contains critical elements for receptor functions, and interacts with a set of cytoplasmic adaptor and scaffold proteins [1,2]. While Receptor-Associated Protein (RAP) functions intracellularly as a molecular chaperone for LRP and facilitates LRP folding and trafficking within the secretory pathway, the recombinant form of RAP has been used extensively in the study of ligand-receptor interactions [3]. At present, a remarkable spectrum of structurally unrelated ligands has been identified for LRP1, and several signal transduction pathways can be modulated by LRP1 [1,2]. Evidence is accumulating to indicate that LRP1 plays an important role in cancer progression.

Studies have demonstrated that low expression of LRP1 is closely related to the aggressive phenotype of several types of cancer. It has been found that a low level of LRP1 expression was associated with aggressiveness and invasiveness in hepatocellular carcinoma [4], and that LRP1 was expressed in a decreased fashion in the progression of melanocytic tumors [5] and Wilms tumors [6]. Furthermore, LRP1 mRNA levels were significantly decreased in lung tumors relative to nontumorous lung tissue, and lower expression of LRP1 in lung adenocarcinomas correlated with less favorable clinical outcome in a cohort of 439 patients [7].

In apparent contradiction to the reports described above, LRP1 overexpression has been reported in several other types of cancer including breast carcinoma [8,9], endometrial carcinomas [10], prostate cancer [11] and glioblastoma [12-14]. For example, LRP was overexpressed in malignant astrocytomas, especially in glioblastomas, and the increased expression of LRP appears to correlate with the expression of urokinase receptor (uPAR) and the malignancy of astrocytomas [13]. LRP 1 expression was also associated with triple-negative and Her-2/neu breast carcinomas but not with hormone-dependent carcinomas, and increased LRP-1 expression was related to proliferation and invasiveness in Her-2/neu and triple-negative breast carcinoma [8].

LRP1 internalizes over 40 different ligands, interacts with numerous cytoplasmic adaptor and scaffold proteins and modulates the activity of other transmembrane receptors [1,2]. Therefore, the predominant effect of LRP1 on cell-signaling and cell migration and invasion in different types of cancer cells may be associated with the abundance of LRP1 and with the availability of LRP1 ligands, cytoplasmic proteins and other transmembrane receptors interacting with LRP1. Knockdown or deletion of LRP1 decreased the migration and/or invasion of glioblastoma cells [14,15], lung cancer cells [15], and thyroid carcinoma cells [16,17]. Consistently, functional blocking of LRP1 by RAP, LRP1 antibody or its ligand α2-macroglobulin inhibited the migration and/or invasion of breast cancer cells [9,18], glioblastoma cells [15,19] and lung cancer cells [15]. Conversely, knockdown or deletion of LRP1 increased the migration and invasion of fibrosarcoma cells [20] and hepatocellular carcinoma cells [4], and neutralization of LRP1 function increased the migration and invasion of fibrosarcoma cells [20], hepatocellular carcinoma cells [4] and thyroid carcinoma cells [21]. *In vivo*, knockdown of LRP1 inhibited the development and growth of pulmonary metastases of breast cancer cells [22,23], but promoted pulmonary and intrahepatic metastases of hepatocellular carcinoma cells [4].

The mechanisms by which LRP1 mediate inhibitory effects on tumor initiation and progression remain largely unknown, however, it appears that LRP1 oncogenic effects are mediated through urokinase receptor system [24], Protease Nexin-1 (PN-1) [25], midkine [26], pro-cathepsin D [27] and secreted Heat shock protein 90 (Hsp90) [14,23]. While LRP1-mediated urokinase receptor signaling and matrix metalloproteinase activity are critical for tumor invasion and metastasis, recent studies indicate that Hsp90 is another important player in LRP1-mediated tumor invasion and metastasis. Hsp90 is a molecular chaperone that is required for the correct folding, stability and function of a range of oncoproteins. Hsp90 is increased in many solid tumors and haematological malignancies. Recently, a pool of Hsp90 has been identified at the cell surface, where it was shown to be involved in cancer cell invasion [28]. Secreted HSP90 was identified as a ligand for LRP1 [29,30]. More recently, Cheng et al. revealed a dual role for secreted Hsp90 in transducing signaling via LRP1, and in facilitating LRP1 co-receptor function for the receptor tyrosine kinase EphA2 [14]. Hsp90/LRP1 signaling facilitates EphA2 dependent glioblastoma cell invasion [14]. Likewise, Sahu et al. reported that inhibition of Hsp90 secretion, neutralization of secreted Hsp90 action, or removal of the cell surface LRP1 receptor for secreted Hsp90 reduces breast cancer cell invasion *in vitro* and lung colonization and tumor formation in nude mice [23].

In summary, as a multifunctional cell surface receptor, LRP1 can internalize diverse biological ligands and regulate many signaling pathways. LRP1 could have a cancer type-specific and patient-specific role that is critical in cancer progression. More in-depth studies in the future will be necessary to improve our understanding of how LRP1 regulates cancer development and progression and may provide insight into developing novel strategies against malignancies.

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