Suppression of Met/HGF Receptor Activation by the Met Juxtamembrane Function and Cell-Cell Contact

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Inhibition of cell proliferation by cell-cell contact is a fundamental characteristic of normal cells by which cellular adhesion successfully maintains highly organized tissue architecture. Proliferation of normal hepatocytes is tightly regulated by cell-cell contact. Hepatocytes do not undergo DNA synthesis even in the presence of excess amount of HGF when the cells are in tight cell-cell contact. Under the sparse condition, HGF induced prolonged Met tyrosine phosphorylation and a marked mitogenic response. Under the confluent condition wherein hepatocytes were in tight cell-cell contact, HGF induced transient Met tyrosine phosphorylation and failed to induce mitogenic response. The activity and expression of the protein tyrosine phosphatase, LAR increased specifically in confluent hepatocytes and not in sparse hepatocytes. LAR and Met were associated, and LAR dephosphorylated Met. Specific inhibition of the LAR expression prolonged activation of Met and released contact inhibition. Thus functional association of LAR and Met underlies the inhibition of Met-mediated signaling through the dephosphorylation of Met, which specifically occurs under the confluent condition (Fig. 1A).

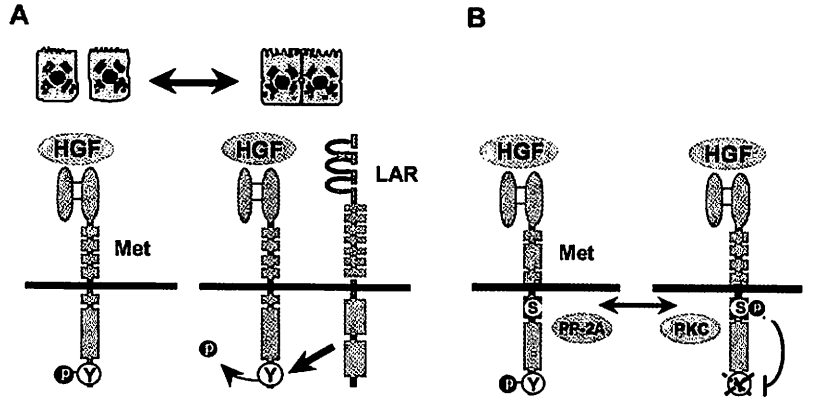

Fig. 1. Suppression of Met receptor activation through cell-cell contact (A) and juxtamembrane Ser985 phosphorylation (B).

In addition to the regulation of Met by cell-cell contact, Met activation is negatively regulated by phosphorylation of Ser985 in the juxtamembrane domain of Met (Fig. 1B). The Met juxtamembrane domain is consisted of highly conserved 47 amino acid residues and the Met lacking the juxtamembrane domain naturally exists as a splicing variant. We showed that Ser985 is phosphorylated by protein kinase-C (PKC) and dephosphorylated by protein phosphatase-2A (PP-2A). Importantly, HGF-dependent Met activation is suppressed by Ser985 phosphorylation. Physiological significance of the negative regulatory mechanisms for Met-dependent signal transduction remains to be further defined, however, we speculate that the Met negative regulation may participate in "the injured tissue-selective" activation of Met. Instead, the loss-of-function in the Met negative regulation may possibly related to malignant progression of tumor cells.