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Macrocyclic Peptide Drug Discovery Targeting Hepatocyte Growth Factor and the Receptor

細胞増殖因子と受容体を標的とする環状ペプチド創薬

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Activation of hepatocyte growth factor (HGF)-MET receptor pathway drives cell proliferation, migration, morphogenesis (3-D tubulogenesis), and survival, thereby participates in regeneration of damaged tissues. On the other hand, aberrant activation of MET is associated with progression of cancer, particularly drug resistance and invasion-metastasis. By RaPID (Random Peptide Integrated Discovery) system, we obtained macrocyclic peptides that specifically bind to either HGF or MET receptor with 1-10 nM Kd values. The cross-linking of MET-binding macrocyclic peptides, that is the bivalent display of MET-binding peptide, conferred them an ability to activate MET. On the other hand, HGF-inhibitory peptide-8 (HiP-8) was obtained as an inhibitory macrocyclic peptide against HGF. Observation by high-speed atomic force microscopy indicated that the binding of HiP-8 to HGF suppress dynamic molecular movement of HGF. Using HiP-8 as a molecular probe, accumulation of HGF in cancer tissue could be detected by PET (Positron Emission Tomography) imaging. Selective detection and/or inhibition of HGF by HiP-8 is expected to be better diagnosis and/or therapeutics in drug discovery targeting HGF-MET.

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