Secretory human ribonuclease 1 functions as Eph receptor A4 ligand to promote breast tumor initiation

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ABSTRACT

The pancreatic human ribonuclease (hRNase) A superfamily is comprised of eight canonical hRNases, including hRNase1, all of which can be detected in various body fluids, e.g., serum and plasma. Secretory hRNase1 exerts its ribonuclease activity to function in extracellular RNA clearance. Moreover, hRNase1 regulates hemostasis, inflammation, and innate immunity, indicating that hRNase1 possesses multiple functions in addition to RNA clearance1,2. Focuses on hRNase1 have been extensively investigated the biochemical properties and post-translational modifications, such as glycosylation3,4. Nonetheless, the biological function of hRNase1 and whether it plays a role in cancer have not yet been completely defined. Recent studies indicated that hRNase1/ANG serves as a ligand for cell surface RTK EGFR and plexin-B2 receptor5 in solid and hematopoietic cancers. Another hRNase called hRNase5 has been recently identified as a high-affinity ligand for RTK ROS1 in liver cancer6. Those findings reveal a role of the hRNase A superfamily in tumor progression and an unconventional ligand-receptor relationship between RNAs and RTK families7. Here, we demonstrate that hRNase1, independently its ribonuclease activity, enriches the stem-like cell population and enhances the tumor-initiating ability of breast cancer cells. Specifically, secretory hRNase1 binds to and activates the RTK Eph receptor A4 (EphA4) signaling to promote breast tumor initiation in an autocrine and paracrine manner, which is distinct from the classical ligand-receptor ephrin-EphA4 juxtaglancing through contact-dependent cell-cell communication. In addition, analysis of human breast tumor microarrays reveals a positive correlation between hRNase1, EphA4 activation, and stem cell marker CD133. Notably, high hRNase1 levels in plasma samples is positively correlated with increased EphA4 intracellular signaling in tumor tissues from the paired breast cancer patients, highlighting the pathological relevance of the hRNase1-EphA4 axis in breast cancer. The discovery of hRNase1 as a secretory ligand of EphA4 to enhance breast cancer stemness suggests a potential treatment strategy for breast cancer by inactivating the hRNase1-EphA4 axis.

BACKGROUND & RATIONALE

Our previous findings demonstrated a RNase catalytic activity-independent role of human RNase 5 (hRNase5), which serves as a bona fide ligand of epidermal growth factor receptor (EGFR), a cell surface receptor tyrosine kinase (RTK), to promote oncogenic transformation in pancreatic adenocarcinoma (PDAC), and acts as a serum biomarker for predicting PDAC patient response to a FDA-approved EGFR kinase inhibitor erlotinib, potentially leading to a prognostic test for PDAC patients (Figure A)8. Recently, we further identified another ligand-receptor relationship between secretory RNase and cell surface RTK families, namely that human RNase 7 (hRNase7) binds to and induces autoprophosphorylation of ROS1, an orphan RTK with no endogenous ligands identified before. The results clarified that hRNase7 promotes the development of hepatocellular carcinoma (HCC), independently of its catalytic activity through wild-type ROS1 activation, and tumors with activated hRNase7-ROS1 axis are vulnerable to the FDA-approved ROS1 inhibitors. Moreover, hRNase7 binds to hRNaseA superfamily, hRNase5/ANG, functions as an EGFR ligand. Identification of the hRNase1/ANG-EGFR axis raises an intriguing question of whether other RNase family members may play a ligand-like function, linking the two unrelated protein families, namely RNases and RTKs for secretory RNase 1, a serum biomarker to stratify patients for anti-RTK treatment (Figure B)9,10. Together, our studies reveal an unknown but novel role of a secretory RNase 1 serving as a cognate ligand of RTK and a serum biomarker to guide cancer therapy (Figure C).