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EDITORS' CHOICE

Cancer

Anticancer Glycyl-tRNA Synthetase from the Outside

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Full-length tRNA synthetases or fragments of them have been reported to function as extracellular ligands for various receptors, including cadherins. Noting that patients with autoimmune diseases have a high frequency of autoreactive antibodies against tRNA synthetases, Park *et al*. examined the abundance of tRNA synthetases in human and mouse serum and found that glycyl-tRNA synthetase (GRS) was abundant. Examination of cultured cells showed that, in response to serum starvation, GRS was specifically released from murine and human macrophage cell lines (mouse RAW264.7 and human U937) and not other cell lines, such as Jurkat T cells, HeLa cells, HCT116 cells, or HEK293 cells. Various apoptotic stresses—including DNA damage, glucose deprivation, or tumor necrosis factor—combined with inhibition of protein synthesis, also induced the release of GRS from the macrophage cell lines, but not the colon cancer cell line HCT116 or the cervical cancer cell line HeLa. This release occurred before the loss of membrane integrity or cell viability, suggesting that the release was not due to leakage from cells undergoing apoptosis. Coculture of either U937 cells or murine primary bone marrow–derived macrophages with specific cancer cells, such as the human large-cell lung cancer cell line H460, showed that the cancer cells released a factor that promoted GRS release from the macrophages. GRS bound to a subset of cancer cell lines (HCT116 and HeLa, but not MCF7), as well as the RAW 264.7 macrophages. Recombinant GRS or coculture of the cells with U937 cells reduced the viability of HCT116 cells, and this was associated with markers of apoptosis. Recombinant GRS failed to reduce the viability of RAW 264.7 cells or the breast cancer cell line MCF7. In vitro binding assays identified cadherin (CDH) 6 and 18 as specific binding partners for GRS. The abundance of CDH6 correlated with the ability of GRS to promote tumor cell death, and knockdown of CDH6 or addition of a competing CDH6 peptide prevented GRS from reducing HCT116 cell viability. Tumor cells that were responsive to the effects of GRS on cell viability also exhibited a greater amount of extracellular signal–regulated protein kinase (ERK) phosphorylation than did GRS-insensitive tumor cells, and GRS decreased the abundance of phosphorylated ERK in the responsive tumor cell lines. Pharmacological inhibition of protein phosphatase 2A (PP2A) blocked GRS-induced reduction in ERK phosphorylation, and immunoprecipitation assays showed that GRS reduced the interaction between CDH6 and PP2A. Thus, GRS may promote the release of PP2A, which dephosphorylates ERK and reduces ERK-dependent cell survival. Xenograft experiments showed that injecting GRS into GRS-responsive tumors or including GRS with the grafted GRS-sensitive cells either reduced the size of the tumors or prevented them from forming, respectively. Thus, some tumor cells appear to promote their own death by releasing a factor that triggers the release of GRS from macrophages, and this pathway could be manipulated for the treatment of certain cancers.

M. C. Park, T. Kang, D. Jin, J. M. Han, S. B. Kim, Y. J. Park, K. Cho, Y. W. Park, M. Guo, W. He, X.-L. Yang, P. Schimmel, S. Kim, Secreted human glycyl-tRNA synthetase implicated in defense against ERK-activated tumorigenesis. *Proc. Natl. Acad. Sci. U.S.A.* **109**, E640–E647 (2012). [Abstract] [Full Text]

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