Mer (MerTK) and Axl receptor tyrosine kinases (RTK) are expressed at abnormally high levels in a variety of malignancies, and these receptors are known to activate strong antiapoptotic signaling pathways that promote oncogenesis. In this study, we found that Mer and Axl mRNA transcript and protein expression were elevated in astrocytic patient samples and cell lines. shRNA-mediated knockdown of Mer and Axl RTK expression led to an increase in apoptosis in astrocytoma cells. Apoptotic signaling pathways including Akt and extracellular signal-regulated kinase 1/2, which have been shown to be activated in resistant astrocytomas, were downregulated with Mer and Axl inhibition whereas poly(ADP-ribose) polymerase cleavage was increased. Furthermore, Mer and Axl shRNA knockdown led to a profound decrease of astrocytoma cell proliferation in soft agar and a significant increase in chemosensitivity in response to temozolomide, carboplatin, and vincristine treatment. Our results suggest Mer and Axl RTK inhibition as a novel method to improve apoptotic response and chemosensitivity in astrocytoma and provide support for these oncogenes as attractive biological targets for astrocytoma drug development [1)].

MERTK is a receptor tyrosine kinase of the TAM (Tyro3, Axl, MERTK) family, with a defined spectrum of normal expression. However, MERTK is overexpressed or ectopically expressed in a wide variety of cancers, including leukemia, non-small cell lung cancer, glioblastoma, melanoma, prostate cancer, breast cancer, colon cancer, gastric cancer, pituitary neuroendocrine tumors, and rhabdomyosarcomas, potentially resulting in the activation of several canonical oncogenic signaling pathways. These include the mitogen-activated protein kinase and phosphoinositide 3-kinase pathways, as well as regulation of signal transducer and activator of transcription family members, migration-associated proteins including the focal adhesion kinase and myosin light chain 2, and prosurvival proteins such as survivin and Bcl-2. Each has been implicated in MERTK physiologic and oncogenic functions. In neoplastic cells, these signaling events result in functional phenotypes such as decreased apoptosis, increased migration, chemoresistance, increased colony formation, and increased tumor formation in murine models. Conversely, MERTK inhibition by genetic or pharmacologic means can reverse these pro-oncogenic phenotypes. Multiple therapeutic approaches to MERTK inhibition are currently in development, including ligand “traps”, a monoclonal antibody, and small-molecule tyrosine kinase inhibitors [2)].

1)
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2)
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