sive tumors such as pancreatic cancer that are relatively hypovascular, are able to survive even in conditions of low nutrients and low oxygen supply. Since chronic nutrient deprivation seldom occurs in normal tissues, one strategy for anticancer agent development is to target cancer cells growing in nutrient-deprived conditions. Thus, we screened to identify cytotoxic agents that function preferentially in nutrient-deprived cells.

We found that AG1024, a specific inhibitor of IGF-1R kinase, showed preferential cytotoxicity to human pancreatic cancer PANC-1 cells grown in nutrient-deprived medium. Conventional chemotherapeutic drugs such as doxorubicin, 5-fluorouracil and paclitaxel, were only weakly cytotoxic to nutrient-deprived PANC-1 cells, suggesting that AG1024 may be a unique and attractive starting compound in the development of an antitumor agent. AG1024 has been reported to induce apoptosis in human breast cancer MCF-7 cells [31]. In our present study, flow cytometric analysis showed that AG1024 increased propidium iodide staining without annexin V of nutrient-deprived PANC-1 cells. Kigamicin D and (6a*R*,11a*R*)-3,8-dihydroxy-9-methoxypterocarpan induced necrosis in nutrient-deprived cells [4,32]. Therefore, AG1024 may induce necrosis under nutrient starvation. I-OMe-AG538, another IGF-1R kinase inhibitor that differs in structure from AG1024, was also cytotoxic to nutrient-deprived PANC-1 cells. These IGF-1R kinase inhibitors also were cytotoxic to other nutrient-deprived human pancreatic cancer cell lines, including Capan-1, MIA Paca-2, BxPC-3 and PSN.

IGF-1 binding to the IGF-1R results in activation of receptor tyrosine kinases that stimulates signaling through intracellular networks, including PI3K-AKT-TOR and RAF-MAPK, which then promote cell proliferation and inhibit apoptosis. We found that the IGF-1R kinase inhibitors AG1024 and I-OMe-AG538 blocked phosphorylation of IGF-1R by IGF-1 preferentially in cells cultured in nutrient-deprived conditions relative to those in nutrient-sufficient conditions. These IGF-1R kinase inhibitors also suppressed phosphorylation of Akt and Erk, demonstrating that activation of pathways downstream of the IGF-1R were also blocked in nutrient-deprived conditions.

Unlike AG1296 (a PDGFR kinase inhibitor) or AG1478 and PD168393 (EGFR kinase inhibitors), which are less cytotoxic in nutrient-deprived PANC-1 cells, preferential inhibition of IGF-1 signaling by IGF-1R kinase inhibitors suggests that this pathway may play an important role in cell survival in stress conditions such as nutrient deprivation. The Akt pathway, which functions downstream of IGF-1R, plays a critical role in the proliferation, survival, motility, morphology and therapeutic resistance of cancer cells [33,34]. Because Akt has been demonstrated to regulate cell survival in various stress conditions, including nutrient deprivation, this kinase is viewed as a promising target for cancer therapeutics. Akt inhibitors have been developed including PX-316, which shows antitumor activity against human MCF-7 breast cancer and HT-29 colon cancer xenografts in mice [35]. Thus, part of the preferential cytotoxicity of IGF-1R kinase inhibitors in nutrient-deprived conditions may be due to inhibition of Akt activation.

The IGF-1 receptor is universally expressed in various hematologic and solid tumor cells. NVP-ADW742, another specific inhibitor of IGF-1R kinase, has been shown to be a significant antitumor agent in an orthotopic xenograft multiple myeloma model [20]. Oral administration of the IGF-1R kinase-specific inhibitor NVP-AEW541 has been shown to inhibit IGF-1R signaling in tumors and to reduce tumor growth in a xenograft fibrosarcoma model [19]. The potent cytotoxicity of AG1024 and I-OMe-AG538 to pancreatic cancer cell lines deprived of nutrients (simulating a tumor microenvironment) makes IGF-1R a promising target for new drugs that may be developed to treat a broad spectrum of malignant tumors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2009.01.065.

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