Small Drug-Like Molecules as Anticancer Agents Selective for Cancer Stem Cells

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Technology description

Novelty:
A new class of anticancer agents which are highly selective for mesenchymal cancer cells with stem cell like properties.
Effective management of advanced cancer requires systemic treatment including small molecules that target unique features of aggressive tumor cells. At the same time, tumors are heterogeneous and current evidence suggests that a subpopulation of tumor cells, called tumor initiating or cancer stem cells are responsible for metastatic dissemination, tumor relapse and possibly drug resistance. Classical apoptotic drugs are less effective against this critical subpopulation and therefore, there is a need for effective chemotherapeutic agents that can selectively kill cancer stem cells to prevent cancer metastasis and recurrence.
Invention description:
Researchers at The University of Toledo have designed and synthesized a class of small drug like molecules that have shown highly selective activity against mesenchymal cancer cells with stem cell like properties. These small molecule anticancer agents kill selected cancer cell lines by harnessing reactive oxygen species to induce ferroptosis.
Specifically, these researchers have demonstrated the use of these small molecules as anticancer agents on NSCLC cell line NCI-H522, fibrosarcoma HT1080, and breast cancer cell lines MDA-MB-231 and MDA-MB-468. NCI-H522 cells treated with these molecules at 10 μM were killed completely in only 13 hours after treatment. These molecules show striking selectivity and are toxic only to a subset of cancer cell lines. Selectivity of these compounds was determined by treating fifteen different tumor cell lines including breast, colon, prostate and lung cancers. Five tumor cell lines were sensitive (LC50 2-5mM), and other lines remained unaffected even after three days of treatment. Two normal cell lines (RPE, HBEC) were not killed by the compounds. The data also indicated that these compounds kill cancer cells by Ferroptosis, an iron-dependent mechanism involving reactive oxygen species. Similar to other ferroptotic molecules, it was observed that cell death is enhanced in tumor cells with elevated Ras signaling. It was also observed that toxicity of compounds is elevated in cells lacking E-cadherin, which exhibit a mesenchymal phenotype. The mesenchymal/Ecadherin(-) phenotype is associated with stem cells of various solid tumors and selective killing of mesenchymal cells may provide a novel way to kill cancer stem cells, thereby reducing metastatic spread and tumor relapse after therapy. These

compounds show enhanced toxicity towards mesenchymal breast cancer populations with cancer stem cell properties and are well tolerated in mice.

Advantages

The disclosed invention embodies small drug-like molecules that show remarkable selective toxicity towards mesenchymal type cancer stem cells, a subpopulation of tumor cells that are responsible for metastatic dissemination, tumor relapse, and possibly drug resistance. The cell death is enhanced in tumor cells with elevated Ras signaling. The other advantages of this technology are:
·Few step synthesis
·Kills cancer cells more rapidly and efficiently than classical drugs taxol and hydroxyurea.
·Cell death mechanism is non-apoptotic and iron-dependent
·Lethality is enhanced in tumor cells with activated RAS-MAPK signaling pathway.

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