Methods and Compositions for Increasing Sensitivity of Cancer Cells to Glutaminase Inhibitors and Applications to Cancer Therapy

Technology #19305

Applications

This technology sensitizes cancer cells to glutaminase inhibitors, and has potential therapeutic and theranostic applications in cancer treatment.

Problem Addressed

Cancer cells proliferate much more rapidly than healthy tissues. The increased metabolic demands of such sustained proliferation results in alterations in metabolic pathways. Therapeutic targeting of these metabolic alterations provides an exciting opportunity for developing generalizable cancer treatments. One metabolic pathway of particular interest is glutamine metabolism. Many cancers require glutamine anaplerosis to fuel the TCA cycle, which provides energy and nutrients for proliferation. Drugs targeting glutaminase, an enzyme required for glutamine anaplerosis, have shown promise in *in vivo* animal studies and Phase I/II clinical trials in a variety of cancers including non-small cell lung carcinoma, renal cell carcinoma, and breast cancer. However, not all cancers are sensitive to glutaminase inhibition, therefore there is a need to sensitize patients to glutaminase inhibition or identify patients that will respond to these drugs.

Technology

These inventors found that a primary predictor of response to glutaminase inhibition is expression of the cystine/glutamate antiporter SLC7A11 (also known as xCT). Cells that express high levels of SLC7A11 are exquisitely sensitive to glutaminase inhibition, while those with low levels of SLC7A11 fail to respond. Therefore, SLC7A11 provides a promising theranostic marker for identifying patients that will respond to glutaminase inhibition therapies. Additionally, these inventors demonstrated that increasing levels of SLC7A11 is sufficient to sensitize cancer cells to glutaminase inhibitors. Interestingly, increasing the level of the amino acid dimer cystine (or monomer cysteine) that cancer cells are exposed to can similarly sensitize cancer cells to glutaminase inhibition, as this is a substrate of SLC7A11. Therefore, sensitizing cancer to glutaminase inhibitors by providing exogenous cysteine or SLC7A11 shows exciting potential as a new cancer therapeutic strategy.

Advantages

- Theranostic identification of patients sensitive to glutaminase inhibitor therapy
- Sensitization to glutaminase inhibitor therapy by activating SLC7A11 or providing cystine

Intellectual Property

IP Type: Published PCT Application

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Categories For This Invention:

Clinical Applications
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Diagnostics
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Publications:

Environmental cystine drives glutamine anaplerosis and sensitizes cancer cells to glutaminase inhibition
Elife
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