Graduate School of Biomedical Sciences

The Graduate School of Biomedical Sciences
Cancer Biology

Announces the PhD Thesis Defense of

ANNE CARLISLE

EXPLORING THE ROLE OF SELENOCYSTEINE BIOSYNTHESIS ENZYME SEPHS2 IN CANCER

Friday, November 6, 2020 at 10 a.m. Via Zoom Meeting

Selenium is a micronutrient that is used by the selenocysteine biosynthesis pathway to produce the amino acid selenocysteine, which is required in selenoproteins. Many of the 25 human selenoproteins, such as glutathione peroxidases and thioredoxin reductases, play important roles in maintaining cellular redox homeostasis. In this study we characterize how this metabolic pathway is upregulated in cancer cells and how this increase in activity creates a unique vulnerability. We have outlined the evidence and underlying mechanisms for how many metabolites normally produced in cells are highly toxic, and we describe this concept as illustrated in selenocysteine metabolism.

My thesis explores how SEPHS2, an enzyme in the selenocysteine biosynthesis pathway, is essential for survival of cancer, but not normal cells. SEPHS2 is required in cancer cells to detoxify selenide, an intermediate that is formed during selenocysteine biosynthesis. Breast and other cancer cells are selenophilic, owing to a secondary function of the cystine/glutamate antiporter SLC7A11 that promotes selenium uptake and selenocysteine biosynthesis, which, by allowing production of selenoproteins such as GPX4, protects cells against ferroptosis. However, this activity also becomes a liability for cancer cells because selenide is poisonous and must be processed by SEPHS2. These results show that SEPHS2 is a cancer specific target and indicates the therapeutic potential of SEPHS2 inhibition in the treatment of cancer. Collectively, this thesis identifies SEPHS2 as a targetable vulnerability of cancer cells, defines the role of selenium metabolism in cancer, and outlines a roadmap for future studies regarding toxic metabolites and cancer.

Mentor

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Dissertation Exam Committee

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