EBioMedicine 39 (2019) 9–10

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

A unique metabolic dependency for liver cancer stem cells

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"Stem Cells": two simple words which invoke ideas from anti-aging treatments to the growth of new hearts, lungs, and kidneys in the laboratory. But stem cells have a darker side. Just as stem cells are the origin for all healthy cells in the body, tumors are thought to originate, and survive, due to cancer stem cells (CSCs) [1]. One of the greatest historical challenges in treating cancer has been the ability of a tumor to survive treatment. Traditional chemotherapeutic regimens, radiation, and surgery can combine to render a tumor undetectable, but the same disease often recurs weeks, months, or years later. Worse, the recurrent disease is often resistant to the treatments originally used to stagger its growth. A number of studies have now suggested that much, if not all, of the recurrence of malignant neoplastic disease may be due to CSCs, which tend to be resistant to radiation and chemotherapeutics [1]. Thus, there has been substantial effort in recent years to target CSCs. In this issue of *EBioMedicine*, Li and coworkers move us one step closer to that goal by finding that the stemness and survival of hepatocellular carcinoma (HCC) CSCs depend upon the activity of the enzyme glutaminase [2].

The glutaminase enzymes exist as two isoforms: kidney glutaminase (GLS) and liver glutaminase (GLS2) [3]. Either enzyme is responsible for converting glutamate to glutamine, and thus they play roles in metabolism (by feeding the citric acid cycle) and managing reactive oxygen species (ROS, by supplying material for the glutathione biosynthetic pathway). These activities are critical in most cancers, which utilize glutamine to fuel energy generation and biomaterial synthesis [4]. Although the glutaminases have identical catalytic functions, the two have frequently been reported to have different roles in cancer, with GLS almost always being reported to support cancer growth [3,5,6], and GLS2 frequently being reported to suppress it [7]. Further, GLS is not required for proliferation or survival in healthy cells, which utilize a different metabolic program than most cancers and do not rely upon glutamine to feed their growth and survival. Because of this, drug development studies have aggressively targeted the enzyme, and one of the best reported GLS inhibitors, CB-839, is currently in clinical trials [6].

It was previously demonstrated that as HCC took on a more stem-like state, it began to express more GLS and less GLS2 compared to well differentiated HCC [2]. Similar observations have been made for other CSCs, with lung or head and neck CSCs tending to express a greater amount of GLS than related non-stem-like cancer cells [2]. Li et al. have expanded upon these findings, and begun to identify the role GLS plays in stemness. The authors identified two particularly important roles for the enzyme. First, the authors focused on ROS. CSCs are very sensitive to ROS, and preserving stemness requires careful control of ROS levels [1]. GLS is an intermediate component of the biosynthetic pathway for glutathione, one of the most important cellular regulators of ROS. The authors found that inhibition of GLS activity in stem-like HCC, either with the small molecule 968 [5] or via glutamine starvation of cells, resulted in accumulation of ROS and subsequent cell death. They were able to prevent cell death by treatment with an ROS scavenger, but not with a metabolite downstream of GLS activity. This showed that the GLS management of ROS levels was crucial in HCC CSCs, and also suggests that treatment of HCC CSCs with GLS inhibitors might be a useful clinical strategy.

The authors also demonstrate that GLS activity enhances Wnt/β-catenin signaling in HCC CSCs. Wnt is an extracellular protein which binds to membrane bound receptors, beginning a signaling pathway that results in buildup of β-catenin in the cytosol and subsequent translocation to the nucleus [8]. Once located in the nucleus, β-catenin activates a variety of transcription factors, many of which target genes that drive stemness and cancer [1,2]. One of the genes upregulated by Wnt/β-catenin signaling is GLS [9]. The authors showed that treatment of HCC CSC with hydrogen peroxide reduced expression of β-catenin. They then showed that inhibition of GLS prevented localization of β-catenin to the nucleus in HCC CSCs, and reduced expression of CSC markers such as Oct4 and Sox2. This suggests a positive feedback loop between GLS and the Wnt pathway, where Wnt signaling enhances GLS expression, and the expressed GLS then reduces ROS levels to allow β-catenin to more easily build up in the cytosol and enter the nucleus. Moreover, attempts have been made to target Wnt signaling via therapeutic approaches, and several drugs have entered clinical trials, but the general importance of Wnt signaling in most cells raises significant safety concerns for any eventual medication [10]. The identification of GLS, an enzyme that can safely be inhibited in most healthy cells [5,6], as a regulator of Wnt signaling in HCC CSCs thus has exciting implications for potential clinical therapies.

Taken together, Li and coworkers demonstrate a novel biological role for GLS, upregulation of Wnt/β-catenin signaling, and show that this enhances the stemness of HCC CSCs. They further demonstrate that GLS is a valid pharmaceutical target in HCC CSCs. It will be interesting in the future to see if this relationship between GLS, ROS and Wnt signaling is maintained in other CSCs, and if this will truly translate to a clinical therapy.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.11.063.
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https://doi.org/10.1016/j.ebiom.2018.12.026

Conflict of interest

The author is a listed inventor on pending patents for several inhibitors of the enzyme glutaminase.

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