"Serine and One-Carbon Metabolism in Breast Cancer Metastasis"–Letter

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Metastasis represents the main route of cancer progression and is responsible for approximately 90% of all cancer-related deaths (1). Metastatic disease is generally considered incurable, emphasizing the need for novel biologically targeted pharmaceutical therapies. In this issue, Li and colleagues show that inhibiting the metabolic enzyme of serine catabolism, serine hydroxymethyltransferase 2 (SHMT2), impairs tumor growth in *in vitro* and *in vivo* preclinical models of metastatic breast cancer (2). They also show elevated *SHMT2* in advanced primary breast tumors and nodal metastases at both the mRNA and protein level. Finally, increased *SHMT2* negatively correlated with disease-specific survival (DSS) in a genetic subgroup of 343 patients with breast cancer. SHMT2 is an essential enzyme for purine biosynthesis and cellular redox balance, due to its pivotal role in in folate metabolism and glutathione biosynthesis. It is, therefore, an attractive target for cancer metastasis, as oxidative stress capacity and folate metabolism are limiting in metastatic tumor formation (3).

Given the authors' findings, we hypothesized that *SHMT2* expression would be prognostic, specifically in patients with metastatic breast tumors. Among patients with distant metastasis ($n = 21$) in the TCGA database (4, 5), high *SHMT2* expression (above median) was associated with significantly poorer overall survival [OS; median survival time (MST) 20 vs. 107 months, $P = 0.01$], progression-free survival [PFS; (MST 20 vs. 34, $P = 0.04$], and DSS (MST 20 vs. 112, $P = 0.02$). Similarly, in patients with nodal metastasis ($n = 550$), high expression (highest vs. lowest quartile) was associated with poorer OS [75% survival time (75ST) 38 vs. 92, $P = 0.01$), disease-free survival (DFS; 75ST 45 vs. 92, $P = 0.06$), PFS (75ST 34 vs. 89, $P = 0.02$), and DSS (75ST 38 vs. 105, $P = 0.004$). In patients with nodal or distant metastasis, defined by advanced stage (AJCC III–IV, $n = 268$), OS (MST 51 vs. 107, $P = 0.02$), DFS (75ST 22 vs. 87, $P = 0.06$), PFS (MST 53 vs. not reached, $P = 0.009$), and DSS (MST 84 vs. not reached, $P = 0.01$) were all poorer in the group with higher expression. Although *SHMT2* expression was associated with a poorer prognosis for all patients with breast cancer, the effect size was much greater in patients with distant metastasis than those without [$n = 894$; HR, 2.57 per SD (95% confidence interval, 1.17–5.62) vs. 1.25 (1.06–1.49), 1.69 (0.84–3.38) vs. 1.33 (1.12–1.58), and 2.54 (1.15–5.61) vs. 1.45 (1.16–1.82) for OS, PFS, and DSS, respectively]. Our results provide further clinical correlation supporting research and development of therapeutic strategies targeting SHMT2 in patients with metastatic breast cancer.

Disclosure of Potential Conflicts of Interest

R.C. Sun reports personal fees and non-financial support from Maze Therapeutics outside the submitted work. S.K. Cheng reports grants from American Lung Association, Polyflex Corp. (unrestricted grant), and Barry Neustein (unrestricted grant) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Received July 22, 2020; revised August 12, 2020; accepted September 1, 2020; published first November 2, 2020.

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Mol Cancer Res 2020;18:1755

doi: 10.1158/1541-7786.MCR-20-0646

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