Cancer Research

Stearoyl CoA Desaturase Regulates Ferroptosis in Ovarian Cancer Offering New Therapeutic Perspectives

Michele Carbone[1] and Gerry Melino[2,3]

Better therapies are urgently needed for ovarian cancer, which is associated with an overall median survival of less than 5 years from diagnosis. In this issue of *Cancer Research*, Tesfay and colleagues show that stearoyl CoA desaturase (SCD1) is expressed at high levels in different isotypes of ovarian cancer and that SCD1 protects ovarian cancer cells from cell death. Pharmaceutical inhibition of SCD1 induces apoptosis and ferroptosis *in vitro* and *in vivo*. Combination therapies of SCD1 inhibitors and ferroptosis inducers significantly decrease ovarian tumor masses in mice. This novel therapy may prove useful to treat women with ovarian cancer.

See related article by Tesfay et al., p. 5355

Ovarian carcinomas are aggressive malignancies, which can be effectively treated at an early stage; when diagnosed at stage I, 5-year survival is over 90%. However, the vagueness of symptoms leads to delayed diagnosis and higher cancer stages for about 85% of women, and at these stages, these tumors are largely resistant to therapy. The overall 5-year survival for ovarian carcinomas, all stages combined, is less than 50%, the higher the stage the poorer the prognosis. Treatment for stages II and above includes surgery and aggressive chemotherapy, most often a platinum-based therapy in combination with taxol given intravenously or intraperitoneally. Many patients with ovarian cancer opt out from these aggressive chemo-regimens as they cannot tolerate the strong toxic side effects. Clearly, more effective and less toxic therapies are needed to treat this malignancy. The study by Tesfay and colleagues (1) suggests that stearoyl CoA desaturase (SCD1) inhibitors in combination with ferroptosis inducers may provide a novel, and hopefully effective and less toxic approach, to treat patients with ovarian carcinomas.

Dividing cells, including cancer cells, must increase their fatty acid pool for structural, energetic, and signaling purposes. SCD catalyze the introduction of a double bond in the cis-Δ9 position of saturated fatty acyl-CoAs. Accordingly, the primary substrates of SCD are palmitoyl-CoA and stearoyl-CoA, which produce palmitoleoyl-CoA and oleoyl-CoA, respectively. Therefore SCD, also known as Δ9-fatty acyl-CoA desaturase, produces monounsaturated fatty acids from saturated fatty acids, which in turn are used to produce cholesterol esters, diacylglycerols, phospholipids, wax esters, and triglycerides, which are all major components of cellular membranes. In humans, there are two SCD isoforms, SCD5, present in the brain and in the pancreas, and the ubiquitous and more abundant SCD1 (2). SCD1 is frequently overexpressed in several cancers and, according to The Cancer Genome Atlas, it is associated with the expression of lipid metabolism genes.

In cancer cells, SCD1 inhibits AMPK, enhances Akt, and modulates lipid metabolism by reducing fatty acid oxidation while fostering lipogenesis, thus promoting cancer cell growth (2). SCD1 inhibition induced apoptotic cell death in aldehyde dehydrogenase 1A1–positive cells and impaired tumorigenicity of lung cancer stem cells *in vivo* (3, 4). Furthermore, SCD1 inhibition impaired spheroid formation of primary lung cancer cells and in parallel reduced aldehyde dehydrogenase activity. Importantly, these effects were observed also in cancer stem cells (5). The biological effects of SCD1 on fatty acid metabolism are mediated by YAP/TAZ signaling, which in turn is regulated, at least in part, by the autocrine activity of the Wnt/β-catenin (CTNNB1) pathway (5). Depending on the experimental model used, SCD1 inhibitors have shown activity in distinct stages of tumorigenesis by modulating EGF, ER stress, PI3K/AKT/HIF2, and NF-κB pathways (2). In addition, ferroptosis and SCD1 metabolism share common lipid mediators (6).

Tesfay and colleagues (1) discovered that SCD1 is highly expressed in different isotypes of ovarian cancer and that SCD1 expression protects ovarian cancer cells from cell death. Moreover, SCD1 direct products, palmitoleic acid, oleate, palmitoyl CoA, and stearolyl CoA C16:1 and C18:1, had similar protective effects. Pharmaceutical inhibition of SCD1 using either MF-438 or CAY10566, and genetic depletion of SCD1 induced both apoptosis and ferroptosis. The effects on ferroptosis were linked to decreased synthesis of cytoprotective lipids such as mevalonate metabolite CoQ_{10}. These effects were supported by experiments using ovarian cancer mouse models. Mice injected with ovarian cancer cells were treated with the ferroptosis inducer erastin and with the SCD1 inhibitor A939572, administered alone or in combination. When used as single agents, both showed antitumor effects by reducing the size of well-established tumors. However, the combination of both erastin and A939572 was

[1]Thoracic Oncology, University of Hawaii Cancer Center, Honolulu, Hawaii. [2]Department of Experimental Medicine, TOR, University of Rome Tor Vergata, Rome, Italy. [3]Medical Research Council, Toxicology Unit, Department of Pathology, Cambridge University, Cambridge, United Kingdom.

Corresponding Authors: Michele Carbone, University of Hawaii Cancer Center, 701 Ilalo Street, Rm 437, Honolulu, HI 96813. Phone: 808-440-4596; Fax: 808-587-0790; E-mail: mcarbone@cc.hawaii.edu; and Gerry Melino, University Tor Vergata, Rome 00133, Italy. E-mail: gm614@mrc-tox.cam.ac.uk

Cancer Res 2019;79:5149–50

doi: 10.1158/0008-5472.CAN-19-2453

much more effective than either drug alone and resulted in a significant decrease of both number of tumor nodules and tumor mass. These results are very encouraging and if reproduced in independent experiments they would justify producing these or similar drugs for clinical trials in humans.

In vitro and *in vivo* results have shown an array of compounds with different degrees of selectivity for SCD1 inhibition. These include piperazinylpyridines, nicotinamide, and pyridazine derivatives, such as A939572, MF-438, CVT-12012, BZ36, SSI-4, and SW203668 (2); these have potential to rapidly evolve into novel therapeutic options. Ferroptosis inducers may act by depleting glutathione, directly targeting and inactivating glutathione peroxidase 4 (GPX4), depleting GPX4 and CoQ10 via the squalene synthase-mevalonate pathway, or they may promote lipid peroxidation by increasing the iron pool and/or by oxidizing iron, offering an array of combination possibilities.

In addition to generating clinically effective inhibitors with low toxicity, it will be critical to identify tumor types or subtypes that might be most susceptible to SCD1 inhibitors. Some of the pathways modulated by SCD1, including apoptosis and ferropoptosis, are regulated by *TP53* (7) and *BAP1* (8). Therefore, we propose that tumors that carry *TP53* and *BAP1* mutations, two of the most potent tumor suppressor genes, might benefit the most.

Although TP53 and BAP1 regulate multiple cellular functions, central to their tumor suppressor activity is their ability to modulate cell death via apoptosis and ferroptosis (7, 8). These activities are critical to (i) eliminate cells that have accumulated DNA damage and thus to prevent cancer and (ii) to induce cell death in tumor cells that characteristically must grow in a "toxic" oxidative environment. Therefore, mutations of these genes promote cancer development and cancer growth. Not surprisingly, *TP53* mutations are common in many cancer types, and *BAP1* mutations are frequent in specific types of very aggressive cancers, such as mesothelioma and metastatic uveal melanoma (9, 10). Moreover, inherited *TP53* and *BAP1* mutations cause the Li-Fraumeni and the BAP1 cancer syndromes. In these syndromes, close to 100% of carriers develop one and often several malignancies during their lifetime, underscoring the very powerful tumor suppressor activities of these tumor suppressor genes (9). There is a great need to find drugs that can benefit *TP53* and *BAP1* mutation carriers as well as patients with tumors containing somatic (acquired) mutations of these genes. The activities of p53 and BAP1 on apoptosis may involve separate pathways. p53 regulates the mevalonate pathway as well as the Hippo pathway, both involved in ferroptosis. Moreover, both p53 and BAP1 sensitize cells to ferroptosis by repressing the *SLC7A11* gene (7, 8). SLC7A11 imports the extracellular oxidized form of cysteine, cystine, in exchange for intracellular glutamate. Reduced SLC7A11 expression lowers the intracellular amount of reduced glutathione, diminishing the antioxidant capacity of the cell, which in turn leads to lipid peroxidation and ferroptosis (7, 8). Human cancer cells express increased amounts of SLC7A11 compared with normal cells, and this overexpression inhibits both ROS-induced ferroptosis and p53-mediated growth suppression in xenograft tumor models (7). This evidence suggests that SCD1 pharmaceutical inhibition might be more beneficial for human cancers with mutated *TP53* and *BAP1* by resensitizing these cells to ferroptosis. Similarly, depending on their toxicity, these same agents might be beneficial to prevent cancer in carriers of *TP53* and *BAP1* mutations. This could be easily tested in existing *TP53*- and *BAP1*-mutant tumor models.

Lipid metabolism plays a key role in cancer progression, it regulates metabolic adaptation, modulates the interaction of cancer cells with the microenvironment, and modulates drug responses. Here, Tesfay and colleagues (1) provide a new exciting opportunity to develop a novel approach to treat ovarian cancer and possibly to treat cancers carrying *TP53* and *BAP1* mutations. In addition, their elegant work provides a model to further study the mechanisms by which *TP53*, *BAP1*, and *SCD1* regulate apoptosis and ferroptotic cell death.

Disclosure of Potential Conflicts of Interest

M. Carbone has ownership interest (including patents) in patent on BAP1and HMGB1, and has provided expert testimony for various law firms. No potential conflicts of interest were disclosed by the other author.

Received August 8, 2019; accepted August 9, 2019; published first October 15, 2019.

References

1. Tesfay L, Paul BT, Konstorum A, Deng Z, Cox AO, Lee J, et al. Stearoyl-CoA desaturase 1 protects ovarian cancer cells from ferroptotic cell death. Cancer Res 2019;79:5355–66.
2. Tracz-Gaszewska Z, Dobrzyn P. Stearoyl-CoA desaturase 1 as a therapeutic target for the treatment of cancer. Cancers 2019;11. doi: 10.3390/cancers11070948.
3. Mancini R, Giarnieri E, De Vitis C, Malanga D, Roscilli G, Noto A, et al. Spheres derived from lung adenocarcinoma pleural effusions: molecular characterization and tumor engraftment. PLoS One 2011;6:e21320.
4. Pisanu ME, Noto A, De Vitis C, Morrone S, Scognamiglio G, Botti G, et al. Blockade of stearoyl-CoA-desaturase 1 activity reverts resistance to cisplatin in lung cancer stem cells. Cancer Lett 2017;406:93–104.
5. Noto A, De Vitis C, Pisanu ME, Roscilli G, Ricci G, Catizone A, et al. Stearoyl-CoA-desaturase 1 regulates lung cancer stemness via stabilization and nuclear localization of YAP/TAZ. Oncogene 2017;36:4671–2.
6. Hassannia B, Vandenabeele P, Vanden Berghe T. Targeting ferroptosis to iron out cancer. Cancer Cell 2019;35:830–49.
7. Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, et al. Ferroptosis as a p53-mediated activity during tumour suppression. Nature 2015;520:57–62.
8. Affar EB, Carbone M. BAP1 regulates different mechanisms of cell death. Cell Death Dis 2018;9:1151.
9. Carbone M, Amelio I, Affar EB, Brugarolas J, Cannon-Albright LA, Cantley LC, et al. Consensus report of the 8 and 9th Weinman Symposia on Gene x Environment Interaction in carcinogenesis: novel opportunities for precision medicine. Cell Death Differ 2018;25:1885–904.
10. Carbone M, Adusumilli PS, Alexander HR Jr, Baas P, Bardelli F, Bononi A, et al. Mesothelioma: scientific clues for prevention, diagnosis, and therapy. CA Cancer J Clin 2019;69:402–29.