Commentary

2-Hydroxylated fatty acids as candidates of novel drugs to promote chemosensitivity of gastric cancer

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Gastric cancer is an important disease, which is one of the leading causes of cancer-related death worldwide. Although the majority of the patients are treated with chemotherapy, resistance can develop, resulting in the limitation of the treatment efficacy [1]. Thus, it is important to clarify the molecular mechanisms regulating the growth of gastric tumor and its chemoresistance. It is also urgent to develop novel therapeutic drugs to promote chemosensitivity.

There are increasing evidences that proliferation and metastasis of cancer cells are modulated by the levels and composition of specific lipids, which could result from altered lipid metabolism. Among them, 2-hydroxylated fatty acids (2-OHFAs) are naturally occurring fatty acid derivatives in mammalian cells. An enzyme, fatty acid 2-hydroxylase (FA2H), catalyzes the introduction of a chiral (R)-hydroxy group at the second carbon atom of long-chain fatty acids, resulting in the formation of (R)-2-OHFAs [2]. The potential anti-proliferative activity of (R)-2-OHFAs biosynthesized by FA2H has been suggested. For example, cell-level analyses using HCT116 colon carcinoma cells have shown that endogenously expressing FA2H and administrated racemic 2-hydroxypalmitic acid (2-OHPA, a saturated type of 2-OHFA) improve sensitivity to Elisidepsin (PM02734), a synthetic plasma membrane-disrupting cyclodepsipeptide drug in cancer treatment [3]. However, integrated analyses using the clinical tumor samples and culture cells have not been performed regarding the role of FA2H and (R)-2-OHFA in the regulation of tumor cell growth and chemosensitivity.

In an article in *EBioMedicine*, Yao and colleagues focused on the cancer of stomach, in which FA2H is highly expressed, and analyzed FA2H levels in 117 clinical samples of gastric tumors [4]. The results showed that the FA2H levels were lower in the tumor tissues than those in surrounding normal tissues. Furthermore, the patients with higher FA2H expression have better overall survival. These results were also confirmed by analyses of four published datasets. Most importantly, FA2H levels were associated with clinicopathological status of patients, and the prognostic value of FA2H levels was evidenced especially for those in the earlier stage of cancer progression (TNM stage I–II). The authors also analyzed the levels of Gli1, a zinc-finger transcription factor composing Hedgehog signaling. Activation of Hedgehog signaling and the Gli1 expression are reported to contribute to the development of

chemoresistance to cisplatin by inhibiting platinum-DNA adduct repair and altering cellular accumulation of the drug [5,6]. The authors found higher Gli1 levels in the tumor tissues than those in surrounding normal tissues. Higher Gli1 levels were also associated with poor survival of the patients. These results suggested the role of FA2H as a prognostic signature in gastric cancer.

In order to analyze the alterations of the signaling pathways by FA2H and their effects on the chemosensitivity, the authors next used gastric cancer cell lines. Experiments using genetic manipulation and pharmaceutical supplementation provided the evidence that FA2H and its product (R)-2-OHPA increased chemosensitivity to cisplatin partially through the inhibition of mTOR/S6K1/Gli1 pathway, the non-canonical pathway for Gli1 activation. Since the levels of Smoothened (SMO), a member of the canonical Hedgehog pathway, were not affected, the involvement of the canonical Hedgehog signaling was unlikely. The authors also suggested AMPK phosphorylation as the major contributor to the mTOR inhibition by FA2H.

Finally, the authors evaluated the role of FA2H and (R)-2-OHPA in cell growth *in vivo* by using two gastric cancer cells implanted in nude mice. The results showed that FA2H knockdown promoted the tumor growth with increased Gli1 levels. Furthermore, (R)-2-OHPA treatment enhanced chemosensitivity to cisplatin with significant decreases in Gli1 levels. Most interestingly, the treatment with (R)-2-OHPA also alleviated cisplatin-induced body weight loss. These results altogether strongly suggested (R)-2-OHPA as a non-toxic endogenous lipid surrogate for inhibiting mTOR and Hedgehog signaling in combination therapy of gastric cancer.

However, the effects of (R)-2-OHPA treatment alone in tumor suppression *in vivo* were minimal, while FA2H knockdown significantly enhanced tumor growth. These results suggested the possible involvement of other (R)-2-OHFAs produced by FA2H. Thus, it is interesting to measure the actual levels of various (R)-2-OHFAs including (R)-2-OHPA by mass spectrometry. Similar quantitative analyses for 2-OHFAs would also be needed for the gastric cancer cells and clinical cancer samples. Another (R)-2-OHFA, 2-hydroxyoleic acid (Minerval), was reported to potently inhibit tumor progression and cause tumor cell death by inducing apoptosis in a xenograft model of human leukemia

Jurkat cells [7]. Although the relative contribution of FA2H in the formation of Minerval remains obscure, the involvement of Minerval may be possible. Considering 2-OHFAs could be rapidly incorporated into sphingolipids [8] and 2-OHFA-containing ceramides (*N*-(2-hydroxyacyl)sphingosines) induced apoptosis at lower concentrations than non-OH counterparts in C6 glioma cells [9], the anti-tumor activity of 2-OHFAs could be partially attributed to the formation of 2-OHFA-containing ceramides and their apoptosis-inducing activity. Other mechanisms may include the structural effects on cell membrane such as the modulation of membrane fluidity. The presence of the specific receptors is also possible, since a G protein-coupled receptor GPR109B is reported to bind to several OHFAs, 2- and 3-hydroxyoctanoic acid [10].

Although more in-depth studies are needed to clarify the mechanisms by which 2-OHFAs exert anti-tumor activity including an increase in the chemosensitivity, the authors strongly suggested 2-OHFAs as candidates of novel drugs for gastric cancer, which promote chemosensitivity to cisplatin. The effects on the chemosensitivity to other anti-tumor drugs than cisplatin is also expected and should be examined.

Disclosure

The author declared no conflicts of interest.

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