New Roles Opined for OPCML
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Summary: OPCML, frequently inactivated in ovarian tumors, mediates its antitumor effect via binding to the extracellular domains of several important oncogenic receptor tyrosine kinases (RTK). This, in turn, leads to the downregulation of RTKs in tumor cells and results in significant inhibition of tumor growth. Cancer Discovery; 2(2): 115-6. ©2012 AACR.

Commentary on McKie et al., p. 156 (1).

The use of an endogenous tumor suppressor protein as a therapeutic agent for cancer treatment opens up a new field of targeted therapy. It not only offers an opportunity for personalized therapy, but also permits simultaneous modulation of several oncogenic pathways in cancer cells. Such an approach may decrease the likelihood of pathway redundancy. In this issue, McKie and colleagues suggest that the use of this strategy to treat cancer may not be that far in the future (1).

OPCML, an opioid-binding protein/cell adhesion molecule, is important for regulation of opioid binding and associated signal transduction (2). It was originally isolated from brain but has recently been shown to be expressed in other tissues such as stomach, ovaries, oviduct, and uterus (3). Although its role in the female reproductive system is currently unknown, the frequent downregulation of OPCML due to loss of heterozygosity or epigenetic inactivation at 11q23 in ovarian tumors triggered investigation into its role as a tumor suppressor (4). It was reported that tumors with ectopic expression of OPCML had a significant reduction in growth rate in mice compared with tumors lacking OPCML expression; this phenomenon has subsequently been observed in other cancer types, including colon, prostate, breast, and cervix (5–7). Despite these intriguing findings, the mechanism by which this protein mediates its antiproliferative intracellular signaling has not been well understood, especially because OPCML is largely extracellular and is linked to the cell membrane only via phosphatidylinositol linkage (2).

The research conducted by McKie and colleagues (1) provides us with some important clues to this mechanism. They showed that OPCML downregulates a variety of important receptor tyrosine kinases (RTK), such as Eph receptor A2 (EphA2), fibroblast growth factor receptors (FGFR), and human epidermal growth factor receptor 2 (HER2), via binding to their extracellular domain in ovarian cancer cells. Using HER2 as a paradigm, they further showed that this protein–protein interaction led to the redistribution of HER2 within the cell membrane, thereby allowing its escape from the canonical clathrin endocytic route. Recycling of HER2 was therefore less likely to occur. This decrease in the recycling of HER2, coupled with its subsequent polyubiquitination, resulted in the efficient downregulation of HER2 (Fig. 1). Although the exact mechanism of downregulation of other RTKs by OPCML needs to be further elucidated, this result opens up opportunities for using rOPCML to treat cancer without the need for intracellular delivery, a major hurdle for cancer treatment. To this end, McKie and colleagues (1) have shown an approximately 50% to 80% reduction in total tumor burden following repeated intraperitoneal administration of rOPCML in orthotopic mouse models of ovarian cancer developed using cell lines lacking OPCML. Although the effect of rOPCML on EphA2 in these tumors was not revealed, a significant reduction in total and phosphorylated HER2 and FGFR1 levels was achieved, which could explain the observed antitumor effect.

Even though these results show the potential of developing therapeutic strategies based on OPCML and open up another potential avenue for treatment of ovarian cancer, several important issues must be considered before its use can be realized in a clinical setting. For instance, it would be important to study the biodistribution of rOPCML and its ability to target tumors following both intravenous and intraperitoneal administration, given the potential involvement of OPCML in several other tumor types. In silico high-throughput identification of other potential receptors that OPCML could bind to would also be important for its future clinical development. Common issues concerning the use of recombinant proteins in humans, such as stability and potential immunotoxicity, will also need to be addressed (8). More important, the combinational effect of rOPCML and current standard therapy in OPCML-negative tumors remains to be seen. Because rOPCML was able to downregulate p-Akt and p-Erk both in vitro and in vivo, rOPCML treatment may enhance killing of cancer cells in conjunction with chemotherapy. An increase

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in OPCML expression in tumors is also likely to occur following platinum-based therapy in the subgroup of patients whose tumors possess unmethylated OPCML promoter yet have low OPCML expression (5). A synergistic antitumor effect between chemotherapy and rOPCML is therefore plausible and warrants further investigation. Other rational approaches for combinational therapy can also be made based on the detailed mechanistic study presented in the article by McKie and colleagues (1). The use of bevacizumab in conjunction with rOPCML, for example, may be appropriate because OPCML does not seem to target VEGF receptors.

Despite the need to evaluate further the feasibility of using rOPCML to treat ovarian cancer, the study conducted by McKie and colleagues (1) provides important insights into the mechanism by which OPCML exerts its tumor-suppressive phenotype. Given the ability of OPCML to modulate several important RTKs in ovarian cancer cells through binding to their extracellular domains, the strategy of using rOPCML to treat cancer seems promising. It is foreseeable that patients who have tumors with low expression of OPCML will benefit the most from rOPCML treatment. However, several questions remain: Will all patients with low OPCML expression respond to rOPCML therapy? What are the other signaling pathways that could govern the therapeutic response to rOPCML? Does it have a direct impact on the tumor microenvironment? Answers to these questions, coupled with an improved understanding of both the biologic and clinical effects of this tumor suppressor protein, could lead to beneficial treatment of ovarian cancer patients with OPCML-based therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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