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# **Dietary omega-3 polyunsaturated fatty acids suppress expression of EZH2 in breast cancer cells.**

[Dimri M](#), [Bommi P](#), [Sahasrabuddhe AA](#), [Khandekar JD](#), [Dimri GP](#).

Department of Medicine, NorthShore University HealthSystem Research Institute, Evanston, IL.

The polycomb group (PcG) protein, Enhancer of Zeste Homologue 2 (EZH2), is overexpressed in several human malignancies including breast cancer. Aberrant expression of EZH2 has been associated with metastasis and poor prognosis in cancer patients. Despite the clear role of EZH2 in oncogenesis and therapy failure, not much is known about chemotherapeutics and chemopreventive agents that can suppress its expression and activity. Here, we show that dietary omega-3 (omega-3) polyunsaturated fatty acids (PUFAs) can regulate the expression of EZH2 in breast cancer cells. The treatment of breast cancer cells with omega-3 PUFAs, but not omega-6 PUFAs, led to downregulation of EZH2. Studies using proteasome inhibitor MG132 suggested that omega-3 PUFAs induce degradation of the PcG protein EZH2 through posttranslational mechanisms. Furthermore, downregulation of EZH2 by omega-3 PUFAs was accompanied by a decrease in histone 3 lysine 27 trimethylation (H3K27me3) activity of EZH2, and upregulation of E-cadherin and insulin-like growth factor binding protein 3 (IGFBP3), which are known targets of EZH2. Treatment with omega-3 PUFAs also led to decrease in invasion of breast cancer cells, an oncogenic phenotype that is known to be associated with EZH2. Thus, our studies suggest that the PcG protein EZH2 is an important target of omega-3 PUFAs and that downregulation of EZH2 may be involved in the mediation of antioncogenic and chemopreventive effects of omega-3 PUFAs.

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