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AUTHOR'S VIEW

The Hippo-YAP/TAZ pathway mediates geranylgeranylation signaling in breast cancer progression

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ABSTRACT
Protein geranylgeranylation (GGylation) regulates the function of various signal transducers including small GTPases and Ggamma subunits. The role of GGylation in breast cancer progression is poorly understood. Recent studies suggest that GGylation promotes the proliferation and migration of breast carcinoma cells through the Hippo-YAP/TAZ pathway.

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Geranylgeranylation (GGylation) is a lipidation process that covalently conjugates geranylgeranyl (GG) to the carboxyl terminal CAAX motif of proteins for anchoring to membranes. GGylation is catalyzed by 2 enzymes: geranylgeranyltransferase I (GGTase I) and GGTase II (also known as Rab geranylgeranyltransferase). Many cellular signaling proteins, particularly Ras, Rho, and Rab small GTPase family members and G-gamma subunits, are known to be modified by GGylation and require GGylation for their cellular function.[1]

Geranylgeranyl pyrophosphate (GGPP), the donor molecule for GGylation, is synthesized by the mevalonate pathway. Statins are inhibitors of 3-hydroxyl-3-methylglutaryl-CoA (HMG-CoA) reductase, a rate-limiting enzyme in the mevalonate pathway, and many studies have used statins to impair GGylation by inhibiting the biosynthesis of GGPP. The inhibitory effect of statins on cancer cell proliferation and survival has been recognized for more than 2 decades. It has been demonstrated that geranylgeranyl, but not farnesyl or other metabolites in the mevalonate pathway, is essential to rescue the inhibitory effect of statins on cancer cell proliferation. Subsequently, treatment of cancer cells with GGTase I inhibitors confirmed the essential role of GGylation in cancer cell proliferation. The downstream signaling pathway that mediates the inhibitory effect of statins has been investigated extensively. Rho GTPase has been proposed as the primary effector of GGylation in mediating cancer cell proliferation based on initial observations of cytoskeletal changes in cells upon treatment with statins.[2] However, the signaling pathway that mediates the effect of GGylation on cancer cell proliferation and survival was not defined until recent studies connected the Rho GTPase and GGylation signaling to the Hippo-YAP/TAZ pathway.

The first breakthrough was the discovery that lysophosphatidic acid (LPA) receptor, a G-protein coupled receptor (GPCR), activates Rho GTPase, subsequently inactivating Lats1/2 and stimulating YAP/TAZ transcriptional activity.[3] This work connects Rho GTPase signaling directly to the Hippo-YAP/TAZ pathway. Later, 3 research groups including our group independently discovered that GGylation signaling activates the YAP/TAZ pathway in breast cancer cells.[4-6] Two of the 3 groups confirmed that Rho GTPase is the mediator transducing GGylation signaling to YAP/TAZ. However, the effect of GGylation signaling on activity of the Hippo cascade (Mst1/2 and Lats1/2) showed discrepancy among the studies. Our data showed that inhibition of GGPP synthesis by atorvastatin or of GGylation by the GGTase I inhibitor GGTI-298 in MDA-MB-231 cells increased phosphorylation of MST1/2 and Lats1, which are the upstream kinases of YAP/TAZ in the Hippo signaling pathway, suggesting that GGylation regulates the Hippo signaling. The other 2 studies, however, reported that GGylation signaling activated YAP/TAZ independent of Lats1/2 in experiments using the Lats1/2 siRNA knockdown approach in MDA-MB-231 cells.[4,5] This discrepancy may result from differences in the experimental approaches. Further studies are necessary to verify the role of the Hippo proteins in mediating GGylation signaling in breast cancer cells.

Our studies also identified the Gγ subunit as the primary effector mediating the GGylation-dependent activation of YAP/TAZ in addition to Rho GTPase.[6] We observed that the G-β/G-gamma blocker gallein inhibited LPA-activated transcriptional activity of YAP/TAZ whereas fluorescein, an inactive gallein analog, did not.[6] A number of G-gamma subunits, such as Gγ2, Gγ5, Gγ7, Gγ10, and Gγ12, are GGylated.[7] It has been reported that ectopic expression of Gγ2, Gγ5, Gγ7, and Gγ12 induces stress fiber formation in HeLa cells, similar to the effect of activation of Rho GTPase.[8] Further studies found that G$\beta\gamma$ subunits activate the small GTPase Rap1a and its downstream effector Radil and promote spreading and adhesion of fibrosarcoma HT1080 cells.[9] Consistent with these observations, our studies have shown that gallein preferentially inhibits MDA-MB-231

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cell migration with a minor effect on cell proliferation,[6] suggesting that G$\beta\gamma$ subunits may specifically transduce breast cancer cell migration signaling to the Hippo-YAP/TAZ pathway. However, how G$\beta\gamma$ subunits transduce the signal to the Hippo-YAP/TAZ pathway is still a puzzle. One possibility that has been proposed is that G$\beta\gamma$ subunits activate Rap1a, which in turn arrests the RASSF proteins that are the activators of Mst1/2, thus inactivating the Hippo protein Mst1/2.[10]

An intriguing observation in our studies is the dependency of GGylation signaling-mediated breast cancer cell proliferation and migration on the Hippo-YAP/TAZ pathway. We have noticed that the intensity of Hippo-YAP/TAZ signaling directly determines the effect of GGylation signaling on breast cancer cell proliferation and migration. For example, Hippo–YAP/TAZ signaling in MCF7 cells is very weak. Accordingly, the response of MCF7 cell proliferation and migration to treatment with atorvastatin or the GGTase I inhibitor GGTI-298 is also weak. We have examined 9 breast cancer cell lines and found that the effect of GGylation on Hippo-YAP/TAZ signaling is highly correlated with its effect on breast cancer cell proliferation.[6] This observation suggests that the role of GGylation signaling in breast tumor growth and metastasis is contingent on establishment of Hippo-YAP/TAZ signaling during breast cancer progression. This observation may be useful in the application of statins or GGTase inhibitors for breast cancer prevention and therapy. It is predicted that statins or GGTase inhibitors would be effective for prevention or therapy only in breast cancer patients with tumors positive for Hippo-YAP/TAZ signaling.

In summary, GGylation signaling promotes breast cancer cell proliferation and migration through activation of the YAP/TAZ pathway. Studies on GGylation/Hippo-YAP/TAZ signaling suggest the GGylation pathway as an important therapeutic target for the treatment of breast cancer, particularly Hippo-YAP/TAZ–positive breast cancer.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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