Keeping a clean house to suppress HER2+ breast tumor growth

Autophagy (*self-eating*) is a process used by normal cells to keep a “clean house”. It degrades abnormal or damaged proteins and organelles, helps to fight infections and also provides energy during periods of fasting or exercise. Besides its function in normal physiological conditions, autophagy also plays a role in diseases such as cancer. Although the specific roles of autophagy in cancer are complex, it has been postulated to help prevent tumor formation by diminishing potential sources of oxidative stress and DNA damage in the cell. In some contexts, however, autophagy may also promote tumor progression by helping to fuel cell growth.

HER2 is a gene that plays an important role in the development of breast cancer. Approximately 20% of breast cancer patients have amplifications (multiple copies) of *HER2* and such amplifications lead to massive production of the HER2 protein. HER2 is involved in cell growth and proliferation, and its over-production makes cells grow and proliferate in an uncontrolled fashion. Breast cancers overproducing HER2 are classified as HER2-positive (HER2+) and are treated with drugs that block the activity of HER2. However, such therapies often have rate-limiting adverse side effects; many patients develop resistance over time; and their efficacy is somewhat limited in the setting of metastatic cancer. Thus, there is a need for new, improved therapies.

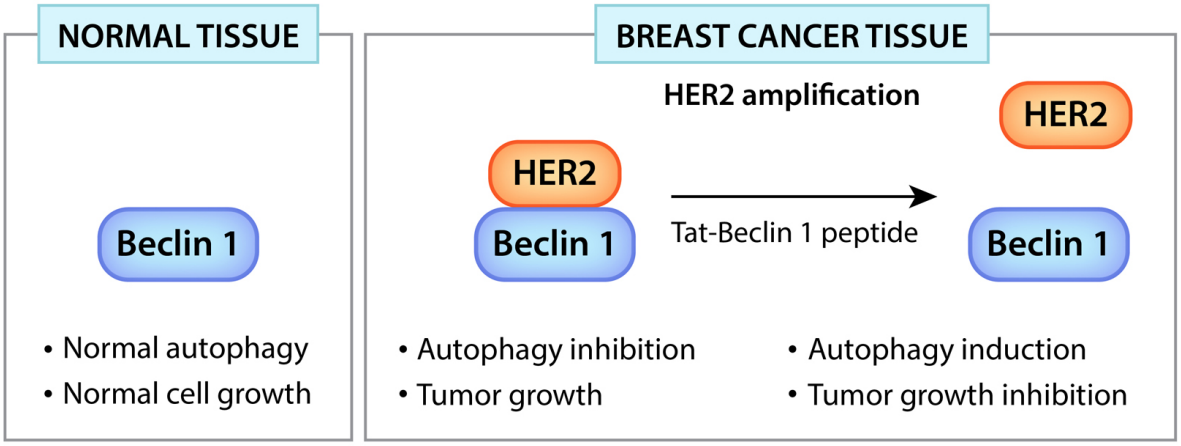

Fig. 1.

We showed that HER2 binds to Beclin 1, a protein essential for autophagy and suppression of tumor growth, and that HER2 renders autophagy inactive in HER2+ breast cancer cells. Thus, we hypothesized that this HER2-mediated block in autophagy might be beneficial for tumor growth and accordingly, that autophagy activation may help prevent tumor formation and/or tumor growth. We

tested this hypothesis using both genetic and pharmacological approaches. We assessed tumor formation in a genetically-engineered mouse model that has elevated levels of basal autophagy due to a knock-in mutation in Beclin 1 that prevents its binding to its inhibitor Bcl-2. These mice do not develop mammary tumors when crossed with mice that overexpress HER2 in the mammary gland and usually develop tumors around six months of age. These findings suggest that increased autophagy activity can prevent tumor formation.

To examine this more directly, we also tested a compound that activates autophagy (Tat-Beclin 1) in HER2+ breast tumor cells. Tat-Beclin 1 is a peptide known to induce autophagy both *in vitro* and *in vivo* in a manner that requires Beclin 1 and downstream autophagy machinery. We found that Tat-Beclin 1 activates autophagy *in vitro* in HER2+ breast cancer cells and disrupts HER2-Beclin 1 binding. We confirmed these results *in vivo* in xenografts formed by HER2+ breast cancer cells injected into mouse mammary glands. Treatment with Tat-Beclin 1, but not a control peptide, also induced autophagy in xenografts and disrupted the HER2-Beclin 1 complex. It induced a unique transcriptional profile distinct from that observed in HER2+ tumors treated with lapatinib (an HER2 tyrosine kinase inhibitor used in the clinic) and, most importantly, Tat-Beclin 1 effectively inhibited tumor growth as effectively as lapatinib.

Thus, our findings suggest that autophagy is a potential pathway to consider targeting in the treatment of certain types of cancers, either alone or in combination with other therapies. Tat-Beclin 1 might have advantages over other treatments since it directly targets autophagy without affecting other pathways, thus having potentially less side effects compared to cytotoxic chemotherapeutic drugs. Furthermore, it is well-tolerated in rodents and it has been shown to be beneficial in murine models of several diseases, including infectious diseases, cardiac and bone diseases, and axonal injury. Taken together, our data indicate that activation of autophagy and/or disruption of the HER2/Beclin 1 complex might be an efficient and safe treatment to inhibit HER2+ tumor growth (Fig. 1).

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