Targeting Glut3 and GABA Receptors Alleviates the Intestinal Side Effects of HER2 TKIs

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The tyrosine kinase inhibitors (TKIs) Lapatinib and Tucatinib are FDA-approved for the treatment of metastatic HER2-positive breast cancer. However, intestinal side effects, especially severe or chronic diarrhea, limit the clinical use of the two medicines. The development of strategies to alleviate these adverse events is required to improve the clinical benefits of HER2 TKIs. 3D organoid culture has been developed to recapture the mammalian intestine with two key aspects, physiological relevance to the intestine and the improvement over traditional 2D culture systems. By using intestinal organoids as the research model, we discovered that Lapatinib suppresses the adult type organoid formation, indicating the interruption of intestinal differentiation. Further, the treatment with Lapatinib not only causes downregulation of gene expression involved in crypt development but also increases Glut3 and GABA receptor expressions respectively contributing to aberrant glucose absorption and chloride flux in RNA seq and Ingenuity pathway Analysis (IPA). Targeting Glut3 by L-ascorbic acid (Vitamin C) or GABA receptors by Bicuculline protects organoids from Lapatinib-induced death. Interestingly, inhibition of Glut3 by L-ascorbic acid reduces the proliferation of lapatinib-resistant breast cancer cells. By using the translational research model, this study indicates that metabolism and electrolyte imbalance may contribute to Lapatinib-induced diarrhea and Glut3 inhibitor and GABA receptor antagonist are possible strategies to alleviate the side effects of Lapatinib.