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The role of mannose-6-phosphate receptor and autophagy in influencing the outcome of combination therapy

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Combining two different treatment modalities for targeting malignancies is gaining importance, with preclinical/clinical results indicating higher success rates in eradicating tumors or having longer remission periods. A better understanding of the synergy between the treatments helps in optimizing the dose and time of administration. We found that chemotherapy enhanced the levels of insulin-like growth factor 2 receptor/cation-independent mannose-6-phosphate receptor (IGF2R) on the surface of tumor cells, which leads to better tumor targeting by cytotoxic T cells (CTLs). Early evidence indicates that upregulation of IGF2R involves the autophagy pathway.

Our recent paper looks at the mechanism of action of combination (chemotherapy with immunotherapy) therapy used in the treatment of various malignancies. We have shown that conventional chemotherapy sensitizes tumor cells to CTLs via the upregulation of IGF2R on the surface of tumor cells. IGF2R functions as a receptor for GZMB/GrzB and may mediate cell killing. We found that tumor cells, with upregulated mannose-6-phosphate receptor (MPR) levels following chemotherapy, are able to bind soluble GZMB leading to the induction of apoptosis even in the absence of direct interaction with CTLs. Thus, chemotherapy allows for a bystander-killing effect in tumor cells, independent of antigen recognition.

Chemotherapy does not induce increased synthesis, nor is it instrumental in inhibiting degradation of MPR, yet immunohistology reveals stronger staining for IGF2R in tumor tissues after treatment of mice with different chemotherapies. We found that chemotherapy causes the redistribution of IGF2R to the surface of the tumor cells. One of the possible mechanisms that could be pivotal to this phenomenon is autophagy. In cancer development and tumor therapy, this catabolic pathway is reported to have paradoxical roles, promoting both cell survival and cell death. Autophagy is initiated by the formation of a phagophore around cytoplasmic oraganelles and/or some portion of the cytosol. The enclosed material is sequestered in a vesicle lined by two membranes called the autophagosome. Autophagosomes then undergo fusion with either endosomes or lysosomes. The role of autophagy as a topological inverter—bringing molecules and objects from the cytosolic side to the lumenal side for degradation or processing and interaction with lumenal receptors—may be of physiological importance to explain our observation. In our study, taxol (TAX), doxorubicin (DOX) and cisplatin (CIS) cause rapid induction of autophagy in tumor cells, which is associated with upregulation of MPR. Inhibiting autophagy with either 3-methyladenine (3MA) that blocks formation of autophagosomes by blocking PtdIns 3-kinases or by downregulating ATG5, a protein involved in the early stages of formation of autophagosomes, results in abrogation of chemotherapy induced upregulation of MPR on the tumor cell surface. Downregulation of ATG5 also completely abrogates GZMB penetration into the tumor cells. It is possible that IGF2R is redirected to autophagosomes either as

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part of clathrin-coated vesicles, or due to the fusion of autophagosomes with endosomes. In both cases, the cargo on IGF2R is released to the autophagosomes due to the low pH and the receptor is shuttled back to the surface. Thus, it is possible that chemotherapy-induced autophagy is associated with blockade of normal turnover of MPR within tumor cells that leads to its redistribution to the tumor cell surface. It has been shown recently that autophagy is superfluous for chemotherapy-induced cell death, but is required for its immunogenicity. Autophagy-competent cancers, in response to chemotherapy, attract dendritic cells and T cells into the tumor bed via ATP release. Thus, this pathway requires careful elucidation to connect the link between chemotherapy-enhanced IGF2R levels and effective immunotherapy.

To understand the role of IGF2R in combination therapy, antigen-specific T cells were adoptively transferred in combination with chemotherapy. The results showed that (1) chemotherapy causes only a transient upregulation of IGF2R on the surface of tumor cells, in vivo and (2) the effect of immunotherapy is significant only during the period when increased levels of IGF2R are present on the tumor cell surface. This showed that the sequence and the timing of administration of the therapies are important and need to be carefully considered for obtaining best results of combination therapy.

Although little is known about the link between IGF2R and autophagy, the evidence indicates that a close relationship exists between these pathways. Given the role of IGF2R in GZMB-mediated apoptosis, it is clear that this could be one of the pathways for successful therapeutic intervention in cases of advanced cancers. Further experiments to decipher the connection of both pathways at a molecular level would help in altering current treatment options to provide optimal results. Confirmation of this concept could lead to the use of IGF2R as a novel biomarker in determining the efficacy of combination therapy and in optimizing the time and sequence of treatment modalities.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.