Eliminating Drug Resistance of Lung Cancer Through Inducing Autophagy by Targeting USP24

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Drug resistance is one of the greatest obstacles during cancer treatment. It is urgent to solve this clinical issue globally. Previous study indicated that USP24, a deubiquitinase, can promote drug resistance and cause genomic instability. In this study, we first discovered that a novel USP24 inhibitor, NCI677397, can induce autophagy. Further, the down regulation of USP24 during mitosis decreased TRAF6, a ubiquitin E3 ligase of Beclin-1, and resulted in the induction of autophagy. Inhibiting autophagy with bafilomycin A1 during mitosis not only delayed the mitotic progression but also increased the amount of DNA debris, implying that mitotic autophagy plays an indispensable role in the maintenance of genomic integrity. We discovered that mitotic autophagy was inhibited by the higher USP24 level in drug resistant cell line, A549-T24, which will cause a higher rate of genomic instability, and contribute to the development of heterogeneity, subsequently leading to drug resistance. Last but not least, we found out that USP24 inhibitor, NCI677397, has the ability to eliminate drug resistance to chemotherapy and target therapy in an autophagy-dependent manner. To sum up, our study not only reveals how USP24 negatively regulates autophagy during mitosis, but also demonstrates that mitotic autophagy can facilitate the maintenance of genomic integrity, thereby preventing the development of drug resistance. Accordingly, we propose that targeting USP24 with USP24 inhibitor can eliminate drug resistance through inducing autophagy in lung cancer treatment.

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