MDM2 drives resistance to Osimertinib by contextually disrupting FBW7-mediated destruction of MCL-1 protein in EGFR mutant NSCLC

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Background: The gain-of-function alterations in epidermal growth factor receptor (EGFR) lead to its auto-phosphorylation and increased kinase activity. The blockade of EGFR pathway by small-molecule tyrosine kinase inhibitors (TKIs) has become the standard-of-care in non-small cell lung cancer (NSCLC) patients with EGFR mutants. Osimertinib is a brain-penetrable TKI and is licensed as a first-line treatment for stage IV NSCLCs with EGFR-activating mutations. Unfortunately, resistance to osimertinib invariably emerges after years of treatment. Overcoming resistance to osimertinib in mutant EGFR-bearing NSCLCs is clinically challenging because the underlying mechanisms are not fully understood. The murine double minute 2 (MDM2) has been extensively described as a tumor promotor in various malignancies. However, the contribution of MDM2 in the sensitivity to osimertinib has not been described.

Objective: To demonstrate MDM2, a largely underestimated candidate for targeted therapy, as a novel resistance mechanism to osimertinib in mutant EGFR-bearing NSCLCs.

Result: The authors modeled the acquired resistance to osimertinib (OR) by generating polyclonal acquired resistant cell pools by using stepwise dose escalation over 10 days followed by maintenance of osimertinib over 3 months. In comparison with parental PC-9 cells, the PC-9 OR resistant cells expressed a high level of MDM2. MDM2 promoted resistance to osimertinib through a PI3K/Akt and MAPK/Erk-independent pathway. Moreover, MDM2 selectively stabilized MCL-1 protein to arrest osimertinib-induced cancer cell apoptosis. The sensitive cells underwent pronounced apoptosis, as measured by TUNEL assay, whereas the proportion of TUNEL-positive signal in PC-9 OR and other MDM2-overexpressing resistant cells was significantly decreased. Following knocking down the expression of endogenous MDM2 in PC-9 OR cells, they found that osimertinib perturbed cell viability and led to a noticeable reduction in colony number. The reversal of resistance was accompanied by MCL-1 destabilization, suggesting that MDM2 launched a defense mechanism against MCL-1 destruction in response to osimertinib. Mechanistically, MDM2 acted as an E3 ligase to ubiquitinate FBW7, a well-established E3 ligase for MCL-1, which resulted in FBW7 destruction and MCL-1 stabilization. Targeting MDM2 to augment MCL-1 protein breakdown overcame resistance to osimertinib in vitro and in vivo. Finally, the clinical relevance of the MDM2-FBW7-MCL-1 regulatory axis was validated in a murine xenograft tumor model and NSCLC specimens.

Conclusion: Overexpression of MDM2 is a novel resistant mechanism to osimertinib in mutant EGFR bearing NSCLCs. MDM2 utilizes its E3 ligase activity to provoke FBW7 destruction and sequentially leads to MCL-1 stabilization. Therefore, targeting MDM2 would be a feasible approach to overcome resistance to osimertinib in mutant EGRR-bearing NSCLCs.