Increase of \( \text{MET} \) gene copy number confers resistance to a monovalent MET antibody and establishes drug dependence

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ABSTRACT

The relevant role in cancer played by the tyrosine kinase receptor encoded by the \( \text{MET} \) oncogene led to the development of specific inhibitors, some of which are now in advanced phases of clinical trials. Previous experience has shown that the main limit to the efficacy of most targeted treatments is the advent of resistance. Mechanisms underlying resistance to \( \text{MET} \)-specific small tyrosine kinase inhibitors (TKIs) have been already described, while nothing is known about resistance to \( \text{MET} \) monoclonal antibodies, nor about bypassing resistance to chemical TKIs by antibodies or vice-versa. EBC1 lung cancer cells are \( \text{MET} \)-addicted as a consequence of gene amplification and thus sensitive to \( \text{MET} \) inhibitors, including the monovalent form of a \( \text{MET} \) monoclonal antibody (MV-DN30). We generated cells resistant to this antibody and found that resistance was due to a further increase of gene copy number and a dramatic overexpression of the \( \text{MET} \) receptor. Such an excess of expression saturated the ‘shedding’ activity of MV-DN30, and prevented both the efficient down-regulation of the \( \text{MET} \) receptor from the surface and the inhibition of the ensuing constitutive activation. Notably, antibody-resistant cells remained \( \text{MET} \)-‘addicted’ and were still sensitive to \( \text{MET} \) TKIs. Moreover, antibody-resistant cells became ‘drug-dependent’, since the removal of MV-DN30 led them to death due to excess of signal. In the mirror experiment, cells made resistant to \( \text{MET} \)-specific TKIs were still sensitive to treatment with the antibody MV-DN30. These findings suggest that a discontinuous, combined treatment by antibodies and chemical kinase inhibitors may increase the clinical response and bypass resistance to anti-\( \text{MET} \) targeted therapies.

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