→ SIGNALLING

Seeing the big picture

SPACESCAPES

In order to improve targeted therapy it is important to understand both the possible systemic effects of targeting a particular pathway and how inhibition of one pathway may influence other pathways in the target cancer cell. Two recent papers have investigated these issues and have uncovered important roles for the receptor tyrosine kinase (RTK) AXL in both resistance to inhibitors of the ERBB family of RTKs and inflammation-induced tumorigenesis.

The underlying mechanisms of alternative RTK-mediated resistance to RTK inhibitors are not clear. Meyer *et al.* used a machine learning analysis of Cancer Cell Line Encyclopedia data to identify RTKs the expression of which could predict resistance to the ERBB inhibitors lapatinib (which targets epidermal growth factor receptor (EGFR) and ERBB2) and erlotinib (which targets EGFR). Reassuringly, lack of expression of the RTK targeted by each drug was the strongest predictor of resistance, but prediction was improved by also considering AXL expression. Triple-negative breast cancer (TNBC) expresses EGFR but is not sensitive to its inhibition. However, TNBC cell lines were sensitive to the AXL kinase inhibitor R428, and given the association of AXL expression with resistance the authors hypothesized that inhibition of AXL would resensitize cells to EGFR inhibitors; however, combination therapy was surprisingly subadditive rather than synergistic. One possible explanation is that the inhibition of one RTK might decrease the activity of the other. Indeed, AXL was activated following stimulation of EGFR (but the opposite did not occur), and knockdown of AXL or treatment with R428 abrogated downstream signalling induced by EGFR ligands. Immunoprecipitation assays showed that EGFR and AXL physically colocalized on the cell surface, suggesting a mechanism for transactivation.

AXL was also found in complex with the RTKs ERBB2, ERBB3 and MET, and the presence of AXL increased the activation of many downstream signalling pathways. These data illustrate the importance of understanding the details of RTK transactivation and crosstalk when designing therapies targeting RTKs — for example, therapies blocking ligand interactions may not be effective when RTKs are activated in *trans*.

In another study, Bosurgi *et al.* analysed the effects of loss of AXL, and the related RTK MER, in the development of inflammation-associated colon cancer. AXL can act as an oncogene in many tissues, but these authors found that $Axl^{-/-}$ $Mer^{-/-}$ mice are more susceptible to tumours induced by treatment with azoxymethane (a carcinogen) and dextran sulphate sodium (which induces colitis). Loss of AXL and MER increased proinflammatory cytokine secretion by leukocytes and reduced phagocytosis of apoptotic neutrophils by macrophages, which is necessary for the resolution of inflammation.

Although the data from Meyer *et al.* suggests AXL as a viable therapeutic target, and various therapeutics targeting AXL and MER are in development, the possible tumour suppressive role of AXL in the colon will be important to consider. If mechanisms of AXL activation in tumour cells are different from those in immune cells, such as RTK-mediated versus ligand-induced mechanisms, this could possibly be exploited for therapeutic benefit.

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> AXL was activated following stimulation of EGFR
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ORIGINAL RESEARCH PAPERS Meyer, A. S. *et al.* The receptor AXL diversifies EGFR signaling and limits the response to EGFR-targeted inhibitors in triple-negative breast cancer cells. *Sci. Signal.* **6**, ra66 (2013) | Bosurgi, L. *et al.* Paradoxical role of the proto-oncogene Axl and Mer receptor tyrosine kinases in colon cancer. *Proc. Natl Acad. Sci. USA* **110**, 13091–13096 (2013)