A high-content EMT screen identifies multiple receptor tyrosine kinase inhibitors with activity on TGFβ receptor

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An epithelial to mesenchymal transition (EMT) enables epithelial tumor cells to break out of the primary tumor mass and to metastasize. Understanding the molecular mechanisms driving EMT in more detail will provide important tools to interfere with the metastatic process. To identify pharmacological modulators and druggable targets of EMT, we have established a novel multi-parameter, high-content, microscopy-based assay and screened chemical compounds with activities against known targets. Out of 3423 compounds, we have identified 19 drugs that block transforming growth factor beta (TGFβ)-induced EMT in normal murine mammary gland epithelial cells (NMuMG). The active compounds include inhibitors against TGFβ receptors (TGFBR), Rho-associated protein kinases (ROCK), myosin II, SRC kinase and uridine analogues. Among the EMT-repressing compounds, we identified a group of inhibitors targeting multiple receptor tyrosine kinases, and biochemical profiling of these multi-kinase inhibitors reveals TGFBR as a thus far unknown target of their inhibitory spectrum. These findings demonstrate the feasibility of a multi-parameter, high-content microscopy screen to identify modulators and druggable targets of EMT. Moreover, the newly discovered ”off-target” effects of several receptor tyrosine kinase inhibitors have important consequences for in vitro and in vivo studies and might beneficially contribute to the therapeutic effects observed in vivo.
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