Drug Resistance via Feedback Activation of Stat3 in Oncogene-Addicted Cancer Cells

Authors
Ho-June Lee¹, Guanglei Zhuang¹, Yi Cao², Pan Du², Hyo-Jin Kim¹, Jeff Settleman¹

¹ Department of Discovery Oncology, Genentech, 1 DNA Way, South San Francisco, CA 94080, USA
² Department of Bioinformatics, Genentech, 1 DNA Way, South San Francisco, CA 94080, USA

Summary
Pathway-targeted cancer drugs can produce dramatic responses that are invariably limited by the emergence of drug-resistant cells. We found that many drug-treated “oncogene-addicted” cancer cells engage a positive feedback loop leading to Stat3 activation, consequently promoting cell survival and limiting overall drug response. This was observed in cancer cells driven by diverse activated kinases, including EGFR, HER2, ALK, and MET, as well as mutant KRAS. Specifically, MEK inhibition led to autocrine activation of Stat3 via the FGF receptor and JAK kinases, and pharmacological inhibition of MEK together with JAK and FGFR enhanced tumor regression. These findings suggest that inhibition of a Stat3 feedback loop may augment the response to a broad spectrum of drugs that target pathways of oncogene addiction.

Cancer Cell, Volume 26, Issue 2, p 207-221, 11 August 2014

Anthony Couturier
(Laboratoire Dr Jean-Yves Masson)

Le mercredi 1er octobre 2014, à 12 h
Auditorium du St-Patrick