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EGFR positive feedback loops and βeta Catenin driven miR-17-92 cluster converge to regulate EMT and drug resistance.

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Epidermal growth factor receptor (EGFR)-targeted cancer drug represents a milestone in oncology. Nevertheless the responses are invariably limited by the emergence of secondary drug-resistance (Misale, Di Nicolantonio et al. 2014). We found that drug-treated "EGFR-addicted" cancer cells engage a positive feedback loop leading to NF-KB/βCatenin axis activation (Lauriola, Enuka et al. 2014), consequently promoting cell survival and limiting overall drug response. Specifically, secondary activation of βCatenin drives the production of an oncogenic cluster of microRNAs 17-92 (Lauriola, Donghwa et al. 2015) implicated in EMT transformation and resistance in colon clones. Hence βCatenin and EGFR combination pharmacological inhibition overcome the colon spheres growth and enhance tumor regression. These findings suggest that inhibition of EGFR feedback loop along with NF-kB/βCatenin axis may increase the response to a broad spectrum of drugs that target pathways of oncogene addiction.

References

Lauriola, M., Y. Enuka, A. Zeisel, G. D'Uva, L. Roth, M. Sharon-Sevilla, M. Lindzen, K. Sharma, N. Nevo, M. Feldman, S. Carvalho, H. Cohen-Dvashi, M. Kedmi, N. Ben-Chetrit, A. Chen, R. Solmi, S. Wiemann, F. Schmitt, E. Domany and Y. Yarden (2014). "Diurnal suppression of EGFR signalling by glucocorticoids and implications for tumour progression and treatment." Nat Commun 5: 5073.

Misale, S., F. Di Nicolantonio, A. Sartore-Bianchi, S. Siena and A. Bardelli (2014). "Resistance to anti-EGFR therapy in colorectal cancer: from heterogeneity to convergent evolution." Cancer Discov 4(11): 1269-1280.

Lauriola, M., Donghwa, K., Li, Y., Francesconi, M., D'Uva G., Shibata, D., Malafa, MP., Yeatman, T., Coppola, D., R. Solmi and JQ Cheng(2015). "Adenomatous Polyposis Coli (APC) regulates miR17-92 cluster through β-catenin pathway in colorectal cancer." Oncogene, *under final revision*

Keywords

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