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Proto-oncogenes Crosstalk, Feedback and Expression, and Anti-cancer Drugs Resistance

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Summary

Proto-oncogenes like C-MYC, EGFR and others have physiological function in regeneration, wound and any stressfully injury to maintain tissue echotexture and healing. Notably, these growth factors work together and had life span to retain to basal level after tissue remodeling and retain its function like what happen in partial hepatectomy. While in cancer, as we work out in 2 transgenic model of liver cancer, we notice that oncogenes do not like each other and just one of them was highly expressive, it keeps other ones at basal level or degraded. Moreover, if one oncogene was inhibited or silenced, other oncogenes become active or expressed and result in anticancer drug resistance. So bispecific antibody could successfully reduce anti-cancer drug resistance.

Introduction

Cross talk of tyrosine growth factors and c-myc in liver regeneration

The liver regeneration in adult mice requires c-Myc [1], postnatal hepatocyte proliferation does not. Our findings demonstrate unexpected physiological roles for c-Myc in hepatocyte growth and proliferation throughout liver development. Here, we demonstrate that decreased hepatocyte size, cell ploidy, and disordered organ architecture are all results of perinatal c-Myc inactivation in the liver [2,3].

Under physiological circumstances, the loss of c-met did not seem to have a negative impact on hepatocyte function [4]. Yet, there was a significant impact on the liver's adaptive reactions to injury [5-7]. Moreover, the contribution of c-Met in the control of HSC response and support a distinct function for HGF/c-Met as a growth-factor-signaling pathway necessary for the regeneration of damaged liver [7-9].

The neuronal and epithelial organs of mice lacking the epidermal growth factor receptor (EGFR) exhibit a variety of abnormalities between mid-gestation and postnatal day 20 [10]. The transmembrane receptor tyrosine kinase known as the EGFR is activated by a number of ligands and results in the activation of several signaling pathways that primarily regulate proliferation, differentiation, and survival. It has been demonstrated that the EGFR signaling axis is crucial for liver regeneration after acute and long-term liver damage, as well as in cirrhosis [11]. While combined disturbance of EGFR and c-Met caused liver failure in normal mice [12].

Notably, High-level data evidence the share of growth factor like c-Met, c-Myc, EGFR in liver regeneration following resection and cytokine serial assessments in blood samples used to forecast liver [13].

Cross talk of tyrosine growth factors and c-myc in liver cancer

Loss of c-met enhanced liver cancer progression in c-Met conditional knockout mice as it extended phosphorylation and EGFR activity were linked to increased hepatocarcinogenesis,

and EGF-induced liver cancer over-expression in a transgenic mouse model [14,15].

In liver cancer, there is a synergy between c-Met and c-Myc, and c-Met transgenic animals have a defective Fas-mediated apoptotic pathway [16]. Although removal or reduction of HGF/c-Met signaling enhanced the tumor progression in both c-Myc transgenic mice and/or c-Myc/TGF transgenic mice, which is a typical function of liver cancers [17].

In our study in both EGF and c-Myc transgenic mouse model (submit article), we notice that in EGF transgenic model, the prolonged activation of EGFR enhanced loss of c-Met and keep the Myc protein at basal level similar to control non transgenic mice. While in ATT-myc model, we notice that both c-Met and EGFR were reduced and degraded with advanced stage of liver cancer [18].

Anti-cancer drugs resistance

Importantly, integrin 1 activation induced by ligands could result in c-Met activation, which would result in EGFR-TKI resistance [19]. In contrast, prolonged contact with the c-Met inhibitor (PF-2341066) caused the cells' EGFR to become activated [20]. Moreover, cells that are resistant to EGFR activation become vulnerable to PF-2341066 and an EGFR inhibitor when used together [21]. This implies that in resistant cells, the c-Met signaling may be balanced out by the EGFR

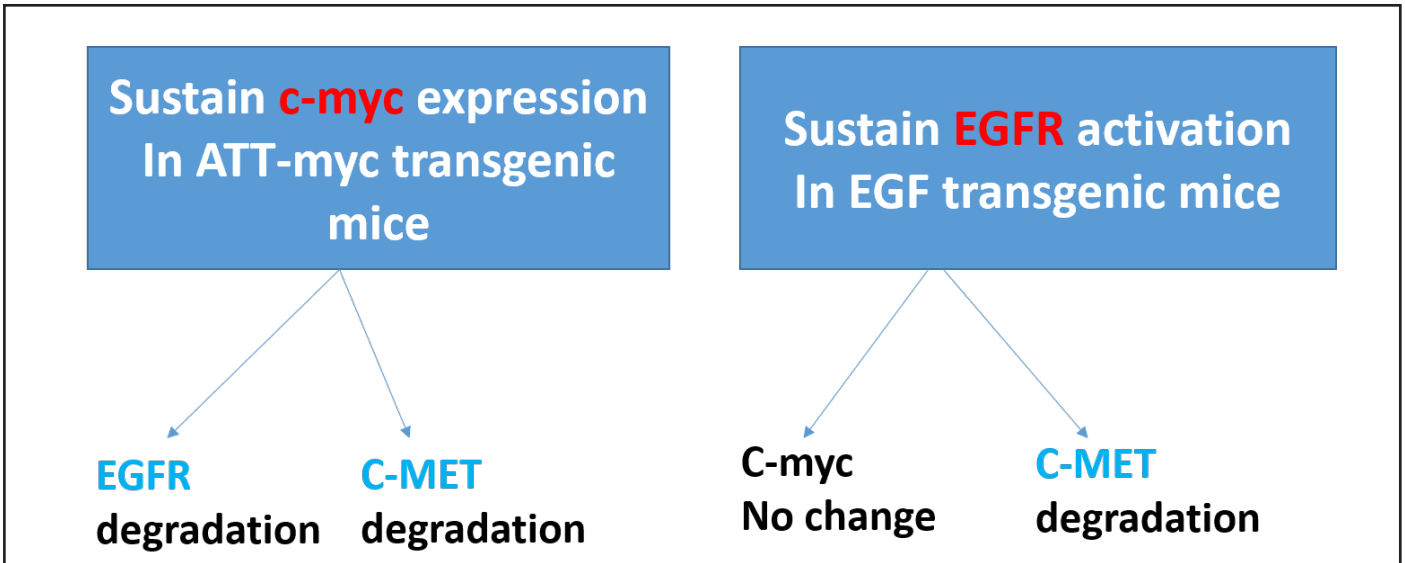

Figure 1.

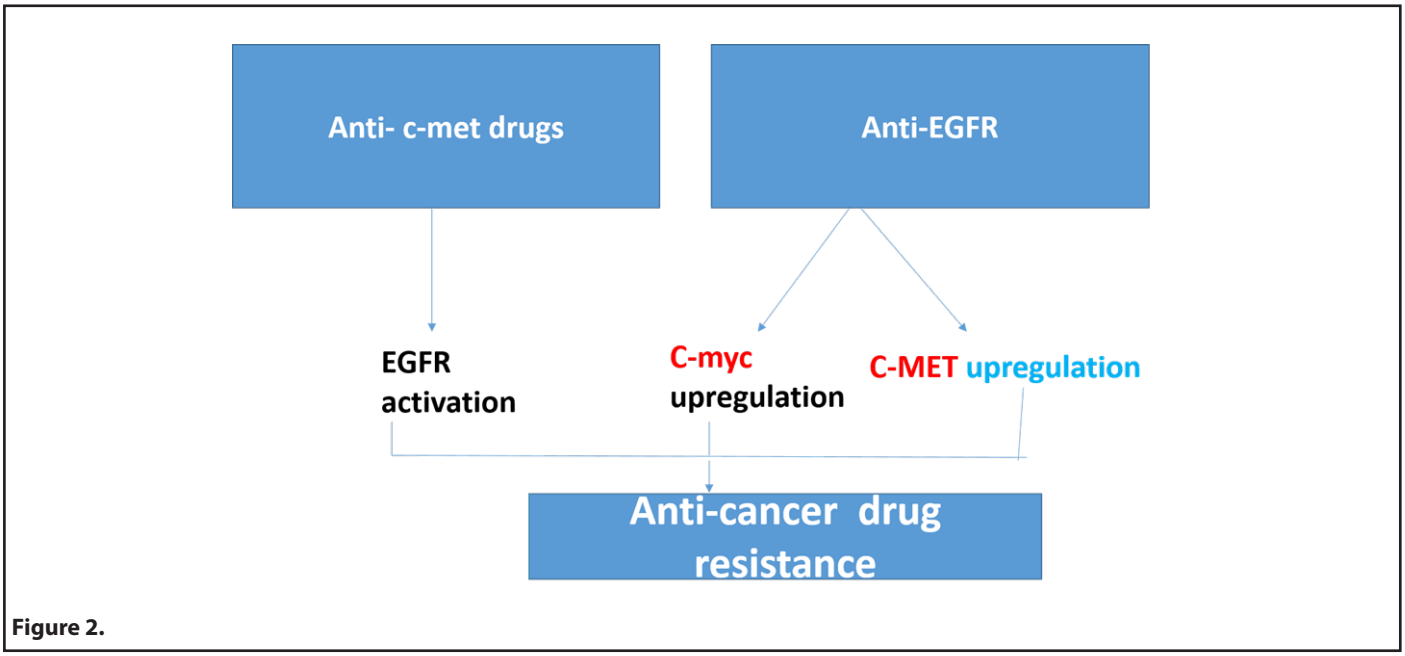

Figure 2.

pathway. Significantly, a recent study found that in NSCLC models, the selective c-Met inhibitor tepotinib can overcome resistance to epidermal growth factor receptor inhibitors caused by aberrant c-Met activation [22]. Also, EGFR tyrosine kinase inhibitor (TKI) resistance on-small cell lung cancer (NSCLC) result from aberrant c-Met activity [23,24] which mean that inhibition of EGFR leads to upregulation of c-Met or inhibition of c-Met could be compensated by activation of EGFR, and thus, this explains the resistance of TKI of both anti-EGFR or anti-c-Met.

Anti-EGFR resistance in metastatic colorectal cancer may be caused by changes to the transcriptional factor c-MYC (mCRC). Also, we discovered a strong relationship between the expression of the c-MYC associated miRNAs indicated above, the level of c-MYC, and anti-EGFR resistance. Moreover, c-critical MYC's function in CRC-related cell-cycle, apoptosis, signal transduction, and cell-growth pathways was highlighted by expression gene profiling [25,26].

Conclusions

The oncogene interaction and feedback expression play important role in tumor progression, and resistance against anti-cancer therapy.

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