Cancer Biology & Therapy 14:11, 997–998; November 2013; © 2013 Landes Bioscience

# ERK plays the baddie (again)

Paul Dent

Department of Neurosurgery; Massey Cancer Center; Virginia Commonwealth University; Richmond, VA USA

**Keywords:** ERK, MKP1, camptothecin, human colon cancer

Submitted: 09/02/2013

Accepted: 09/02/2013

http://dx.doi.org/10.4161/cbt.26377

Correspondence to: Paul Dent;
Email: pdent@vcu.edu

Commentary to: Lee M, Kim SY, Kim J, Kim H, Kim SM, Kim EJ. Mitogen-activated protein kinase phosphatase-1 inhibition and sustained extracellular signal-regulated kinase 1/2 activation in camptothecin-induced human colon cancer cell death. Cancer Biol Ther 2013; 14:1007-15; PMID:24005240; http://dx.doi.org/10.4161/cbt.26044

**It has been known for many years that elevated signaling by the ERK1/2 pathway is frequently associated with the growth and survival of many tumor cell types under a variety of normal and stressful conditions, including the response of cells to other cancer interventional therapeutic strategies e.g., references 1–4. There is, however, a modest significant literature showing that enhanced ERK1/2 signaling can also cause tumor cell death e.g., references 5–8. The role of ERK1/2 signaling is clearly complex, for example as shown by the Koumenis group where inhibition of radiation-induced ERK1/2 signaling caused radiosensitization, whereas inhibition of curcumin-hyper-stimulated ERK1/2 signaling reduced radiosensitivity.[7] Presumably this Janus-faced behavior of the ERK1/2 pathway in terms of cell survival regulation will depend upon the tumor cell type, the intensity of ERK1/2 stimulation, and the molecular intervention/drug being used.**

In the manuscript by Lee et al., the role of signaling by the ERK1/2 (MAP kinase) pathway was investigated in response to the standard of care agent camptothecin in colon cancer cells.[9] Activation of MAP kinase proteins such as ERK1/2 requires dual phosphorylation at a Thr-X-Tyr motif, with phosphorylation catalyzed by a dual specificity kinase; a MEK. Dephosphorylation of the Thr residing in ERK1/2 can be catalyzed by PP2A; however dephosphorylation of both the Thr and Tyr residues has been ascribed to dual-specificity phosphatases, in particular the MAP kinase phosphatase (MKP), MKP-1. MKP-1 is an immediate early inducible gene that catalyzes the dephosphorylation of ERK1/2, JNK1/2, and p38 MAPK.

Lee et al. first examined the activity of MAPK pathways in colon cancer cells and correlated this with MKP-1 mRNA and protein levels; MKP-1 protein and mRNA levels did not simplistically correlate, arguing MKP-1 protein expression was regulated at a posttranscriptional level. The K-RAS or p53 mutational status of these cells was not presented by the authors. In response to camptothecin treatment it was noticable that the most resistant cell line (CaCo2) had high basal levels of ERK1/2 activity whereas the most sensitive cell line (HCT116) had low ERK1/2 activity and high MKP-1 expression. In HCT116 camptothecin treatment strongly activated ERK1/2 that correlated with reduced MKP-1 expression. However, under these treatment conditions MEK1/2 phosphorylation declined while ERK1/2 activity was rising arguing that camptothecin effects on the ERK1/2 pathway are more complicated than just altered MKP-1 expression. That MKP-1 expression was only weakly altered during the initial phase of ERK1/2 activation would suggest other mechanisms, PP2A inactivation, regulating the pathway. Inhibition of proteasome function increased MKP-1 levels arguing that expression of this MKP is mediated by the proteasome. More importantly, inhibition of MEK1/2 using PD98059 or U0126 protected HCT116 cells from camptothecin toxicity, reducing the amount of sub-$G_1$ DNA using flow-cytometry assays.

Several questions remain unresolved from the present studies. No molecular approach was used to directly manipulate

MKP-1 expression or ERK1/2 pathway activity. The role of p53 in the ERK1/2-dependent response to camptothecin exposure in HCT116 and CaCo2 cells was not explored (CaCo2 are reported to be p53-null). As ERK1/2 can stabilize p21 expression a positive/negative role for p21 in regulating cell survival may be relevant in this system. No doubt the authors of the present manuscript will address these issues in future studies.

### Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.


### Acknowledgments

P Dent is funded by R01 DK52825 and R01 CA150214.


### References


1. Sajithlal GB, Hamed HA, Cruickshanks N, Booth L, Tavallai S, Syed J, Grant S, Poklepovic A, Dent P. Sorafenib/Regorafenib and PI3K/AKT Inhibition Interact to Kill Tumor Cells. Mol Pharmacol 2013; In press; PMID:23877009; http://dx.doi.org/10.1124/mol.113.088005
2. Andreadi C, Cheung LK, Giblett S, Patel B, Jin H, Mercer K, Kamata T, Lee P, Williams A, McMahon M, et al. The intermediate-activity (L597V)BRAF mutant acts as an epistatic modifier of oncogenic RAS by enhancing signaling through the RAF/MEK/ERK pathway. Genes Dev 2012; 26:1945-58; PMID:22892241; http://dx.doi.org/10.1101/gad.193458.112
3. Patwardhan RS, Checker R, Sharma D, Sandur SK, Sainis KB. Involvement of ERK-Nrf-2 signaling in ionizing radiation induced cell death in normal and tumor cells. PLoS One 2013; 8:e65929; PMID:23776571; http://dx.doi.org/10.1371/journal.pone.0065929
4. Hetman M, Kanning K, Cavanaugh JE, Xia Z. Neuroprotection by brain-derived neurotrophic factor is mediated by extracellular signal-regulated kinase and phosphatidylinositol 3-kinase. J Biol Chem 1999; 274:22569-80; PMID:10428835; http://dx.doi.org/10.1074/jbc.274.32.22569
5. Obitsu S, Sakata K, Teshima R, Kondo K. Eleostearic acid induces RIP1-mediated atypical apoptosis in a kinase-independent manner via ERK phosphorylation, ROS generation and mitochondrial dysfunction. Cell Death Dis 2013; 4:e674; PMID:23788031; http://dx.doi.org/10.1038/cddis.2013.188
6. Bareford MD, Hamed HA, Allegood J, Cruickshanks N, Poklepovic A, Park MA, Ogretmen B, Spiegel S, Grant S, Dent P. Sorafenib and pemetrexed toxicity in cancer cells is mediated via SRC-ERK signaling. Cancer Biol Ther 2012; 13:793-803; PMID:22673740; http://dx.doi.org/10.4161/cbt.20562
7. Javvadi P, Segan AT, Tuttle SW, Koumenis C. The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased reactive oxygen species production and overactivation of the mitogen-activated protein kinase pathway. Mol Pharmacol 2008; 73:1491-501; PMID:18252805; http://dx.doi.org/10.1124/mol.107.043554
8. Valerie K, Yacoub A, Hagan MP, Curiel DT, Fisher PB, Grant S, Dent P. Radiation-induced cell signaling: inside-out and outside-in. Mol Cancer Ther 2007; 6:789-801; PMID:17363476; http://dx.doi.org/10.1158/1535-7163.MCT-06-0596
9. Lee M, Kim SY, Kim JG, Kim HS, Kim SM, Kim EJ. Mitogen-activated protein kinase phosphatase-1 inhibition and sustained extracellular signal-regulated kinase 1/2 activation in camptothecin-induced human colon cancer cell death. Cancer Biol Ther 2013; 14:1007-15; PMID:24005240; http://dx.doi.org/10.4161/cbt.26044