Cancer Chemother Pharmacol (2008) 62:1113
DOI 10.1007/s00280-008-0696-8

LETTER TO THE EDITOR

Is oncogenesis a normal cellular defense mechanism?

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Received: 25 January 2008 / Accepted: 30 January 2008 / Published online: 15 February 2008

To the Editor:

Recently, Korystov et al. (*Cancer Chemother Pharmacol 2008; 61:15–21*) reported on the effects of irradiation in altering multidrug resistance (MDR) in tumor cells. Remarkably, tumor cells not only develop resistance after exposure to irradiation, but also develop resistance to chemotherapy or the newer so-called "targeted" therapies. Moreover, the authors' results and those of others demonstrate that conferring resistance can be induced by the insult, rather than merely as an inevitable consequence of the malignancy. For example, the epidermal growth factor receptor (EGFR) resistance mutation, T790M, occurs in about half of patients with acquired resistance to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib, but is rarely seen in patients not previously exposed to these agents (*Cancer Sci 2007; 98:1817–1824*).

Since malignant cells can activate specific pathways to remain viable, could oncogenesis itself sometimes be a defense pathway in non-malignant cells, which is activated in order to avoid cellular death? Evolution might favor selection of non-malignant cells, which could activate such pathways. Korystov et al. clearly demonstrated that the factors affecting MDR in tumor cells are factors that non-malignant cells are also subject to in vivo, such as variations in the density of cells. In addition, Sorrentino et al. (*Science 1992; 257:99*) induced MDR in non-malignant cells after exposure to paclitaxel.

Common mechanisms of oncogenesis involve insults (e.g., carcinogens or errors in mitosis), which activate protoncogenes into their oncogenic counterparts or inactivate tumor suppressor gene function. While it has been generally held that the oncogenesis in these cases is inadvertently caused by the insults, perhaps activation of these pathways, which result in the malignant phenotype, are in fact evolved pathways that protect normal cells. These pathways may be activated as an alternative to those resulting in cell death (e.g., apoptosis or autophagy). In such cases, it seems possible that the malignant phenotype could actually be due to selection, through evolution, of genomes within normal cells that allow cells to avoid cellular death.

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