Picropodophyllotoxin or Podophyllotoxin Does Not Induce Cell Death via Insulin-like Growth Factor-I Receptor

To the Editor:

The cyclolignan picropodophyllotoxin (PPP) was recently launched as an anticancer drug specifically targeting insulin-like growth factor-I receptor (IGF-IR; ref. 1). PPP is an epimer of podophyllotoxin (PPT), an established inhibitor of microtubule assembly used to treat genital warts. PPT binds to the colchicine binding site of tubulin (2). PPT-resistant cells are cross-resistant to colchicine, colcemid, and vinblastine (3). PPP is 20- to 50-fold less potent than PPT in inhibition of microtubule assembly (4) and the GI_{50} of PPP is ≈50-fold that of PPT (≈500 versus ≈10 nmol/L). This would be expected if growth inhibition by PPP is due to microtubule inhibition (discussed in ref. 3). Also consistent with this notion is that PPT-resistant cells are resistant to PPP (3).

Despite the documented microtubule effects, an association between IGF-IR expression and sensitivity to PPT/PPP was reported (1). Eleven cell types expressing IGF-IR were found sensitive to PPP, and three cell types lacking IGF-IR expression were resistant *in vitro* and/or *in vivo* (1). The *in vitro* GI_{50} for cell types lacking IGF-IR expression (R− cells, HepG2 cells) was >15 μmol/L for both drugs (1).

S. Linder and M. C. Shoshan reexamined PPT/PPP effects on IGF-IR–deficient R− cells, which were reported resistant to 15 μmol/L PPT/PPP (1). R− cells (from Dr. Renato Baserga, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA) and mouse embryo fibroblasts (MEFs) were exposed to 0.5 μmol/L PPT or PPP (from Dr. Girnita, Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden), a concentration used to inhibit IGF-IR (5). Both cell types were equally sensitive; PPP reduced viability of R1− cells to 52.6 ± 7.5% of control and of MEFs to 58.3 ± 6.4% of control, whereas PPT reduced viability to 51.8 ± 2.2% and 58.3 ± 6.4% of control, respectively [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay; 40 h]. Four independent experiments yielded similar results. Both drugs induced sub-G_1 debris in R− cells, indicative of cell death (PPT, 64% of total counts; PPP, 56%; controls, 6%).

PPP induces G_2-M arrest (5). This effect is not dependent on IGF-IR: PPP (0.5 μmol/L, 12 h) induced G_2-M arrest in IGF-1R–deficient cells (43.5% in G_2-M; 24.8% in untreated cells).

R. S. Gupta reexamined PPT/PPP effects on HepG2 cells, which were reported resistant to >15 μmol/L PPT/PPP (1). HepG2 cells were sensitive to PPT and PPP; the IC_{90} was 30 nmol/L for PPT and 0.5 μmol/L for PPP.

PPT treatment of cancer is limited by severe side effects. Although IGF-IR is an attractive cancer therapy target, our data showing that PPT and PPP induce loss of viability and cell death in IGF-IR–deficient cells contest their potential as IGF-IR–specific anticancer drugs.

Stig Linder
Maria C. Shoshan
Cancer Center Karolinska,
Department of Oncology-Pathology,
Karolinska Institute,
Stockholm, Sweden
Radhey S. Gupta
Department of Biochemistry
and Biomedical Sciences,
McMaster University, Hamilton,
Ontario, Canada

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