Induction of Apoptosis by Celecoxib in Cell Culture: An Uncertain Role for Cyclooxygenase-2

To the Editor:

A recent report by Kern et al. (1) described molecular mechanisms of apoptosis in human hepatocellular carcinoma cell lines in response to treatment with the selective cyclooxygenase-2 (COX-2) inhibitor (coxib), celecoxib. In their study, the authors treated Huh7 and HepG2 hepatocellular carcinoma cell lines with up to 100 μmol/L of celecoxib and found that this treatment led to tumor cell death via the activation of death receptor signaling and apoptosis originating from mitochondria; critical to these processes was the down-regulation of myeloid cell leukemia-1 (Mcl-1) protein, an antiapoptotic member of the Bcl-2 family. The authors concluded that the observed effects were mediated via the inhibition of COX-2.

In my laboratory, we have done similar experiments with the same and other cell lines that point to the opposite conclusion, i.e., that the effects of celecoxib are independent of any involvement of COX-2.

It has been well established that in cell cultures, coxib concentrations of 0.1 to 1.0 μmol/L are generally sufficient to rapidly and effectively block prostaglandin E2 production in different types of cells, including tumor cells with varying levels of overexpressed COX-2 (for example, see ref. 2). Therefore, one would expect that those drug effects that are dependent on COX-2 inhibition should be detectable at very low micromolar concentrations, and, furthermore, that they should be mimicked by other COX-2 inhibitors, such as the coxib rofecoxib or some of the traditional COX-1/COX-2 inhibitory nonsteroidal anti-inflammatory drugs. In contrast, structural analogues of celecoxib that lack the ability to inhibit COX-2 (3) should not be able to duplicate the COX-2–dependent effects of celecoxib.

We treated Huh7 and HepG2 cell lines with celecoxib, rofecoxib, indomethacin (a traditional COX-1/COX-2 inhibitor with an IC50 towards COX-2 that is comparable to celecoxib), or with 2,5-dimethyl-celecoxib (DMC, a close structural analogue of celecoxib that lacks COX-2–inhibitory activity; ref. 4). As shown in Fig. L4, celecoxib and DMC, but not rofecoxib or indomethacin, greatly reduced the viability of these cells; celecoxib and DMC of <100 μmol/L killed the vast majority of the cell population, whereas rofecoxib and indomethacin—even at 250 μmol/L—did not potently stimulate cell death. When the levels of Mcl-1 protein in drug-treated cells were analyzed, it became apparent that only celecoxib and DMC, but not rofecoxib or indomethacin, were able to down-regulate this antiapoptotic protein (Fig. 1B).

We repeated the above approach in a number of tumor cell lines with varying levels of COX-2 expression and obtained essentially the same results, i.e., that celecoxib and DMC, but not rofecoxib and indomethacin, potently down-regulated Mcl-1 protein expression and caused growth arrest and apoptosis. For example, as shown in Fig. 1, BxPC-3 and MIA-PaCa-2 pancreatic carcinoma cells responded nearly identically to these drugs, even though COX-2 protein is absent in the former and was expressed at very high levels in the latter (5).

Therefore, in consideration of the above-presented rationale for using these four drugs in parallel, in combination with their application to COX-2–positive and COX-2–negative cell lines, one would conclude that the observed effects of celecoxib on cell death and Mcl-1 are independent of COX-2—in agreement with
numerous other reports that have presented COX-2–independent
growth-inhibitory effects of this coxib.

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References

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