The Magnetic Resonance Imaging Contrast Agent Mangafodipir Exerts Antitumor Activity via a Previously Described Superoxide Dismutase Mimetic Activity

To the Editor:

It was recently described in Cancer Research by Laurent et al. (1) how low molecular weight superoxide dismutase (SOD) mimetics increase H2O2 levels, which in turn killed colon (CT26) and liver (Hepa 1-6) tumor cells. In contrast, the SOD mimetics stimulated proliferation of normal cells. Profound additional effects on the antitumor activity of oxaliplatin were shown after treatment with mangafodipir (manganese dipiridoxyl diphosphate, MnDPDP).

In 1994, our group suggested that MnDPDP possessed SOD activity and later confirmed this by spin trap electron spin resonance in 1999 (2). It was subsequently shown that MnDPDP possessed cardioprotective effects due to SOD mimetic activity (3). By omitting the original references, relevant mechanistic details are lost. In 2003, Batteux et al. reported in Journal of Hepatology, protective effects of MnDPDP in vivo against acetaminophen-induced murine acute liver failure (4). Without mentioning our original work, they stated: “Considering the structure of Mangafodipir trisodium (MnDPDP), a contrast agent currently used in MR imaging of the liver neoplasm, we hypothesized that this molecule could also exert an antioxidant activity and be possible used as treatment of APAP-induced ALF.” Although one of us made it clear in a Letter to the Editor of the journal that this was a discovery made many years ago, Batteux still refers to their 2003 article as being an original discovery. Furthermore, Kensler et al. first described the antineoplastic activity of SOD mimetics already in 1983 (5).

Cellular effects described by us and Batteux require that the SOD mimetic enters the intracellular space. Due to its hydrophilicity, it is unlikely that MnDPDP penetrates the plasma membrane. After being injected, MnDPDP is diphosphorylated into lipophilic MnPLED, which probably crosses the membrane (3). By omitting the original references, relevant mechanistic information is omitted from the discussion.

Another relevant item for discussion is Batteux’s earlier finding that MnDPDP possesses catalase activity (4), which is in opposition to our results showing no catalase activity (2). Whether or not MnDPDP possesses catalase activity is of course crucial to the suggested mechanism behind the tumor killing effect of SOD mimetic drugs (i.e., increase in H2O2). This interesting matter is not discussed in the Cancer Research article. It would be highly valuable to have Batteux’s comments on their previously described catalase activity of MnDPDP.

Although there is little doubt that the work done by Batteux et al. on liver protective (4) and antitumor (1) effects of MnDPDP represents high-quality science, it is regrettable that they have omitted our original references showing SOD mimetic activity of both MnDPDP and its metabolite MnPLED.

In Response:

I acknowledge that we did not quote the publications referenced in the letter by Karlsson et al. The first reason is that their demonstration of the superoxide dismutase (SOD)–like activity of mangafodipir was incomplete because they did not quantify the enzyme-like activity and made no comparisons with other standard SOD mimics. The second reason was that their work dealt with ischemic heart disease, which is far from our own field of research.

The aim of our work was to analyze the modulation of tumor growth by reactive oxygen species (ROS). For that purpose, 13 pharmacologic modulators of ROS have been studied. Three of them were SOD mimics: CuDIPS, MnTBAP, and MnDPDP (mangafodipir) that was only tested in the two last experiments (Figs. 5 and 6). As stressed by Karlsson et al., the mechanism of intracellular penetration of mangafodipir does not modify the enzymatic properties of the molecule. Therefore, we feel that there would have been no relevance in discussing the mechanism of intracellular penetration of mangafodipir.

Many SOD mimics have several enzymatic properties, but SOD activity remains their principal characteristic. In our report, we have used MnDPDP because of its SOD activity, which is 300-fold higher than its catalase activity. To modulate the catalase pathway, we have used catalase NAC and ATZ. The low level of catalase activity of mangafodipir compared with its SOD activity certainly explains the high effectiveness of mangafodipir against cancer cells and is consistent with our observation that a high level of catalase activity stimulates cancer cell proliferation. This has been discussed in-depth in our article.

Frederic Batteux, Ph.D.
Laboratoire d’Immunologie,
Hardy RDC, Hopital Cochin,
Cedex 14, Paris, France

References
The Magnetic Resonance Imaging Contrast Agent Mangafodipir Exerts Antitumor Activity via a Previously Described Superoxide Dismutase Mimetic Activity

Jan Olof G. Karlsson, Heidi Brurok, Rob Towart, et al.