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Oberley L W & Buettner G R. Role of superoxide dismutase in cancer: a review.
Cancer Res. 39:1141-9, 1979.
[Radiation Research Laboratory, University of Iowa, Iowa City, IA]

This paper reviewed the role of the enzyme superoxide dismutase (SOD) and its substrate, superoxide radical, in cancer. Lowered levels of SOD are found in most tumor cells compared to an appropriate normal cell control. The effect of this diminished activity on tumor cell phenotype and cancer treatment was discussed. [The *SCI*® indicates that this paper has been cited in more than 250 publications.]

Superoxide Dismutase and Cancer

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In March 1975, I started work as an instructor of physics in the Radiation Research Laboratory, University of Iowa, Iowa City. As a newly trained PhD physicist, I wondered how I was to set up a research program in a radiation biology department with little physics research apparatus. It quickly became obvious that radiation biology would have to be my research field.

After studying the literature, I decided that the radiobiological oxygen effect would be an interesting area to pursue. As luck would have it, an article by I. Fridovich on the superoxide dismutases (SODs) appeared at that time.¹ Mention was made of the possible role of these enzymes in the oxygen effect, so I decided this was the avenue to pursue. I have spent the last 15 years studying the SODs—a tribute to the eloquence of Fridovich.

After it was demonstrated that SOD was a radioprotector, I wondered whether SOD could be used in radiation therapy of cancer to protect normal tissue. I thought we should measure the levels of SOD in tissues before starting these experiments. New impetus to make these measurements occurred when I became aware of an article showing lowered levels of SOD in cultured virally transformed cells.² The first papers demonstrating diminished SOD in *in vivo* tu-

mors appeared shortly thereafter, including our first report in this area.³ These studies caused me to switch from radioprotection to cancer cell biochemistry, since I felt that loss of an important antioxidant like SOD must have drastic consequences to the cell.

In 1976, Garry R. Buettner, a new postdoctoral fellow, joined my research group. Soon after his arrival, I started pestering him about the importance of SOD in cancer. Garry became even more enthusiastic about this concept than I. He was soon carrying around an enormous chart detailing possible chemical reactions in the tumor cell. He kept saying we should write this up. I kept stalling, but eventually relented. This review was the result.

This paper is frequently cited because it was the first review of a new area of cancer research. In addition, the last part of the paper presented three hypotheses about the role of SOD in cancer. Many scientists have referenced this review because of their attempts to disprove these hypotheses; to date, none have done so.

This research has never won any awards. In fact, obtaining support for this research has been exceedingly difficult. Nevertheless, the ideas presented in this paper have borne the test of time. For instance, in this review we predicted that addition of SOD to tumor cells should lead to loss of part of the tumor cell phenotype; it has recently been demonstrated that addition of liposomal SOD to erythroleukemia cells causes differentiation.⁴ We also predicted that SOD had a role in cancer therapy; recently, G.H.W. Wong and D.V. Goeddel, in collaboration with our group, have demonstrated that resistance to the direct killing of tumor cells by tumor necrosis factor is due partially to SOD induction.⁵ We also assumed in this review that the superoxide radical is one of the agents that causes carcinogenesis; this fact has since been demonstrated by numerous investigators.⁶ I believe this work will continue to be cited because of the increasing recognition that superoxide radical and the superoxide dismutases are important in cancer.

1. Fridovich I. Oxygen: boon and bane. *Amer. Sci.* 63:54-9, 1975. (Cited 90 times.)
2. Yamanaka N T & Deamer D. Superoxide dismutase activity in WI-38 cell cultures. Effects of age, trypsinization, and SV-40 transformation. *Physiol. Chem. Phys. Med. NMR* 6:95-106, 1974.
3. Sahu S K, Oberley L W, Stevens R H & Riley E F. Superoxide dismutase activity of Ehrlich ascites tumor cells. *J. Nat. Cancer Inst.* 58:1125-8, 1977.
4. Beckman B S, Balin A K & Allen R G. Superoxide dismutase induces differentiation of Friend erythroleukemia cells. *J. Cell. Physiol.* 139:370-6, 1989.
5. Wong G H W, Elwell J H, Oberley L W & Goeddel D V. Manganese superoxide dismutase is essential for cellular resistance to tumor necrosis factor. *Cell* 58:923-31, 1989.
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Received October 16, 1990