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Review

Selenoproteins that function in cancer prevention and promotion

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ABSTRACT

Of the many health benefits attributed to selenium, the one that has received the most attention is its role in cancer prevention. Selenium-containing proteins (selenoproteins) have been shown in recent years to have roles in cancer prevention. However, selenoproteins have diverse functions and their view as antioxidants is oversimplified. Some selenoproteins appear to have a split personality in having roles both in preventing and promoting cancer. The contrasting roles of one selenoprotein, thioredoxin reductase 1, in cancer are discussed in detail, but as also noted, at least one other selenoprotein may also have such a dual function. In addition, we discuss examples of inhibition of cancer development by selenoprotein deficiency in mouse models. These studies highlight the complex nature of selenium in relation to cancer.

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1. Introduction

Among the many health benefits attributed to selenium that include roles in cancer prevention, inhibiting viral expression, delaying the progression of AIDS in HIV-infected patients, preventing heart disease and other cardiovascular and muscle disorders, slowing the aging process, and having roles in mammalian development, male reproduction and immune function [1], the one that has received the most attention is its role as a cancer chemopreventive agent.

The manner in which this element acts in preventing cancer is poorly understood; and there has been considerable debate in the field whether selenium-containing proteins (selenoproteins) or low molecular weight (non-protein) selenocompounds, or both, are effective in preventing cancer [e.g., see [2–11]. Investigators favoring the proposal that selenocompounds have more influence have argued that the effectiveness of selenium in cancer prevention is seen only following supplementation of the diet with amounts of selenium that are significantly higher than the normal dietary intake [12] and these higher amounts do not increase selenoprotein levels in circulating blood [13,14]. Although substantial experimental data have been obtained supporting the selenocompound proposal [e.g., see [2–5,7,11], many of these studies were carried out in mice supplemented with selenocompounds at levels that could not be used in humans for safety reasons and at the time when an in-depth understanding of only a limited number of selenoproteins was available. We now know that humans have 25 selenoprotein genes and rodents 24 [15].

Our knowledge about the roles of several selenoproteins in cancer is rapidly developing from different approaches that include biochemical, genetic and animal studies. These studies have provided strong evidence that selenoproteins play a major role in cancer prevention and other health benefits in a number of settings and model systems [e.g., see [1,6,8–11,16–19]. For example, two recent studies involving mouse models have shown a direct role of selenoproteins in colon [20] and prostate [21] cancers. Interestingly, one of these studies demonstrated that low molecular selenocompounds also had a role in cancer prevention [20].

Several excellent articles in this special issue on "Selenoprotein expression and function" cover related topics on the roles of selenoproteins in cancer. In the present review, we highlight the complexity of the roles of selenium in cancer and discuss selenoproteins that appear to have roles in both preventing and promoting cancer. We have used thioredoxin reductase 1 (TR1) as a model example to examine the possible molecular mechanisms of how a single protein can have such opposing functions. Finally, in contrast to the well-established role of selenium in preventing cancer, we discuss incidences where selenium deficiency may inhibit tumorigenesis.

2. Selenoproteins harboring a split personality in their roles in cancer

It is becoming more and more apparent that some selenoproteins can serve roles as both a cancer preventing agent and, once the malignancy is initiated, as a cancer promoting agent [e.g., see [22] and references therein]. We will focus on one such selenoprotein, TR1, and also consider another selenoprotein, the 15 kDa selenoprotein (Sep15).

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