

Commentary: Biochemistry

Superoxide Dismutase Switch in Breast Cancer: A Potential Target for Cancer Therapy

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Abstract. Superoxide Dismutases (SODs) are enzymes involved in converting toxic superoxide radical into either molecular oxygen or hydrogen peroxide in biological systems. A switch from Superoxide Dismutase (SOD) 2 to SOD1 activity in breast cancer cells functions as a key adaptive mechanism to protect the mitochondria from increased oxidative damage. This switch is critical for cancer cells to maintain proliferative growth. Importantly, inhibition of SOD1 could serve as a potential anti-cancer therapy.

Reactive oxygen species (ROS), such as superoxide radicals, hydrogen peroxide, singlet oxygen and hydroxyl radicals, are predominantly produced in the mitochondria as by-products of the electron transport chain (Waris & Ahsan, 2006). Elevated ROS levels in the mitochondria not only result in oxidative damage within the organelle, but also oxidise deoxyribonucleic acids in the nucleus, lipids in cellular membranes and cysteine residues in cellular proteins (Jacob & Burri, 1996).

Cells possess a well-developed defense system against ROS. This system functions both to limit the formation of ROS and to eliminate the accumulated ROS. The SOD family of antioxidant enzymes, namely SOD1 (copper-zinc superoxide dismutase, Cu-Zn- SOD) and SOD2 (manganese superoxide dismutase, Mn-SOD), are the first line of defence against ROS. SOD1 localizes primarily to the cytoplasm and in small amounts to the inter-membrane space of the mitochondria. On the other hand, SOD2 is solely found in the mitochondrial matrix where its activity is regulated by sirtuin-3 (SIRT3) deacetylase (Tao *et al.*, 2010). Both SODs catalyse the conversion of highly reactive superoxide radicals into oxygen and hydrogen peroxide, the less

reactive oxygen species. The hydrogen peroxide is subsequently converted to water by other antioxidant enzymes, including catalase and peroxiredoxin (Chen *et al.*, 2009).

A wide range of human diseases are known to be associated with elevated ROS levels. In fact, cancer cells are specifically characterised by increased ROS levels (Lu *et al.*, 2007). A recent study has found a significant reduction in the expression levels of SIRT3 deacetylase in 87% of breast cancers (Finley *et al.*, 2011). This potentially explains the elevated ROS levels observed in cancer cells. SIRT3 deacetylase binds to, deacetylates and activates SOD2. However, with reduced SIRT3 deacetylase expression in cancer cells, as in the case of breast cancer, SOD2 remains inactivated, resulting in an increase in ROS levels.

In line with the decreased levels of SIRT3 deacetylase and consequently compromised SOD2 activity, Papa *et al.* (2014) have reported that breast cancer cells undergo a SOD switch from SOD2 to SOD1. The authors hypothesised that under conditions of compromised SOD2 activity, in the absence of SIRT3 deacetylase, an alternative mechanism would be operating to limit and maintain low ROS levels in the mitochondria. Since SOD1 can serve as an alternate isoform of SOD present in the mitochondria, the aim of Papa *et al.* (2014) was to analyse SOD1 activity in a variety of breast cancer models.

The initial findings indicated that SOD1 was indeed overexpressed in 70% of human primary breast cancers and also showed increased expression levels in different mouse models of mammary tumours. These results were further supported by subsequent experiments conducted in a panel of five breast cancer cell lines. The authors found a combined reduction in SOD2 and overexpression of SOD1 in these cell lines, strongly suggesting that SOD1 could possibly be the vital dismutase activity in breast cancer.

Papa *et al.* (2014) proposed that the switch from SOD2 to SOD1 activity in cancer cells serves as an adaptive mechanism to maintain low ROS levels in the mitochondria. Moreover, based on their findings, they have suggested the possibility that SOD1 could potentially be an important anti-cancer target.

The findings by Papa *et al.* (2014) are supported by a previous study by Oberley and Buettner (1979). These authors had also shown that cancer cells contained mainly Cu-Zn SOD (SOD1), with almost no detectable Mn-SOD (SOD2) activity. The authors suggested that loss of Mn-SOD (SOD2) activity was a characteristic of cancer cells but not normal cells, which has been further experimentally confirmed by Papa *et al.* (2014). The consistency of the results published by Papa *et al.* (2014) with the previous study serves to validate the conclusions by Papa *et al.*

The suggestion by Papa *et al.* (2014) that SOD1 could potentially be an important anti-cancer target is also biologically grounded. In a recent study by Glasauer *et al.* (2014), the authors reported that inhibition of SOD1 with the small molecule ATN-224 induced cell death in various non-small-cell lung cancer (NSCLC) cell lines. Experiments conducted by the authors showed that SOD1 is expressed at elevated levels in NSCLC as compared to normal lungs,

consistent with what was reported by Papa *et al.* (2014). The authors then identified SOD1 inhibition to potentially induce cancer cell death. The small molecule ATN-224 is an analog of tetrathiomolybdate and inhibits SOD1 by binding to and removing copper from the active site of the enzyme. Since SOD1 is the key dismutase in cancer cells, its inhibition resulted in an increase of superoxide levels in NSCLC cells. As a result, the increased oxidative damage in these cancer cells led to their cell death. Notably, the results in Glasauer *et al.* (2014) also indicate that ATN-224 has potential clinical applications, as a single drug or in combination with other drugs, for various forms of NSCLC. Hence, the study by Papa *et al.* (2014) provides a strong groundwork for future clinical trials to exploit SOD1 as a promising target for cancer therapy.

Taken together, the important findings by Papa *et al.* (2014) of a switch from SOD2 to SOD1 expression in breast cancer cells are well-supported by complementary experimental studies. The future direction to therapeutically target SOD1 in breast cancer, as proposed by the authors, may lead to a novel approach for tumour selective induction of cell death.

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