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Is Oxidative Stress in Cancer Cells a Real Therapeutic Target?

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Editorial

Cancer remains one of the major public health problems and represents second leading cause of death worldwide [1]. Despite concerted efforts to improve the current therapies, the prognosis of cancer remains very poor [1]. In the past few decades, research scientists have mainly focused on development of highly selective anticancer drugs by exploiting the genetic differences between cancer cells and normal cells. Several highly selective anticancer drugs have been developed. Some of these drugs such as sorafenib, gefitinib, erlotinib and afatinib have been approved by FDA and made available in public domain. However, genetic instability, aberrant activation of signaling pathways and development of secondary drug resistance have become the major limitations of such drugs [2]. It is necessary now to explore alternative novel anticancer strategies that can effectively kill cancer cells. It is well established now that cancer cells preferentially use aerobic glycolysis for their energy demand and high proliferation rate. Due to altered metabolism, cancer cells produce higher level of reactive oxygen species (ROS) as compared to normal cells. To protect themselves from ROS, cancer cells have evolved a variety of sophisticated mechanisms [3]. ROS act as double-edged sword in living cells. At low level, ROS act as signaling molecules and play a vital role in various biological processes including cell survival, proliferation, differentiation and gene expression, at higher level however; ROS exert oxidative stress and induce cell death through various signaling pathways [4]. Recent research has shown that this unique biochemical property of cancer cells (high ROS level) can be exploited for therapeutic benefits. Killing cancer cells by exploiting this biochemical vulnerability of cancer cells with ROS-targeting phytochemicals to induce oxidative stress in cancer cells has been shown to be feasible in various *in vitro* and *in vivo* experimental models [1,5,6]. ROS-targeted anticancer drug development strategy hold the promise to set the cancer cells effectively on the road to ruin as it can be applied more broadly against various human cancers of multiple origins irrespective of their genotype and are less likely to suffer from drug resistance.

What would be the major strategies to induce oxidative stress over a toxic threshold in cancer cells while minimizing the possibilities of drug resistance?

Several approaches have been used to induce oxidative stress in cancer cells. One approach to induce oxidative stress in cancer cells is to induce ROS generation by exogenous small molecules over a toxic threshold which can be easily achieved in cancer cells compared to normal cells. A large number of phytochemicals including flavonoids have been documented to kill cancer cells by inducing ROS generation through mitochondrial dysfunction [7]. However, to the best of my knowledge, none have reached cancer clinical trial. Another approach is to inhibit antioxidant system of cancer cells to expose them to endogenous ROS production. Since cancer cells have evolved a number of defensive mechanisms to counteract ROS production, targeting only one antioxidant system is not enough to induce oxidative stress to a toxic threshold. Glutathione (GSH) is the most important antioxidant system of cells. Depletion of intracellular reduced GSH has been shown to induce apoptosis in cancer cells via oxidative stress [5]. However, induction of oxidative stress by mere GSH depletion is expected to rescue by cancer cells. In evolutionary point of view, cancer cells are the most advised cells and can rescue themselves from oxidative stress induced by depletion of a single antioxidant system (GSH) through metabolic reprogramming. During higher oxidative stress, cancer cells switch from glycolysis to pentose phosphate pathway by inactivating pyruvate kinase M2 (PKM2) and stabilizing HIF-1 to generate NADPH which is used to titrate ROS by reducing oxidized glutathione (GSSG) to GSH [8]. Since NADPH could also be produced by the activity of malic enzyme 1 (ME1) and Isocitrate dehydrogenase (IDH) 1 and 2 [9] in addition to pentose phosphate pathway, inhibition of NADPH synthesis would not be an appropriate strategy. Therefore, induction of NADPH oxidase (NOX) would be the most feasible approach to deplete NADPH in cancer cells. Induction of NOX on one hand would oxidize NADPH to $NADP^+$, leaving

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no NADPH for glutathione reductase (GR) to convert GSSG back into GSH and on the other hand will generate ROS, ultimately resulting in higher oxidative stress in cancer cells. Thus simultaneous targeting of GSH metabolism and NOX activation will be a feasible approach to induce oxidative stress for effective tumor therapy in order to avoid from drug resistance. Hence, a systematic way to measure cellular antioxidant capacity and NOX activity in cancer cells and normal cells would be instructive for the development of such ROS-based combinatorial therapies that could potentially kill cancer cells with minimum toxic effects on normal cells.

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