

### More Than a Vitamin

*“At high dose given intravenously, Vitamin C selectively kills cancer cells, and is a low-toxic cancer treatment under active clinical investigation”*

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#### COLUMN ARTICLE

Vitamin C (ascorbate) is an essential nutrient that human beings need to ingest from food. It is an essential co-factor for at least 8 enzymes that exert important bio-functions, including collagen synthesis and dopamine synthesis, wound healing, and anti-oxidant defense. Recent research has revealed its actions beyond function as a vitamin. When intravenously given, ascorbate bypasses the absorption barrier of the intestines, and achieves high systematic concentrations in millimolars. At these high concentrations, ascorbate facilitates H<sub>2</sub>O<sub>2</sub> and other ROS formation through Haber-Weiss reaction, and therefore cast oxidative stress to cells [1-3]. This oxidative stress has been found to selectively induce cancer cell death, while spares the normal cells. The selectivity is like based on multiple cellular pathways that are targeted by ascorbate treatment. First, the ascorbate-generated ROS induce DNA damage and deplete NAD<sup>+</sup>. Depletion of NAD<sup>+</sup> first resulted in decrease of ATP production in cancer cells but not in normal cells [4]. Known as Warburg Effect [5], cancer cells depend on glycolysis for glucose metabolism. Since glycolysis is not an efficient way for ATP production compared to oxidative phosphorylation, primarily used by normal cells, cancer cells could be more sensitive to ascorbate-induced metabolic stress than normal cells. Second, NAD<sup>+</sup> depletion also suppressed activity of a cytosolic deacetylase Sirt2, resulting in elevated acetylated tubulin, which is over-stabilized and thus inhibit cell division and mobility. This would influence fast dividing

and invasive cells such as cancer cells. Third, ascorbate inhibited matrix metalloproteinases (MMPs) which are needed for cancer cell dissemination and metastasis. Ascorbate also showed activity in inhibiting cancer cell epithelial to mesenchymal transition (EMT), which is regarded as the first step for cancer metastasis. Furthermore, ascorbate greatly enhanced collagen levels in tumor stroma, which functions as a host defense mechanism to prevent cancer cell invasion[6]. These multiple mechanisms working together, makes ascorbate an ideal anti-cancer agent, because targeting multiple pathways in cancer treatment has the key advantage of synergistic effectiveness and to decrease development of resistance, a substantial problem in cancer treatment. This strategy is used clinically by employing several chemotherapeutics in cancer treatment. However, other agents that targeting multiple pathways also have collateral/multiple toxicity, whereas ascorbate has the advantage of being low-toxic, which is now well documented by more than 10 clinical trials. Taken together, the function of ascorbate goes beyond vitamin C. At high dose given intravenously, it is a low-toxic cancer treatment that is under active clinical investigation.

#### BIBLIOGRAPHY

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