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Advances of Green Tea Catechins towards Smart Anticancer Agents

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Differential Cellular Responses to EGCG of Cancer Cells versus Normal Cells

Green tea catechins (GTCs) have shown cancer chemopreventive and chemotherapeutic effects in numerous cell culture systems, animal tumor models, and epidemiologic studies [1,2]. EGCG targets multiple essential survival proteins and pathways in human cancer cells. The anticancer activities of GTCs are believed to be mostly mediated by epigallocatechin-3-O-gallate (EGCG), the most abundant and bioactive compound in green tea [1]. Many researchers have already reported that EGCG or its analogs results in cell cycle arrest and apoptosis of several cancer cells, but not of normal cells [3-8]. However, the underlying mechanism of these differential responses to EGCG in cancer cells versus their normal counterparts is not fully elucidated yet. Even though the selective anticancer mode of action mechanism of EGCG is multifaceted, some of feasible mechanisms, known so far, are as follows:

1. One scenario is supported by some evidence that EGCG selectively modulates and affects cell cycle-related molecular targets (e.g. genes and proteins) involved in cell proliferation, survival and apoptosis in cancer cells from normal cells [9-11] ;

2. Another story emphasizes that cellular uptake and further nuclear translocation pattern of EGCG in cancer cells are completely different from their normal counterparts – EGCG became concentrated predominantly in the nucleus of cancer cells, while it widely distributed into the cytoplasm of normal cells and partly translocated into the nucleus [12-14] ; and

3. The third mechanism suggests that preferential death of cancer cells by EGCG could be caused by the cancer-specific induction of reactive oxygen species [8,15].

Taking all things into consideration, it is suggested that differential effects of EGCG on cancer cells versus normal cells may be exploited to craft target-specific strategies, such as the cytoprotection of normal cells and chemoprevention of cancer cells.

Nano-chemo prevention by Encapsulation of EGCG with Nanoparticles

EGCG and its analogs have proven excellent anticancer potential in the preclinical setting, however, the observed effects in vitro do not translate into even limited progress from "bench to bedside" for human use where they fails to live up to their expectations [16]. Among a few of the reasons that are considered to be responsible for the lack of chemoprevention in the clinical trials, the most important includes inefficient systemic delivery and poor bioavailability [17,18]. To overcome this impediment, the novel concept of nano-chemo prevention, which uses nanotechnology for improving the outcome of chemopreventive intervention has been firstly introduced by Mukhtar and group since 2009. This revolutionary strategy demonstrated that EGCG encapsulated in polylactic acid–polyethylene glycol nanoparticles (nano-EGCG) was found to retain its biological effectiveness with over 10-fold dose advantage for exerting its proapoptotic and angiogenic inhibitory effects, critically important determinants of chemopreventive effects of EGCG in both in vitro and in vivo systems [19,20]. Such a seminal study paved the way for the use of nanoparticle-mediated delivery to enhance bioavailability and limit any unwanted toxicity of EGCG. During the last decade, rapid advancement has been witnessed in the development of nano-chemo preventive technology with emergence of many nano-encapsulated formulations of some other chemopreventive agents, such as curcumin and resveratrol via liposomes, polymeric nanoparticles and micelles conjugates to small molecules (e.g. amino acids) or miscellaneous nanoformulations [21-24].

In conclusion, nano-chemo preventive strategy could make advances of EGCG towards a smart anticancer agent and would be certainly promising for future multifunctional chemotherapeutic application due to enhancing bioavailability and limiting any unwanted toxicity of chemopreventive agents.

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