Antiapoptotic proteins as targets for bioactive compounds

B. Pająk

Department of Physiological Sciences, Faculty of Veterinary Medicine, Warsaw Agricultural University, Nowoursynowska 159, 02-776 Warsaw, Poland

Abstract

One of the most promising strategies in colon cancer therapy is the sensitization of cancer cells to natural proapoptotic cytokines, such as death ligands and interferons, which are able to eliminate abnormal cells. The investigation of mechanisms determining the immune escape of cancer cells revealed the presence of antiapoptotic proteins, such as cFLIP, which inhibit cell death signal transduction. Numerous studies showed that the use of different metabolic inhibitors, such as cycloheximide (CHX), reduces the cFLIP protein level, thus restoring the susceptibility to TNF-α-induced apoptosis. However, high non-specific toxicity of CHX excludes the clinical use of this substance. The current efforts are focused on identification of bioactive compounds which could safely support immunotherapy. The review presents in vitro and in vivo evidence that butyrate (Bt), fatty acid produced in colon during fermentation process and parthenolide (PN), sesquiterpene lactone isolated from Tanacetum parthenium specifically affect different cancer cells. Among described various molecular mechanisms of Bt and PN action, one reduces the level of antiapoptotic proteins. This paper clearly demonstrates that bioactive compounds, especially combined with immune cytokines could be seriously considered as an alternative for routine colon anti-cancer therapy.

Key words: butyrate, parthenolide, antiapoptotic proteins, immune escape, colon cancer

Review

Colon cancer is the second leading cause of cancer-related deaths. Despite the wide knowledge how colon cancer develops, the progress in the field of preventing or treatment of this fatal disease is insignificant. While there are chemotherapeutic drugs available for the treatment of colon cancer the majority of the patients do not respond to these drugs and side effects remain problematic. Nowadays, the emphasis has been put to conduct a variety of basic and clinical studies in order to make use of chemoprevention based on naturally occurring substances. These substances, by their multidirectional actions might provide useful strategies to inhibit colon cancer development with minimal toxicity (Kelloff et al. 2000). The immunoediting (Dunn et al. 2002), evolutionary developed ability to modify the apoptotic signal transduction, is one of the major mechanisms of resistance of cancer cells to cell death induction. Intensive efforts have been made to explore the molecular mechanisms of the anti-apoptosis and possible targets for new compounds. To overcome refractory behavior of tumor cells one of the investigated stra-