Breast Cancer: Basic and Clinical Research

COMMENTARY

Targeting DNA Damage and Repair by Curcumin

Zhenyu Ji

Wellman Center for Photomedicine and the Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, 02114, USA. Email: jizhenyu2000@gmail.com.

Abstract: Curcumin is a compound with anti-tumor effects in a tolerable dose. A recent paper by Rowe et al described that curcumin induced DNA damage in triple negative breast cancer cells and regulated BRCA1 protein expression and modification.[1] Related research and potential use of curcumin will be discussed in this article.

Keywords: curcumin, DNA damage, breast cancer cells

Breast Cancer: Basic and Clinical Research 2010:4 1–3

This article is available from http://www.la-press.com.

Curcumin (diferuloylmethane), a low-molecular-weight polyphenol derived from the rhizome *Curcuma longa*, is an active ingredient in the spice turmeric.[2] The compound is considered generally safe and studies in animals and humans have shown it has antineoplastic activity in a well tolerable dose.[3] Curcumin has anti-proliferative activity and inhibits tumor initiation in a variety of tumor models. Although the precise mechanism of the anti-tumor activity of curcumin remains elusive, several possible mechanisms have been proposed, including p53-dependent apoptosis induction, up-regulation of carcinogen-detoxifying enzymes, such as glutathione *S*-transferases, antioxidation, and suppression of cyclooxygenase.[3]

Lu et al recently discovered that curcumin induced DNA damage in a mouse-rat hybrid retina ganglion cell line.[4] The real time PCR analysis showed that curcumin decreased expression levels of DNA damage response genes, including ATM, ATR, BRCA1, 14-3-3σ, DNA-PK and MGMT. Therefore, reduction of DNA damage response may be the reason for curcumin-induced growth inhibition.[4] The findings by Rowe et al further demonstrated that regulation of BRCA1 protein might mediate of the anti-tumor reponse of curcumin.[1]

The FA/BRCA pathway regulates the cellular response to DNA damage response.[5,6] The pathway is governed by the coordinate activity of several FA proteins. In response to various DNA damage, a protein complex composed of at least eight FA proteins (A, B, C, E, F, G, L, M) monoubiquitinates the FANCD2 protein,[7] which is subsequently targeted to chromatin and interacts with the FANCD1/BRCA2 protein. This interaction seems to be required for homologous recombination repair and cross-link repair. Curcumin was identified as an inhibitor of FA/BRCA pathway in a chemical screen.[3] It inhibits the monoubiquitination of the FANCD2 protein and sensitizes ovarian and breast tumor cell lines to cisplatin through apoptosis.[3] However, the whole picture of curcumin puzzle hasn't been solved. Rowe et al showed that BRCA1 could be a target of curcumin when it's used to treat breast cancer.[1] Curcumin induced DNA damage was associated with phosphorylation, increased expression, and cytoplasmic retention of the BRCA1 protein.[1] In addition, curcumin promotes apoptosis and prevents anchorage-independent growth and migration of triple negative breast cancer cells. Interestingly, apoptosis and BRCA1 modulation were not observed in non-transformed mammary epithelial cells,[1] suggesting some breast cancer cells have intrinsic defects that make them more sensitive to curcumin. This study indicates that curcumin may be of therapeutic use in the context of triple negative breast cancer.

As cancer formation involves more than just one signaling pathway dysregulation, targeting multiple pathways is now more preferred. To this end, curcumin may be useful as a component of combinational therapy for human cancers. Previous studies have shown that curcumin could enhance toxicity of cyclophosphamide (CTX) on a drug-resistant human lymphoma cell line HT/CTX through inhibition of FA/BRCA pathway,[8] while the curcumin or CTX alone did not show cytotoxic effect and had no inhibition of FA/BRCA pahtway. It is concluded that combination of curcumin and CTX produces synergistic effects and reverses multiple drug resistance of HT/CTX cells effectively. The prevention of cells from entering the next cell cycle and down-regulation of FANCD2 protein monoubiquitination may also be involved in the anti-tumor mechanism of curcumin.[8] Synergistic proliferation inhibition also occurred when curcumin is combined with FDA approved drugs like cisplatin, 5-fluorouracil (5-FU) or celecoxib, to treat a variety of human cancer cells.[3,9,10]

In a word, future combinational therapy development with curcumin may provide another remedy for cancer patients. The detailed mechanistic studies may further shed light on novel and selective cancer therapies.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author reports no conflicts of interest.

References

1. Rowe DL, Ozbay T, O'Regan RM, Nahta R. Modulation of the BRCA1 Protein and Induction of Apoptosis in Triple Negative Breast Cancer Cell Lines by the Polyphenolic Compound Curcumin. *Breast Cancer: Basic and Clinical Research*. 2009 Sep;3:61–75.
2. Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res*. 2001 Jul Aug;21(4B):2895–900.

3. Chirnomas D, Taniguchi T, de la Vega M, et al. Chemosensitization to cisplatin by inhibitors of the Fanconi anemia/BRCA pathway. *Mol Cancer Ther*. 2006 Apr;5(4):952–61.
4. Lu HF, Yang JS, Lai KC, et al. Curcumin-induced DNA damage and inhibited DNA repair genes expressions in mouse-rat hybrid retina ganglion cells (N18). *Neurochem Res*. 2009 Aug;34(8):1491–7.
5. Litman R, Gupta R, Brosh RM Jr, Cantor SB. BRCA-FA pathway as a target for anti-tumor drugs. *Anticancer Agents Med Chem*. 2008 May;8(4): 426–30.
6. D'Andrea AD, Grompe M. The Fanconi anaemia/BRCA pathway. *Nat Rev Cancer*. 2003 Jan;3(1):23–34.
7. Thompson LH. Unraveling the Fanconi anemia-DNA repair connection. *Nat Genet*. 2005 Sep;37(9):921–2.
8. Xiao H, Zhang KJ. Antiproliferative effect of curcumin combined with cyclophosmide on the growth of human lymphoma cell line HT/CTX with drug resistance and its relation with FA/BRCA pathway. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2008 Aug;16(4):804–8.
9. Du B, Jiang L, Xia Q, Zhong L. Synergistic inhibitory effects of curcumin and 5-fluorouracil on the growth of the human colon cancer cell line HT-29. *Chemotherapy*. 2006;52(1):23–8.
10. Lev-Ari S, Strier L, Kazanov D, et al. Celecoxib and curcumin synergistically inhibit the growth of colorectal cancer cells. *Clin Cancer Res*. 2005 Sep 15;11(18):6738–44.