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Regulation of calpain-mediated glucose-regulated protein modulates colon cancer development

Joshua K Ko, Kathy K Auyeung and **Yue Wang**
Hong Kong Baptist University, China

Background: Glucose-regulated proteins (GRP) are induced in the cancer microenvironment to promote tumor survival, metastasis and drug resistance. In our previous studies, AST was obtained from the medicinal plant *Astragalus membranaceus*, which possesses anti-tumor and pro-apoptotic properties in colon cancer cells and tumor xenograft. The present study aimed to investigate the involvement of GRP in endoplasmic reticulum (ER) stress-mediated apoptosis during colon cancer development, with focus on the correlation between AST-evoked regulation of GRP and calpain activation.

Methods: The effects of AST on GRP and apoptotic activity were assessed in HCT 116 human colon cells. GRP78 gene silencing was performed to confirm the importance of GRP in anticancer drug activities. Modulation of GRP and calpains was also studied in tumorxenograft.

Results: ER stress-mediated apoptosis was induced by AST, as shown by elevation in both spliced XBP-1 and CHOP levels, with parallel up-regulation of GRP. Nevertheless, the initial increase in calpain activity as well as calpain I and II protein level was gradually declined at later stage of drug treatment. Besides, the induction of GRP was partly reversed by calpain inhibitors, with concurrent promotion of AST-mediated apoptosis. The knockdown of GRP78 by gene silencing resulted in higher sensitivity of colon cancer cells to AST-induced apoptosis and reduction of colony formation. The association between calpains and GRP78 had been confirmed by immunofluorescence staining and immunoprecipitation. Modulation of GRP and calpains by AST was similarly demonstrated in nude mice xenograft, leading to tumorgrowth inhibition.

Conclusion: Our findings exemplify that calpains, in particular calpain II, play a permissive role in the modulation of GRP78 and consequent regulation of ER stress-induced apoptosis. Combination of calpain inhibitors and AST could exhibit a more pronounced pro-apoptotic effect. These results help to envisage a new therapeutic approach in colon cancer by targeting calpain and GRP.

jksko@hkbu.edu.hk