Targeting Inhibitors of Apoptosis Proteins in Treatment of Cancer

Benjamin CY Wong

MBBS(HK), MD(HK), MRCP(UK), FHKCP, FHKAM, FRCP(Edin, Glasg), FACG

Department of Medicine, The University of Hong Kong

Apoptosis is an important pathway in various physiological and pathological conditions. Inherited or acquired resistance to the physiological apoptotic process is an important cause in carcinogenesis. Genes identified earlier on including p53 and the Bcl-2 family are fairly upstream in the control of apoptosis. Therapeutic approaches targeting p53 and Bcl-2 family are being tested in cancer. However the diverse downstream effectors of these genes/proteins make it a less desirable target.

The Inhibitors of Apoptosis Proteins (IAPs) were discovered recently that control a fairly downstream part of the apoptosis process. The members include survivin, livin, X-linked inhibitor of apoptosis (XIAP), XIAP-Associated Factor-1 (XAF-1), and others. Like the Bcl-2 family, these proteins can be pro- or anti-apoptotic. The key member is survivin, which is expressed in most of the common human tumors, but not in normal adult differentiated tissues. Apart from its major role as antagonist of caspases, hence anti-apoptotic, it also has important role in regulation of microtubule stability, mitotic progression, cytokinesis and angiogenesis.

We have generated mutant and dominant negative plasmids of survivin and demonstrated their ability to inhibit tumour growth and formation both *in vitro* and *in vivo* for gastric cancer [1]. We then generated the recombinant adeno-associated virus (AAV) survivin mutant (Cys84Ala) which inhibited cell proliferation and induced apoptosis and mitotic catastrophe *in vitro* in colon cancer[2]. Intratumoral injection of rAAV-Sur-Mut (Cys84Ala) significantly induced apoptosis and mitotic catastrophe, inhibited angiogenesis and tumor growth in a colon cancer xenograft model *in vivo.* No obvious cytotoxicity to other tissues was observed. More importantly, rAAV-Sur-Mut(Cys84Ala) expression strongly enhanced the antitumor activity of 5-Fluorouracil (5-FU), resulting in regression of established tumors. Hence survivin is a promising target for cancer treatment.

We are investigating the effect of XAF1 in gastrointestinal carcinogenesis. Using the yeast two hybridization method, we have also identified several XAF1 interacting proteins, including the Four and a Half Lim protein-2 (FHL2). Further characterization of the functional interaction is in progress. In conclusion, IAPs are more tumour specific and serve as a promising target for cancer treatment in future.

Reference:

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2. Tu SP, Cui JT, Liston P, Xu R, Jiang XH, Lin MCM, Zhu YB, Zou B, Jiang SH, Wong WM, Yuen MF, Lam SK, Kung HF, Wong BCY. Gene therapy for colon cancer by adeno-associated viral vector-mediated transfer of survivin Cys84Ala mutant. Gastroenterology – in press.