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Molecular cancer therapy via modulating autophagy

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Radioresistance markedly impair the efficacy of cancer therapy. Anti-apoptotic Bcl-2 family proteins such as Bcl-xL, Bcl-2 and Mcl-1 are overexpressed in prostate cancer and contribute to prostate tumor initiation, progression and resistance to radiotherapy. A natural BH3-mimetic, small molecule inhibitor of Bcl-2, (-)-gossypol, shows promise in ongoing Phase II clinical trials for human prostate cancer. We have recently shown that (-)-gossypol preferentially induces autophagy in androgen-independent (AI) prostate cancer cells that have high levels of Bcl-2 and are resistant to apoptosis, both in vitro and in vivo, but not in androgen-dependent cells with low Bcl-2 and sensitive to apoptosis. Our results demonstrate for the first time that (-)-gossypol can also interrupt the interactions between Beclin1 and Bcl-2/Bcl-xL at the endoplasmic reticulum, thus releasing the BH3-only pro-autophagic protein Beclin1, which in turn triggers the autophagic cascade. (-)-Gossypol-induced autophagy is Beclin1- and Atg5-dependent, together with Bcl-2 downregulation and Beclin1 upregulation. (-)-Gossypol increased autophagy induced by X-ray radiation in the AI prostate cancer cells. Orally administered (-)-gossypol achieved a much greater efficacy with long-term tumor regression when used in combination with ionizing radiation. (-)-Gossypol significantly enhances the anti-tumor activity of radiotherapy in vitro and in vivo, and represents a promising new regime for treatment of hormone-refractory human prostate cancer with overexpression of Bcl-2. Our data provide new insights into the mode of cell death induced by Bcl-2 inhibitors, which would facilitate the rational design of clinical trials by selecting patients who are most likely to benefit from the Bcl-2-targeted molecular therapy.

Biography

Dr. Liang Xu obtained his M.D. and Ph.D in China and did postdoctoral studies in Louvain University in Belgium, Stanford University and Georgetown University in USA. He has been an Assistant Professor at University of Michigan and now an Associate Professor with Tenure at University of Kansas. He has published more than 75 papers and serving as an editorial board member of multiple journals. He holds many USA and international patents including two agents in Phase I and II clinical trials. His major research interest is molecular cancer therapy targeting cancer and cancer stem cells.