化学学报 2006 64 (22): 2215～2220 ISSN: 0567-7351 CN: 31-1320/06

研究论文

# Bcl-2蛋白与Bcl-$x_L$蛋白活性腔比较和底物选择性

郑灿辉, 周有骏*, 朱驹, 陈军, 李耀武, 盛春泉, 宋云龙, 蒋庆锋, 吕加国

(第二军医大学药学院药物化学教研室 上海 200433)

收稿日期 2006-7-11 修回日期 2006-9-11 网络版发布日期 2006-11-16 接受日期 2006-9-19

摘要 Bcl-2蛋白与Bcl-$x_L$蛋白是Bcl-2蛋白家族抗凋亡亚家族最主要的两个成员, 是目前抗肿瘤药物研究很具前景的新靶点. 两者具有类似的结构和功能, 但在很多方面也存在差异, 如高表达的肿瘤谱有所不同; 与其他抗凋亡亚家族成员的结合具有一定的选择性; 在不同凋亡刺激下对细胞的保护作用也有较大差异等. 本文通过对两者的氨基酸序列联配和活性腔结构比较, 表面静电性质的计算和比较, 及对几类底物选择性的研究, 明确了它们活性腔特性的主要差异所在及对底物选择性的影响. 研究结果为理解Bcl-2蛋白与Bcl-$x_L$蛋白功能差异的分子机制及设计合成具有良好选择性的小分子抑制剂打下了坚实基础.

关键词 Bcl-2蛋白家族 序列联配 结构比较 表面静电势 分子对接

分类号

## Comparison between the Active Sites of Bcl-2 and Bcl-xL Proteins and Their Substrate Binding Selection

ZHENG Can-Hui, ZHOU You-Jun*, ZHU Ju, CHEN Jun, LI Yao-Wu, SHENG Chun-Quan, SONG Yun-Long, JIANG Qing-Feng, LÜ, Jia-Guo

(*Department of Medicinal Chemistry, School of Pharmacy, Second Military Medical University, Shanghai 200433*)

**Abstract** Bcl-2 and Bcl-$x_L$ proteins are main members of Bcl-2 protein family, which are new targets of anticancer drugs with bright prospect. These two proteins have similar structure and functions, while differ in many aspects, such as the tumor spectra with high expression of these two proteins, binding selection with other proapoptosis subfamily members, and cell protection function under various apoptosis stimulations. By sequence aligning, structure and surface electrostatic potential comparing of the active sites in Bcl-2 and Bcl-$x_L$ proteins, the dominant differences between them are identified. Then the effect of these differences on substrates binding selection is showed by studies of some substrates for example. The result of this paper provides good basis for understanding molecular mechanism of the function difference between Bcl-2 and Bcl-$x_L$ proteins, and design, synthesis of small molecule inhibitors with good selection.

**Key words** Bcl-2 protein family sequence alignment structure comparison surface electrostatic potential molecular docking

DOI:

通讯作者 周有骏 zhouyoujun2006@yahoo.com.cn