

论文

新烯二炔类大分子抗肿瘤抗生素C1027的分子构成与活性关系

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摘要:

C1027是含烯二炔发色团的大分子肽类新抗肿瘤抗生素,由一个蛋白和一个烯二炔发色团两部分构成。后者是活性部分,对肿瘤细胞有强杀伤作用,蛋白对发色团的活性有保护作用。蛋白和发色团在一定条件下可以重新组建成完整的C1027。C1027分子内的二硫键有辅助蛋白保护发色团的作用,当二硫键被还原后,C1027活性丢失加快。C1027被链霉菌蛋白酶降解产生一个分子量为3~5kDa的中间产物,此产物对肿瘤细胞的杀伤作用与完整C1027相同,表明C1027是可以裁剪的,保护发色团的最小肽段为3~5kDa。

关键词: 抗肿瘤抗生素C1027 烯二炔 C1027片段 毛细管电泳

RELATIONSHIP BETWEEN THE MOLECULAR COMPOSITION OF C1027, A NEW MACROMOLECULAR ANTIBIOTIC WITH ENEDIYNE CHROMOPHORE, AND ITS ANTI-TUMOR ACTIVITY

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Abstract:

The molecule of C1027, an antitumor antibiotic with extremely potent cytotoxicity against cultured cancer cells, is composed of an enediyne chromophore and an apoprotein of 10.5 kDa. These two parts of the molecule, connecting each other through non-covalent binding, can be dissociated and reconstituted. As determined by clonogenic assay, the chromophore served as the active part of the molecule, displaying potent cytotoxicity similar to that of intact C1027. The activity of free chromophore decreased more rapidly than that of intact C1027, indicating that apoprotein played a role in protecting the chromophore from inactivation. By incubating together in phosphate buffer, the chromophore and apoprotein were reconstituted to form an intact C1027. The ratio of chromophore and apoprotein remained 1:1 in the reconstituted molecule, even though extra amount of chromophore was added. The optimal condition for the reconstitution was pH 7.0, at 20°C for 12 h. When the disulfide bond of the apoprotein was reduced by DTT, the activity of C1027 decreased more rapidly. C1027 was digested by pronase and the produced fragments of various molecular weights were examined by capillary electrophoresis. The cytotoxicity of 3~5kDa fragment approximated that of intact C1027 and its IC50 value was 0.07 fmol·L<sup>-1</sup>. The results indicate that the intactness of the apoprotein is not indispensable for stabilizing the chromophore and a smaller molecule of 3~5kDa consisting of a peptide fragment and a chromophore may retain full C1027 activity.

Keywords: Enediyne :C1027 fragment Capillary electrophoresis Antitumor antibiotic C1027

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