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综述·

TRAIL 与 TRAIL 受体①

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摘要:TRAIL/ TRAIL - R 是 TNF 超家族的一个新亚群,TRAIL 可引起肿瘤细胞的凋亡,但不引起正常细胞凋亡。目前 TRAIL 已发现五种受体:DR4、DR5、DcR1、DcR2、OPG,各具有不同的生物活性。本文就 TRAIL 及其受体的结构、功能和其机制作一综述。

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的分子:DcR1、DcR2 和 OPG, CrmA、zVAD 和 v - FLIPS 等。

如前所述,DcR1、DcR2 和 OPG 是不含完整死亡域 DD 的 TRAIL 受体。已有实验证明 DcR1、DcR2 和 OPG 的过表达可以抑制 TRAIL 的凋亡效应;此外还发现 DcR1、DcR2 和 OPG 主要表达在正常细胞中,在转化细胞中不表达或很少表达,因此这被认为是 TRAIL 为什么只对转化的细胞有作用,而不引起正常细胞凋亡的原因所在[3-7]。然而也有一些实验证明,DcRl、DcR2 和 OPG 的过表达在某些细胞并不能阻断 TRAIL 的凋亡效应,出现这种情况的原因大概有以下几种可能:各个实验室选取的实验条件不同;DcR1、DcR2 和 OPG 的表达水平不一致,DcR1、DcR2 和 OPG 对 TRAIL 的阻断作用具有细胞种属特异性;另外的可能是 DcR1、DcR2 和 OPG 仅仅是生物进化过程中的二种近似中性突变的突变体,保留了与 TRAIL 结合的能力,却丢失了部分 DD 结构,他们阻断 TRAIL 凋亡的作用,并不是机体原来固有的抑制机制,只不过是大自然赋予细胞的一种非正常保护作用。

至于 CrmA、zVAD、v - FLIPs 等 caspase 抑制剂对 TRAIL 凋亡途径的抑制作用,已得到大多数实验的证实,正如上面所提及的,在体外实验中用 CrmA, zVAD 等 caspase 抑制剂可明显的阻断或减弱 TRAIL 引起的细胞凋亡;这同他们对 CD95L 的作用是相同的[2-4,9]。

综上所述,由于 FADD - DN 对 TRAIL 和 CD95 抑制作用的差异,caspase 抑制剂对 TRAIL 和 CD95L 共同的抑制作用,结合 TRAIL 和 CD95L 的同源性、交叉敏感性和交叉抗性,提示 TRAIL 和 CD95L 诱导凋亡途径的中上游不同,但在下游却共用某些细胞内分子。

3 TRAIL 的临床应用前景

自从 TRAIL 及其受体被发现以来,便被认为具有光明的临床应用前景。现已证明 TRAIL 可以杀伤多种肿瘤细胞,如白血病细胞,乳腺癌细胞,结直肠肿瘤细胞,黑色素瘤细胞,恶性神经胶质瘤细胞及 HIV 患者的淋巴细胞等。另外,由于以前发现的 TNF 超家族成员,如 CD95L, TNFRI 等仅表达于局限的细胞组织,而 TRAIL 广泛表达于各种组织,且 TRAIL 能特异性地只诱导肿瘤细胞凋亡,因此 TRAIL 被看作是一种很有前途的广谱的抗癌治疗方法[8,12,13]。

综上所述,由于 TRAIL 同以前发现的各种肿瘤坏死因子相比,具有更适于临床应用的优良特点,因此在临床抗癌治疗的研究方面, TRAIL 有广阔的发展前景。

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