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• 中文摘要

綠膿桿菌爲革蘭氏陰性桿菌，在自然界中分佈很廣，是目前院內感染之主要致病菌。但此菌極易產生抗藥性引起治療上之困難，故發展免疫治療法來預防、治療綠膿桿菌感染，以取代傳統的抗生素療法，是近年來對抗綠膿桿菌感染主要研究的方向。而由臨床統計資料顯示綠膿桿菌最常感染燒傷病人，是燒傷病人治療時最大的困擾。本計劃以燒傷小老鼠的動物模式，探討如何依據已知之綠膿桿菌致病機制，發展出更安全、有效的免疫治療法。我們模擬臨床治療時之可行方法，直接在老鼠皮膚燒傷處先皮下注射家兔抗綠膿桿菌各種主要致病因子的抗血清，同時亦在健康皮膚處注射多價的抗綠膿桿菌融合疫苗，評估此種局部被動免疫療法及接種融合新疫苗在預防、治療綠膿桿菌感染的效果。已知綠膿桿菌會分泌多種有毒物質，其中以綠膿桿菌外毒素 A (PE)之毒性最強，而其所分泌會破壞組織的水解酵素中，則以彈性蛋白酵素(Elastase)的活性最強。本計劃亦利用遺傳工程技術，大量純化無毒性之綠膿桿菌 PE 類毒素(Toxoid)、彈性蛋白酵素及在綠膿桿菌 17 種不同血清型的細胞壁上抗原性均相同之綠膿桿菌外膜蛋白 I 和 F，再將各種純化蛋白免疫家兔，以製備有中和毒性作用、或加強巨噬細胞吞噬作用之抗血清，我們曾評估這三類抗血清對燒傷老鼠進行局部被動免疫(Passive local immunotherapy)的治療效果。同時我們亦以遺傳工程技術，將外膜蛋白 I、F 和彈性蛋白酵素的基因依序接於已刪除毒性區域 III 之綠膿桿菌外毒素 A (PE△III)之羧基端，以製造綠膿桿菌融合新疫苗(Recombinant hybrid vaccine)。結合多種可刺激宿主產生有保護作用之抗原，來製造融合疫苗是目前細菌疫苗發展的新趨勢。本計劃之完成除可提供燒傷病人最佳之治療方法，亦可進一步瞭解綠膿桿菌所分泌之各種毒素在其致病機制中所扮演之角色，尤其重要的是本計劃的完成已證實此融合新疫苗能刺激患者產生全方位對抗致病菌之免疫能力，故本計劃兼具基礎及臨床應用之雙重意義。

- 英文摘要

Pseudomonas aeruginosa is an opportunistic pathogen which has become a major cause of nosocomial infections. Therapy for P. aeruginosa infection is hindered by its well-known antibiotic resistance. Thus, a potential therapeutic alternative to antibiotic drugs is the development of immunotherapy through either passive or active immunization. Since the leading cause of morbidity and mortality in severe burn wound patients is infection of P. aeruginosa, we have used a mouse burn wound infection model to evaluate the efficacy of passive local immunotherapy and active immunization by a new hybrid vaccine against P. aeruginosa. The pathogenesis of P. aeruginosa is multifactorial; this bacteria is invasive and toxigenic after infection. The most potent cytotoxic agents produced by P. aeruginosa is Pseudomonas exotoxin A (PE) and hydrolytic enzyme elastase. In this study, we have used genetic engineering technique to purify nontoxic PE, elastase and the outer membrane proteins I and F (OprI and OprF) of P. aeruginosa. Rabbit antiserum against PE, elastase, OprI or OprF has been administrated directly to the burned wounds inoculated with lethal doses of P. aeruginosa. The survival rate and quantification of P. aeruginosa in local burned skin and systemic liver tissue have been measured. In addition, a more potent vaccine containing the receptor binding, membrane translocation domains of PE, elastase and the outer membrane proteins I and F of P. aeruginosa have been constructed. We have demonstrated that this chimeric protein may induce antibodies not only neutralizing the toxicity of PE and elastase but also preventing the colonization of P. aeruginosa by fixing the complement and promoting the opsonophagocytic activity of macrophages. Therefore, this study has supplied the burned patients an effective treatment, and also gave us more evidences to understand the pathogensis of P. aeruginosa infection. Especially, it is a good example to show us the potential of a new hybrid vaccine against infectious agent.