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【Abstract】

Streptococcus pyogenes is a Gram-positive bacterium that causes mild (pharyngitis, scarlet fever), invasive [bacteraemia/septicaemia, necrotizing fasciitis, streptococcal toxicshock syndrome (STSS)] and non-suppurative (rheumatic fever, glomerulonephritis) infections. STSS is a re-emerging infectious disease in many developed countries. The pathogenesis of STSS is not completely understood, but quantitative and qualitative changes in the expression of virulence factors are believed to be contributing factors. There are several proteins in *S. pyogenes* that regulate the production of virulence factors. Recent studies have suggested that mutations in CovRS, a two-component regulatory system in *S. pyogenes*, play important roles in the pathogenesis of STSS. CovR was reported to influence transcription of 15% of the *S. pyogenes* genome, including many genes involved in virulence. Mutation of CovRS was first reported to result in enhanced virulence in murine infection models. In addition, the mutation of *covS* was suggested to be a very important step in the transition from a pharyngitis strain to an invasive strain. Other reports also indicated a highly frequency of CovRS mutations in STSS isolates. One possible explanation is that a mutation within CovRS promotes resistance to neutrophil-mediated killing by altering the production of proteins such as Sda1, M protein and hyaluronic acid capsule. However, in vivo evidence of the significance of CovRS in human infections has not been fully demonstrated. We investigated five *S. pyogenes* strains isolated simultaneously from the pharynx, sputum, knee joint, cerebrospinal fluid and blood of a single STSS patient. All were *emm*89-type strains, and multilocus sequence typing (MLST) analysis revealed that the strains of pharynx and blood were isogenic. The growth rates of the strains from pharynx and sputum were faster than those of the other strains. Protein profiles of the culture supernatants of strains from the pharynx and sputum were also different from those of the other strains. Sequence analyses revealed that strains from the knee joint, cerebrospinal fluid and blood contained a single nucleotide difference in the *covS* coding region, resulting in one amino acid change, compared with the other strains. Introduction of a plasmid containing the *covS* gene from the pharynx strain to the blood strain increased the production of SpeB protein. This suggests that the one amino acid alteration in CovS was relevant to pathogenesis. This report supports the idea that mutated CovS plays important roles in vivo in the dissemination of *S. pyogenes* from the upper respiratory tract of human to aseptic tissues such as blood and cerebrospinal fluid.