

MiniReview

# Bacterial virulence: can we draw the line?

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## Abstract

The molecular approach to microbial pathogenesis has resulted in an impressive amount of data on bacterial virulence genes. Bacterial genome sequences rapidly add candidate virulence genes to electronic databases. The interpretation of this overwhelming information is obscured because every gene involved in pathogenicity is called a virulence gene, regardless of its function in the complex process of virulence. This review summarizes the changing concept of bacterial virulence and the detection and identification strategies followed to recognize virulence genes. A refined definition of virulence genes is proposed in which the function of the gene in the virulence process is incorporated. We propose to include the life-style of bacteria in the assessment of their putative virulence genes. A universal nomenclature in analogy to the EC enzyme numbering system is proposed. These recommendations would lead to a better insight into bacterial virulence and a more precise annotation of (putative) virulence genes, which would enable more efficient use of electronic databases. © 2001 Federation of European Microbiological Societies. Published by Elsevier Science B.V. All rights reserved.

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## 1. The concept of bacterial virulence

In 1890 Robert Koch postulated guidelines to establish a standard for evidence of causation in infectious disease. His postulates became the gold standard to define microbial virulence for over 100 years, despite limitations to their experimental applications for a number of microorganisms. Revisions of Koch's postulates were introduced to encompass those limitations in which immunological and/or epidemiological proof of causation was added (see [1] for a recent review). With the development of molecular biological techniques, it became possible to identify the genes encoding those factors responsible for virulence. This resulted in molecular microbiology, in which the role and function of specific genes (and the factors they encode) in (bacterial) virulence was the subject of investigation.

The quest for virulence genes evolved together with the technical development of molecular biology and genetic modification of microorganisms. In the beginning of molecular microbiology, genes were identified that encoded virulence factors of known reputation and these were used as probes to find analogs in other organisms. The function of individual genes and the factors they encode in virulence could be determined by random and targeted mutagenesis. Later, identified genes with unknown function were tested for their role in virulence. At present the challenge is to filter out virulence genes from complete bacterial genomes, which can now be sequenced faster than the time needed to establish the role of one single gene in virulence. To give such evidence, a molecular form of Koch's postulates was defined [2]: (i) the phenotype or property under investigation should be associated with pathogenic members of a genus or pathogenic strains of a species; (ii) specific inactivation of the gene(s) associated with the suspected virulence trait should lead to a measurable loss in pathogenicity or virulence; and (iii) reversion or allelic replacement of the mutated gene should lead to restoration of pathogenicity. An alternative postulate was added in case genetic manipulation was not possible: (iv) the induction of specific antibodies to a defined gene prod-

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