Volume 335, number 1, 136–137 FEBS 13287 November 1993

Commentary

Comment on the paper by Shchelkunov et al. (1993) FEBS Letters 319, 80–83. Two genes encoding poxvirus cytokine receptors are disrupted or deleted in variola virus

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Received 10 August 1993

1. INTRODUCTION

Shchelkunov et al. [1] compare the genes present in variola major virus (strain India-1967) and vaccinia virus (strains Copenhagen and WR) that encode proteins involved in the modulation of the host response. Comparison of the sequence of the genome of variola virus, the causative agent of smallpox, with that of vaccinia virus, the smallpox vaccine, provides an opportunity to identify the genes that may have contributed to the high pathogenicity of variola virus. Shchelkunov et al. conclude that the genes encoding receptors for interleukin-1β (IL-1β), tumour necrosis factor (TNF) and interferon-γ (IFN-γ) are present and presumably active in variola virus. However, a detailed analysis of the DNA sequence of variola virus, deposited by the authors in the EMBL Data Library (accession number X69198), reveals that some of these genes are in fact fragmented or deleted in the variola genome, which substantially changes the conclusions of the paper.

2. TNF RECEPTOR

During evolution poxviruses have acquired two genes encoding soluble TNF receptors which are both active in cowpox [2]. One such gene (B28R) is fragmented in vaccinia virus Copenhagen [3], but its homologue is intact and probably active in variola virus (gene G4R) [1]. This is an important finding since blocking TNF action with a soluble receptor will probably increase viral pathogenicity, as has been shown for the closely related T2 protein of *Leporipoxviruses* [4]. The second gene encoding a soluble TNF receptor is present, although fragmented and inactive, in vaccinia virus strains Copenhagen (A53R) and WR (SalF16R) [3,5,6]. Remarkably, this gene is deleted from variola major virus strains India-1967 [1] and Harvey [7] (Fig. 1A). Although we do not yet understand the reasons for the acquisition of a second TNF receptor gene, it is likely that this provided an advantage for virus replication in the host. Consequently, the fact that variola virus has lost one TNF receptor gene, although it contains another intact TNF receptor, cannot be ignored.

3. IL-1β RECEPTOR

The vaccinia IL-1β receptor is encoded by gene B15R in vaccinia virus strain WR [8] and gene B16R in the Copenhagen strain [3], although in Copenhagen the gene is defective due to a non-sense mutation near the N-terminus. The variola virus homologue is not gene B14R reported by Shchelkunov et al. [1], which encodes a protein of 149 amino acids with only 17% amino acid identity to the 326 amino acid vaccinia IL-1β receptor, but is a gene found downstream. Remarkably, the variola gene encoding the IL-1β receptor is fragmented into eight pieces by non-sense and frameshift mutations, and the initiator methionine is absent owing to the deletion of the thymidylate residue in the ATG codon (Fig. 1B). The variola virus genes B15R and B17R reported in the DNA sequence correspond to two of these fragments [1]. These mutations make it impossible for this gene to encode a soluble IL-1β receptor. This result is unexpected since loss of the soluble IL-1β receptor would be predicted to enhance those aspect of the immune response mediated by IL-1β and, therefore, attenuate the virus, as has been shown in mice infected through the intracranial route with a vaccinia virus mutant containing a disrupted B15R gene [9]. However, it correlates well with results obtained in our laboratory in which deletion of the B15R gene from vaccinia virus increases the severity of the infection in mice inoculated through the intranasal route, probably due to the detrimental effects produced by increased circulating IL-1β during

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 Published by Elsevier Science Publishers B.V.

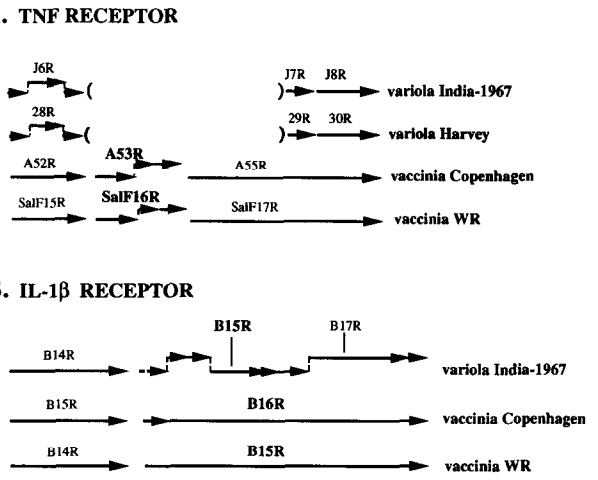

Fig. 1. Schematic alignment of the open reading frames in the genomes of variola and vaccinia viruses.

infection [10]. This intranasal route of inoculation has some similarity with the infection of humans with variola virus, which usually entered via the respiratory track and led to a systemic infection [11]. Perhaps disruption of the IL-1β receptor gene in variola virus contributed to its high pathogenicity.

4. CONCLUSIONS

Variola virus strain India-1967 is predicted to express an active IFN-γ and one TNF receptor [1]. However, the analysis presented here shows that a second TNF receptor is deleted and the IL-1β receptor is fragmented. Disruption or deletion of nine genes in variola virus has been reported as the major difference with vaccinia virus over a 21.8 kbp fragment of the Harvey strain [7], and in this region there are only 29 nucleotide changes between variola strains Harvey and India-1967. A more detailed comparison of the complete DNA sequences of variola and vaccinia viruses is required to identify not only the conserved genes, but also those that are fragmented or deleted, to know whether inactivation of genes is a general phenomenon that may have contributed to the high pathogenicity of variola virus.

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