Division Retroviral Gene Expression (F0800)

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Spumavirus Gene Expression
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The major aims of our research efforts are the elucidation of the mechanism of action of human spumaretrovirus (HSRV) gene expression. The research tasks include the delineation of the functions of the novel bel genes, their gene products and the identification of their cellular targets and ligands. This approach is directed towards the identification of those cellular genes that are expressed after an HSRV infection. The long-term goals are to find out whether or not HSRV can be associated with a clinically defined disease, and to develop the virus genome into a novel and safe retroviral vector system.

HSRV is a complex and replication-competent retrovirus that expresses the three characteristic viral genes gag, pol, and env, and, in addition, regulatory and accessory bel genes, see genome map (Fig.1). HSRV isolates were obtained from patients of different diseases that included tumours and leukemias. Spumaviruses induce an immunosuppressive effect. The cytopathic effects of HSRV in cell culture and HSRV-transgenic mice are noteworthy, since formation of specific multinucleated giant cells was observed in the hippocampal area of the brain. Sero-epidemiological detection with feline spumaretroviral (FSRV) specific antisera revealed that there is high prevalence of FSRV in wild and domestic cats in Australia and Germany. [1, 7, 15]. Expression of HSRV and FSRV Pol is unusual and has several unique features among known retroviruses. The Propol is expressed from a subgenomic spliced, propol-specific transcript. The splice acceptor of the propol mRNA is located in the gag gene [2]. The protease (PR) domain is not cleaved off from the Propol polypeptide, again in contrast to the expression of other retroviral Pol proteins [4]. The PR has a novel cleavage site specificity and is unusually long even as a subdomain of Propol [11, 13]. The HSRV PR is enzymatically active as a dimer as expected. The active FSRV PR, however, has an active center motif, Asp-Ser-Gln-Ala different from other known retroviral aspartic acid PRs [1, 11]. Furthermore, the subcellular localization of FSRV Gag is perinuclear [5]. Cryo-electronmicroscopy allowed the direction observation of trimers of the intact HSRV Env glycoprotein [8]. Further studies to explore the role Env in budding and virus release are currently carried out.

Expression profiling of human genes in human cells either infected with HSRV or transfected with Bel1 transactivator expression plasmids showed a surprisingly specific pattern of induced cellular genes [9]. Insulin like growth factor 2 (IGF2), a known oncogene and cyclin-dependent protein kinase inhibitor (p57Kip2), a tumor suppressor were among those human genes that were strongly activated [9]. The specific trans-activation of the IGF2 and p57Kip2 genes were confirmed by RNA blot hybridization and by means of immunoblot analysis with monoclonal antibodies.

Figure 1: Regulation of spumavirus gene expression by the transcriptional trans-activator Bel 1. The different boxes represent the viral genes. The bent arrows mark the bel1 DNA target sequences. The two rectangular arrows indicate both start sites of transcription symbolized by red boxes marked RNA. LTR, long terminal repeats.
directed against these proteins [9]. This result will have impact on spumavirus vectors.

Publications (* = external coauthor)


