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The Polarity of Entry and Release of *Canine Coronavirus* From Epithelial Cells

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Introduction

Canine coronavirus (CCoV) is an enveloped, single-strand RNA virus belonging to the *Alphacoronavirus genus* in the *Coronaviridae* family Pratelli [1,2] Despite their labile nature, RNA viruses are able to rapidly adjust to negative pressures of immune system, generating novel strains that might have selective advantages over parental genomes. As a consequence of the high mutation frequency, in the last years CCoV has evolved and new genotypes/types were identified, raising several questions regarding the biology of these viruses Pratelli, Cirone and Pratelli [3-5]. CCoVs are responsible for enteritis in dogs of all breads and ages and clinical signs may vary from mild to severe gastroenteritis in young pups. Though fatal infections are unusual unless mixed infections with other pathogens occur or in the presence of overcrowding and unsanitary conditions Pratelli et al., [6], the virus is an important pathogen responsible for epizootics in dog population Pratelli [5]. Recently, a CCoV type 2a pantropic variant was identified in a systemic fatal disease in young dogs Buonavoglia et al. [7], and a subsequent experimental study has raised important questions on the pathobiology of CCoVs, demonstrating that the new virus was able both to infect CCoV-seropositive dogs and to induce clinical signs irrespective of the viral dose administered in the challenged dogs Decaro et al. [4].

Epithelial cells in the gastrointestinal tracts are the target of CCoVs infection.Two domains can be distinguished in the epithelial plasma membranes: the apical face, exposed towards the intestinal lumen, and the basolateral face. Each domain has a different composition and the tight junctions with neighbouring cells separate the two faces preventing mixing of membrane components Rossen et al., [8].The epithelial cell surface from which viruses are released conditions the development of virus pathogenesis Tashiroet al. [9]. Entry and release of viruses from epithelial cells can occur through either domains as a result of the distribution of viral receptors. Polarized virus release influence viral spread: basolateral release allows the infection of underlying tissues leading to a systemic infection, and apical release can limit viral spread by preventing the infection of cells other than epithelial ones Rossen et al. [8]. The distribution of viral receptors, and their interaction with epithelial cells was investigated in vitro for different viruses, being essential elements in determining the susceptibility of cells to virus infection. The polarity of entry and release of CCoV from epithelial cells was established using theMinicell 24-Well Cell Culture Device (*Millipore Corporation*), expressly designed to support suspension and adherent cell growth and differentiation. The amounts of infective virus in the apical and in the basolateral media was determined and compared, bringing out interesting data Pratelli [10].

A72 and CrFK cell lines were cultivated in the Minicellin order to form tight monolayers, as assessed by transepithelial resistance measurement at different post-infection time points. The filter-grown A72 and CrFK cells were infected with 100TCID50/50µl of CCoV, strain 257/98-3c, from either the apical or the basolateral side. Infected cells were employed for titration, immunofluorescence assays and for inhibition of infection trials. Infection of A72 cells after different times post seeding demonstrated that CCoV grew after infection from both apical and basolateral sides. CrFK cells appeared less accessible to CCoVinfection and the virus was observed only in the later phase of the infection both in the apical and in the basolateral compartments. An infection-inhibition experiment established the correlation of the polarity of CCoV entry with the receptor distribution on A72 cell plasma membranes. For this purpose, cells grown on permeable supports were preincubated with a monoclonal antibodies specific for CCoV from both the apical and the basolateral side and the production of progeny virus was evaluated. The infection from the apical side was blocked by monoclonal antibodies applied on apical side; in contrast, the treatment from the basolateral side had no effect on the infectious process through the apical membrane. Similarly, the low levels of CCoV observed after the basolateral inoculation was abolished following monoclonal antibodies treatment from that side.

CCoV is considered a pathogenmostly responsible for enteric disease. Consequently, the expression of receptors should be located on apical surface of epithelial cells to permit viral infection

via the intestinal lumen. The study by Pratelli [10] highlights a new pathogenetic characteristic of CCoV *in vitro*. The virus was able to infect epithelial cells from both apical and basolateral compartments, and even if with different titres, CCoV was released both in the apical and in the basolateral medium after infection. Consequently, the current view that CCoVinfection is restricted to the intestine should be modified, arguing that the direction of release may be toward the blood stream inducing systemic infection. The recent identification of the pantropic CCoV support this hypothesis, raising important questions on CCoVs biology. Although in recent years new data have shed light on obscure aspects of the infection, new studies are necessary to complete knowledge on these viruses, both in terms of evolution and pathogenesis.

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