The direct route of herpes simplex virus 1 from the nucleus to the cell periphery

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Background: Herpesviruses comprise the capsid, tegument proteins and an envelope with embedded glycoproteins. Capsids, containing the genome, are assembled in the nucleus and translocated to the cytoplasm acquiring tegument proteins and the envelope.

Dogma: For production of infectious progeny virus, capsids must be translocated into the perinuclear space (PNS) by budding at the inner nuclear membrane (INM) acquiring tegument and the envelope. Then, the envelope must fuse with the outer nuclear membrane releasing capsid and tegument into the cytoplasmic matrix where the capsids are re-enveloped at the trans Golgi network [1].

Queries: Mutants lacking the gene encoding the Us3 protein, which is involved in nucleus to cytoplasm translocation, are infective [2, 3] although they accumulate in the PNS because they cannot be released by fusion of the viral envelope with the ONM [4]

Hypothesis: i) The process taking place at the ONM is budding not fusion, ii) virions are transported from the PNS via endoplasmic reticulum (ER) to Golgi transitions into Golgi cisternae for packaging, and iii) naked capsids gain access to the cytoplasmic matrix via impaired nuclear envelope[5].

Methods: Vero cells inoculated with wild type herpes simplex virus 1 (wt HSV-1) or a Us3 deletion mutant thereof (R7041) kindly provided by Bernard Roizman, University of Chicago, USA) were analysed by confocal microscopy and electron microscopy employing protocols for improved spatial and temporal resolution.

Results: Electron microscopy of high pressure frozen and freeze substituted cells showed the following: i) Impairment of the nuclear envelope probably starting by impairment of nuclear pores that became morphologically manifest as dilation (Fig. 2) through which capsids gain direct access to the cytoplasm. ii) These capsids are enveloped by budding at ER and Golgi membranes or by wrapping at Golgi membranes (Fig..). iii) Virions derived by budding at the INM are intraluminally transported into the ER. iv) ER to Golgi transitions are established in Vero cells (Fig,) - as in many other cells[6] - through which virions can be transported into Golgi cisternae. v) Golgi cisternae are filled with virions that are packaged into transport vacuoles for delivery to the cell periphery (Fig..). vi) The process at the ONM is budding not fusion taking place in the absence of the fusion proteins gB/gH (see Fig. 2 in [7].

Conclusion: HSV-1 nucleus to cytoplasm translocation follows two direct routes: by budding at the INM followed by intraluminal transportation into Golgi cisternae, and later in infection also via impaired nuclear pores followed by envelopment at any site of the ER and Golgi complex.

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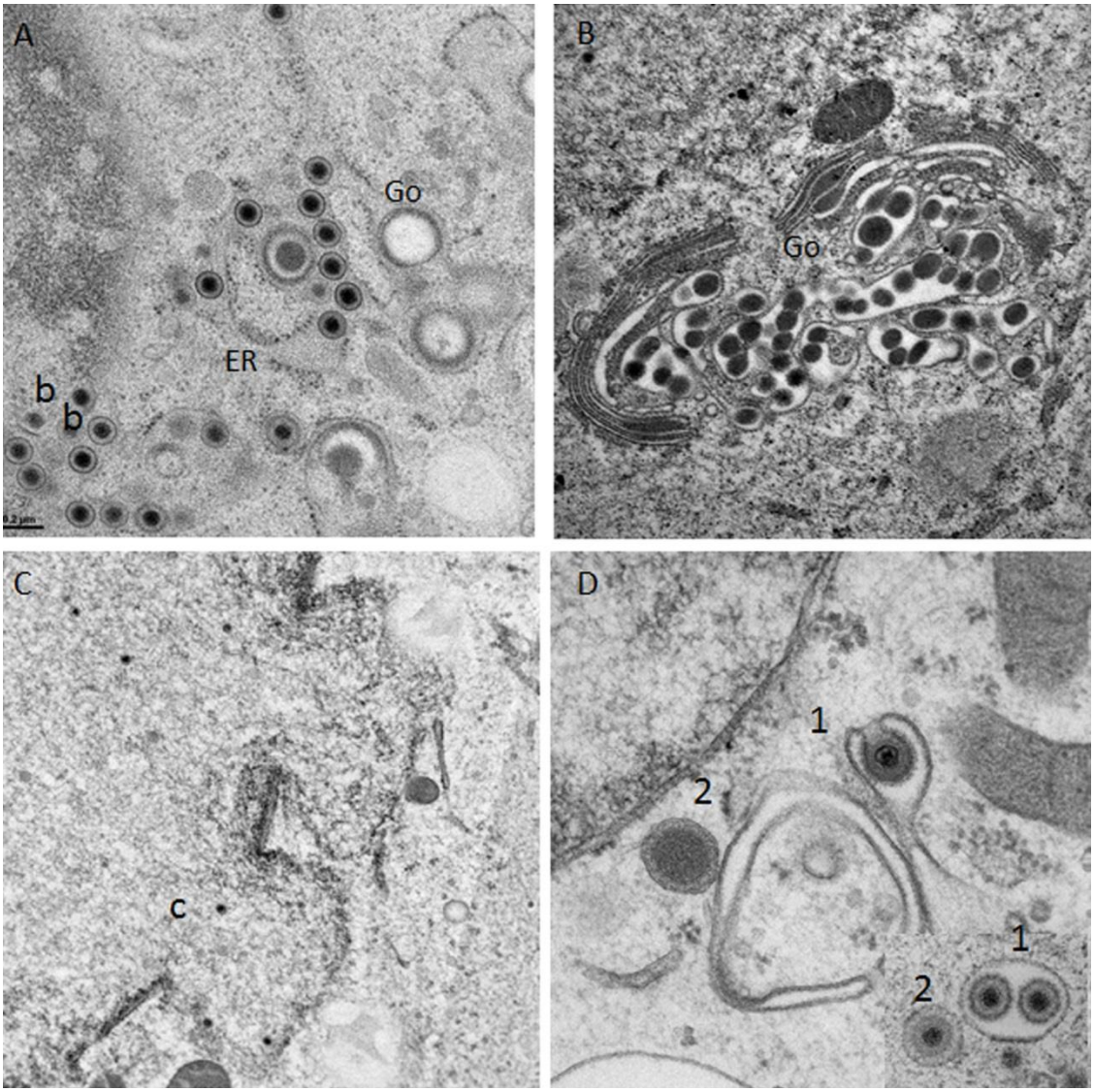

A-B: Capsids bud (b) at the INM are transported with the ER into Golgi cisternae (Go) C-D: Capsids are released via impaired nuclear envelope and bud at Golgi membranes either into Golgi cisternae (1) for packaging into transport vacuoles or form concomitantly a transport vacuole (2: tangential section), a process designed wrapping