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Chromatin Reorganization during Viral Infection

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DNA viruses target the cell nucleus due to their need of the cellular DNA reproduction machinery. Lytic infection with herpes simplex virus 1 (HSV-1) is known to elicit the formation of a large nuclear viral replication compartment and redistribution of the cell chromatin. The final nuclear steps of infection include the assembly of viral capsids in the replication compartment area and and their egress through the nuclear envelope. To reach the nuclear envelope, the viral capsids have to be transported through the host chromatin. The infection-induced quantitative changes on the spatial and molecular organization of chromatin, and their effect on the viral capsid translocation toward the nuclear egress site have remained unknown.

Despite their many achievements in biological applications, light- and electron-based imaging techniques face some fundamental limitations in 3D imaging of the subcellular architecture of the entire cell. They have been unable to provide sufficient details on the spatial and molecular organization of chromatin to allow elucidation of whether chromatin constitutes an accessibility barrier for the translocation of viral capsids toward the nuclear envelope. We employed a new combination of methods integrating 3D soft X-ray tomography (SXT) imaging [1], confocal and transmission electron microscopy, advanced data analysis, and numerical modeling, so as to study in more detail the HSV-1-induced changes in the molecular organization of host chromatin and intranuclear mobility of viral capsids.

Our quantitative SXT analysis revealed that the formation of the enlarged viral replication compartment at late infection resulted in heterochromatin enrichment near the nuclear periphery accompanied by compaction of the B cell chromatin (Fig. 1) [2]. The infection-induced changes in host chromatin increased the linear absorption coefficient (LAC) values of heterochromatin in comparison with those of the non-infected cells (Fig. 1). Surface-rendered 3D tomographic reconstructions of the nuclear periphery of the infected cells revealed low-LAC gaps in the compact layer of marginalized host chromatin [3]. Further studies revealed that the low LAC regions formed channels, some of which penetrated the peripheral (compacted) chromatin in both infected and non-infected cells (Fig. 2A). Notably, in the infected cells the total number and area density of low LAC gaps, 900 and 2.4 μm^{-2} were significantly higher than in the non-infected cells (170, 0.65 μm^{-2}). The smallest diameter of these channels was at least 200 nm, which is big enough to allow the passage of at least one viral nucleocapsid (diameter 125 nm) at a time. In line with that, confocal and electron microscopy analysis showed presence of viral nucleocapsid-containing channels extending through the chromatin. In the infected cells these channels were almost always located independently of nuclear pore complexes (NPCs), whereas in the non-infected cells they were located adjacent to the NPCs [3]. Finally, random walk modeling of HSV-1 sized particles in a 3D SXT tomography reconstruction of an infected cell nucleus demonstrated that the peripheral, compacted chromatin restricts viral capsid motility, but due to interchromatin channels the transport of the progeny viruses to the nuclear envelope is possible (Fig. 2B) [2,3].

In summary, lytic infection with HSV-1 induces profound modification of the host cell chromatin architecture. Using a new combination of methods, including SXT imaging combined with advanced data analysis and capsid transport simulations, to study virus-cell interactions allowed us for the first time to quantitatively analyze the changes in chromatin distribution during infection.

References:
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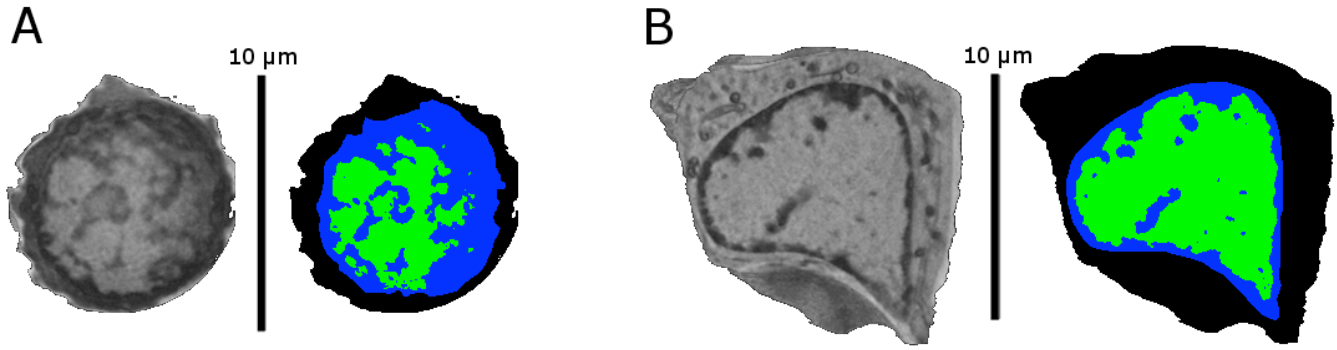

Figure 1. Virus-induced re-organization of the host chromatin. SXT orthoslices and volume-rendered views of nuclei of (A) a non-infected cell and (B) an infected cell. The high linear absorption coefficient (LAC) region of heterochromatin (blue) and low-LAC region of euchromatin and viral replication compartment are shown.

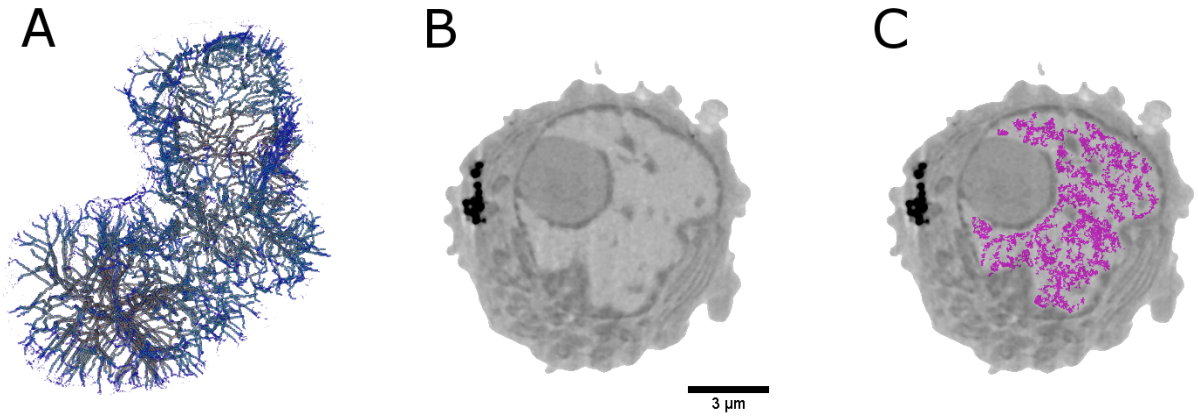

Figure 2. Distribution of HSV-1 infection-induced channels and numerical simulations of capsid motion. (A) A computationally reduced skeletonized structure of the SXT low-LAC regions in the infected cell nucleus showing channels across the peripheral heterochromatin. (B) SXT orthoslice of an infected cell and (C) paths of diffusing capsids (magenta) simulated using the time-domain random walk method.

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