

Molecular Mechanisms of HPV Infection in the Lower Genital Tract

Editorial

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Received: August 18, 2014**Published:** September 29, 2014

Citation: G Androutsopoulos, G Adonakis, G Decavalas (2014) Molecular Mechanisms of HPV Infection in the Lower Genital Tract 1:101
doi: <http://dx.doi.org/10.19070/2572-7427-140001e>

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Human papillomaviruses (HPV) are small, non-enveloped viruses.[1] They contain circular double-stranded DNA within an icosahedral capsid.[2] Despite their small size, they have very complex molecular biology.[3] They have 2 structural proteins (L1 and L2) that compose the viral capsid.[3-5] Also, they have 3 oncogenes (E5, E6 and E7) that modulate the transformation process.[3,4] Moreover, they have 2 regulatory proteins (E1 and E2) that modulate transcription and replication.[3,4]

The infectious cycle of HPV is conducted entirely within a fully differentiated squamous epithelium.[1] HPV infection requires that virus particles gain access to the epithelial basal layer and enter the dividing basal cells.[2] It is necessary a micro-abrasion of the epithelial surface, that removes the epithelium but keeps the basement membrane intact.[1] The thinner and more fragile metaplastic epithelium may be more susceptible to the micro-abrasion process and thus to HPV infection.[1] HPV infection is very common in young sexually active women.[1]

The viral L1 protein binds to the exposed basement membrane of probably via heparan sulphate proteoglycans (HSPGs) [primary receptor].[1,6-8] This binding results in conformational changes and distortion of the virus capsid.[1,6-8] This distortion exposes the viral L2 protein to cleavage by furin or by proprotein convertase 5/6.[1,6-10] This cleavage site is absolutely conserved among all HPV types[1,9-11] Proteolytic cleavage by furin, is essential for successful infection.[6,8-11]

After cleavage, the viral L2 protein binds to the cell surface and this triggers a second conformational change in the virus capsid.[1,6,11] This conformational change either exposes the binding

site for the secondary receptor on the viral L1 protein or it lowers the affinity for the primary receptor.[1,6,8,10,11] Then viral L1 protein binds to $\alpha 6$ integrin on the cell surface [secondary receptor] and triggers receptor mediated endocytosis of HPV.[1,6,7,10,11]

Most HPV types generally use clathrin dependent endocytic pathway.[6,8,10-13] However, some HPV types use alternative endocytic pathways (caveolae dependent endocytic pathway or clathrin and caveolae independent endocytic pathway).[6,8,10,11,14,15]

HPV has the ability to avoid lysosomal degradation.[13-16] It can escape from the endosomes to the cytosol, with fusion independent mechanisms.[16] The decrease of pH in early endosomes results in conformational changes of HPV capsid and trigger the endosomal escape of the HPV genome or the complex of HPV genome and L2 protein.[13,17]

Viral L2 protein is required for egress of viral genomes from endosomes, but not for initial uptake and uncoating.[8,18] Moreover viral L2 protein interact with the microtubule network via the motor protein dynein.[10,18] This interaction mediates the transport of the complex of HPV genome and L2 protein along microtubules towards the nucleus.[10,18]

Moreover, viral L2 protein contains nuclear localization signals (NLSs).[19] Those NLSs interact with a network of karyopherins and mediate nuclear entry of HPV genome and L2 protein via several pathways (karyopherin $\alpha 2\beta 1$ heterodimers, karyopherin $\beta 2$ and karyopherin $\beta 3$).[19,20] Binding of Ran-GTP to the karyopherin β causes dissociation of the import complexes and release the complex of HPV genome and L2 protein inside the nucleus.[19-21] Finally the complex of HPV genome and L2 protein enters the nucleus.10 18 Then it localizes at punctate nuclear regions known as PML nuclear bodies (PML-NBs), promyelotic oncogenic domains (PODs) or nuclear domain 10 (ND10).[22-24] Those nuclear structures are responsible for transcriptional processes.[23,25,26] HPV transcription and replication occur in association with PML-NBs.[10,23,27,28]

During latent infection, HPV maintains its genome as autonomous replicating episomes in the proliferating basal cells of the squamous epithelium.[29,30]

It is obvious that HPV has very complex molecular biology. Despite significant advances regarding molecular biology of HPV infection, there are many questions to be answered. Moreover, the better understanding of molecular mechanisms of HPV infection is very important for further development of new generation HPV vaccines.

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