

## E5 and E6/E7 of high-risk HPVs cooperate to enhance cancer progression through EMT initiation

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**I**t is estimated that 10–20% of human carcinogenesis is linked to virus infection including papillomaviruses (HPVs). Moreover, since metastatic cancer disease is a major cause of morbidity and mortality in cancer patients, the role of oncoviruses in cancer progression to a metastatic form is of particular interest. Recent studies reported that E5 and E6/E7 onco-proteins of high-risk HPVs could enhance cancer progression via the initiation of the epithelial–mesenchymal transition (EMT) event. Herein, we discuss the association between E5 as well as E6/E7 of high-risk HPV and cancer progression.

Human papillomaviruses are episomal, double-stranded DNA viruses. Today more than 150 known types have been identified, however only some of them contribute to malignancies. The majority of HPV types infect the non-mucosal, cutaneous epithelium. However some of these viruses infect mucosal tissues and the genital tract, which are sub-divided into high-risk and low-risk categories based on their ability to transform the host cell and therefore initiate cancer development.<sup>1–3</sup> The HPV genome is circular with dual promoters that encode 2 separate groups of viral proteins: the early genes (E1, E2, E4, E5, E6, E7, E8) and the late genes (L1, L2). Certain early HPV genes are essential for maintaining the viral replicative cycle, while late HPV genes encode the major (L1) and minor (L2) capsid proteins.<sup>1–2</sup> E1 and E2 are primarily involved in transcription and replication.<sup>1</sup> However, E4 protein is less well characterized, but several studies implicate E4 in virion release via its association with keratin

filaments.<sup>1–2</sup> In parallel, the role of E5, E6/E7 of high-risk HPVs in cellular alteration and transformation and consequently tumor initiation is very well documented;<sup>2–5</sup> however, there are a limited number of investigations about the role of high-risk HPVs and especially their E5 and E6/E7 onco-proteins in human cancer progression.<sup>4,5</sup> Accordingly, we read with great interest the article by Ranieri et al.<sup>6</sup> “HPV16 E5 expression induces switching from FGFR2b to FGFR2c and epithelial-mesenchymal transition.” Their study clearly demonstrated a strong association between the presence of E5 of high-risk HPV type 16 and the changes in the expression of the mutually exclusive splice variants of the fibroblast growth factor receptors (FGFR2b and FGFR2c), due to the epithelial splicing regulatory proteins (ESRP)-dependent switch. Particularly since the restored expression of ESRP1 is able to contrast the effect of the E5 onco-protein. More significantly, their data showed that the altered FGFR2 splicing leads to changes in the ligand specificity of FGFs and cellular response, triggering the epithelial-mesenchymal transition (EMT), which is an essential event in cell motility and invasion and consequently cancer progression to a metastatic form.<sup>7</sup>

Well, High-risk HPVs are considered among the major viruses associated with several human cancers especially cervical as well as head and neck (HN), colorectal and breast cancer; as roughly 96, 30, 80 and 50% of these cancers were revealed positive for these viruses, respectively.<sup>4</sup> Moreover, it was observed that the presence of high-risk HPVs serve as a prognostic factor in early-stage cervical, HN, and colorectal cancers, and are associated with

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vascular invasion, lymph node metastases and tumor size.<sup>5</sup> In parallel, it has been shown that high-risk HPVs are present in human breast cancer and their presence is associated with more aggressive phenotype;<sup>4,5</sup> accordingly, we have demonstrated that E6/E7 of high-risk HPV type 16, which is the most frequent type of the high-risk group worldwide, converts non-invasive and non-metastatic breast cancer cells to invasive and metastatic form; this occurs via the activation of the Id-1 full promoter by E6/E7 onco-proteins.<sup>8</sup> In addition, several recent investigations reported that E6/E7 of HPV type 16 induce EMT and consequently cell motility and invasion via epidermal growth factor receptor (EGFR) signaling pathways.<sup>9,10</sup> In parallel, it has been shown that E5 onco-protein of HPV type 16 up-regulates the expression of vascular endothelial growth factor (VEGF) through the activation of EGFR, MEK/ERK1 and 2 as well as PI3K/Akt,<sup>11</sup> which could induce cell invasion via EMT initiation. Thus, we believe that E5 and E6/E7 of the high-risk HPV group cooperate together to enhance cancer progression through the initiation of EMT and its signaling pathways. However, this avenue has not been investigated yet. We consider that it is necessary to develop new cellular and animal models to explore the cooperation effect of E5 and E6/E7 of high-risk HPV, which is an important step to determine the exact role of such cooperation in human carcinogenesis and eventually identify new targets to manage high-risk HPVs-positive cancers.

Alternatively and with regards to high-risk HPV-associated cancers prevention, we assume that the 2 available vaccines of high-risk HPV types 16 and 18,<sup>12</sup> which are against the 2 most frequent viruses worldwide, could diminish the development of these malignancies and their metastases. Moreover, it is important to highlight that the new generation vaccine of HPVs is a nonavalent (9-valent) and is expected to include HPV types 16, 18,

31, 33, 45, 52, and 58 altogether which are implicated in more than 90% of HPV-related cancers, in addition to types 6 and 11 of low risk.<sup>13</sup> This vaccine will considerably reduce HPV-associated cancers and their metastatic forms, which are responsible for the majority of cancer-related deaths.

In conclusion, it is evident that high-risk HPVs are present in several human carcinomas, which could contribute to the initiation and progression of these cancers, as clearly demonstrated by Ranieri et al.<sup>6</sup> and other investigators; however, the real role of these viruses and particularly the cooperation effect between their oncoproteins in the initiation and progression of high-risk HPV-related cancers needs more investigations. Thus, more molecular and cellular studies are necessary to elucidate the cooperation outcome of high-risk HPV onco-proteins especially E5 and E6/E7 in human normal epithelial and carcinoma cells from cervical, HN and colorectal tissue.

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No potential conflicts of interest were disclosed.

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