HUMAN PAPILLOMAVIRUS (HPV) AND PROSTATIC CANCER OSTEOBLASTIC BONE METASTASIS: HPV E6 CONTAINS AN ENDOThELIN ACTIVE SITE TRYPTOPHAN

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TRAN Guy Mong Ky

Retired, Public Health (Agence Régionale de Santé ARS Auvergne Rhône Alpes), Hospital Hôtel-Dieu, Clermont-Ferrand, FRANCE. Correspondence: 31 Avenue du Bois 92290 Chatenay Malabry. E-mail: mkg_tran@yahoo.fr.

Phone: +33 9 81 89 38 70.

BACKGROUND Endothelin (ET-1, 2, 3) (Yanagisawa M, 1989) is mitogenic for 3T3 fibroblasts (Takuwa N, 1989) and induces osteoblast proliferation and is involved in osteoblastic bone metastases of Prostatic Cancer (PK) with translocation TMPRSS2:ERG gene fusion (Delliaux C, 2014). We found earlier by centering on the HQLL motif that:

| HPV-18 E2   | IQTLNHQVL |
|            | ET² SHQLL |

contains the osteoprotegerin active site as well as parathormone (PTH) IQ LMHNL.
and PTH-related Protein (PTHrP)  

that could explain PK osteoclastic bone metastasis *(Tran GMK, 2004).* We search for an endothelin in HPV that could explain osteoblastic bone metastasis.

**METHODS** Amino acid sequences and three dimensional structure (3D) comparison between HPV and ET.

**RESULTS** By centering on the crucial tryptophan W21, which removal decreases ET potency by a factor > 1000 *(Kimura S, 1988)*, we found that

HPV (cand 89), -150, -160 E6  

34-**EL**-35  

48-**LDIVW**-52  

is homologous to the ET-1,-2,-3/sarafotoxin active site  

5-**DM**-6  

17-**LDI IW**-21

In 3D structure, HPV E6 has 2 separated functional sites, centered on the COOH-terminal tryptophane W 21 and on 5-DM-6 (of sarafotoxine). The homologous sequence LNVVW is found in HPV-3, -28, -29, -68 ME 180. In HPV-18 E6, W was replaced by Y. Burrowing asp *Attr actaspis engaddensis* sarafotoxin, which induces a coronary spasm, differs slightly from ET:

Q  

D  

VI  

W  

(where Q replaced L).

Weak but highly selective ET-A Receptor antagonists were isolated from *Streptomyces Misakienisis*  

7338  

and sp n° *(Miyata S, 1992)*  

Highly potent and selective ET-A Receptor antagonist structures are pentapeptides:
cyclo \text{(D-Asp-Pro-D-Val-Leu-D-Trp)} \text{(Ihara M, 1992)} \text{and}

cyclo \text{(D-Asp-Pro-D-Ile-Leu-D-Trp)} \text{ (D=Dextrogyre) (Lippton, 1993)}.

**CONCLUSION** The molecular homology of HPV E6 with the active site of Endothelin, implicated in PK bone metastasis, supports further the HPV role in KP, not only in the primary tumor, but also specifically in osteoblastic bone metastasis. Interestingly, **high doses of Vitamin C has an anti-Endothelin action** \text{(Dow C, 2015)}

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