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

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BACKGROUND Endothelin (ET-1, 2, 3) (*Yanagisawa M, 1989*) is mitogenic for 3T3 fibroblasts (*Takuwa N, 1989*)

, 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**

contains the osteoprotegerin active site **ET□ SHQLL**

as well as parathormone (PTH) **IQ LMHNL**

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and PTH-related Protein (PTHrP)

S EHQLL

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 Misakiensis*

and sp n°
(*Miy*

7338

ata S, 1992)

. Highly potent and selective ET-A Receptor antagonist structures are pentapeptides:

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cyclo (**D-Asp-Pro-D-Val-Leu-D-Trp**) (*Ihara M, 1992*) and

cyclo (**D-Asp-Pro-D-Ile -Leu-D-Trp**) (*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** (*Dow C, 2015*)

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