There are no translations available.

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

ARTP 18 Nov 2015 Paris Porte Maillot

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.

BACKKROUND 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**

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:
QDVIW
(where Q replaced L).

Weak but highly selective ET-A Receptor antagonists were isolated from *Streptomyces Misakiensis* and sp n° 7338 *(Miy ata S, 1992)*
. Highly potent and selective ET-A Receptor antagonist structures are pentapeptides:

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)*.

BIBLIOGRAPHY **Delliaux C**, Endothelin-1, a gene regulated by TMPRSS2:ERG fusion proteins in prostate cancer bone metastases. *ARTP,* Paris, Nov 19 2014. **Ihara M.**
Biological profiles of highly potent novel endothelin antagonists selective for the ETA receptor.
Life Sci
1992, 50: 247-55.
Dow C
.Vitamin C Supplementation Reduces ET-1 System Activity in Overweight and Obese Adults.14th Int Conf on Endothelin: Physiology, Pathophysiology and Therapeutics. Press release of the Am Physiol Soc, 4th September 2015,
www.the-aps.org/mm/hp/Audiences/Public-Press/2015/44.html
.
Kimura S
. Structure-activity relationships of endothelin: importance of the C-terminal moiety.
Bio Bio Res Com
1988, 156: 1182-6.
Miyata S
. WS-7338, new endothelin receptor antagonists isolated from Streptomyces sp. No. 7338. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activities.
J Antibiot (Tokyo)
1992, 45: 74-82; 83-7; 698-703;788-91; 1029-40; 1041-6.
Lippton
.
Am Heart Assoc, 66
th
Scientific Sessions, Georgia World Congress,
Nov 8-11, 1993.
Takuwa N
. A novel vasoactive peptide endothelin stimulates mitogenesis through inositol lipid turnover in Swiss 3T3 fibroblasts.
J Biol Chem
1989, 264: 7856-61.
Tran GMK

, Role of human papillomavirus type 18 in a subgroup of prostatic cancer with bone metastasis: Its protein E2 contains the osteoprotegerin active site
EuroConf Cancer, Pasteur Inst.
Jan 15-16 2004.

Yanagisawa M
. Molecular biology and biochemistry of the endothelins.
Trends Pharmacol Sci
1989, 10: 374-8. Review.