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Role of human papillomavirus type 18 in a subgroup of prostatic cancer with bone metastases: Its protein E2 contains the osteoprotegerin active site.

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INTRODUCTION

In Japan, the oncogenic human papillomavirus (HPV) type 18 is found by polymerase chain reaction (PCR) in **80%** (12/15 cases) prostatic cancer (PC) with bone metastases versus 0% in controls (Anwar K, 1992)

oncogenic HPV-18,-16,-33 are frequent in a PC subgroup in Germany [HPV-16 in 10/47(

21

%)]

(Serth J, 1999)

, Canada [13/27 (

48.1

%)]

(McNicol P.J., 1991)

, Japan (

41

%)]

(Anwar K, 1992)

, in Michigan (USA) [3/23(

13

%)]

(Sarkar F.H., 1996)

, Italy [6/8(

75

%)]

(Rotola A., 1992)

and in Montpellier, France (HPV-16 in

53

%)

(Moyret-Lalle C., 1995)

. In Sweden, high antibody levels against HPV-33 multiplied the risk by 2,3 fold

(Adami H.O., 2003)

. In Finnish men, in a prospective study, the presence of antibodies against HPV-16 was associated with an odds ratio (OR) of 2.58 and antibodies against HPV-18 with a statistically significant

odds ratio

of

2,88

(Dillner J., 1998)

. Hisada M. (2000)

found also an OR of 2.7 for HPV-16 antibodies in a prospective cohort study.

Numerous negative results have been reported, and this very important point was analyzed in detail (for tables, see: Terris M.K., 1997 and Strickler H.D., 1998) :

Discrepancies are explained in DISCUSSION below : All positive PCR studies (80%, 75%, 53%, 48.1%, 41%, 21%) have used HPV

E6

as primers set, and

fresh frozen

prostatic tissues (except Anwar K, who used archival tissue) ; whereas negative (0%) and weak results employed HPV consensus

L1

and archival formalin-fixed, paraffin-embedded tissues . In seroepidemiological studies, the prospective cohort studies were positive whereas the retrospective case-control studies generally negative.

The very low concordance of PC in homozygotic twins, (where concordance was observed only 16 times, whereas discordance is 135 times) (Morganti G, 1956) very strongly favoured an environmental factor : Viral (papillomavirus, polyomavirus) or toxic (

cadmium

, tobacco). Epidemiology

(Sarradet A., 1997)

speaks for a sexual transmission [militaries, multipartenarism, herpes virus type 2 infection
(Haid M., 1984)
, prostitutes frequentation , non use of condoms, gonorrhoea, syphilis
(Hayes R.B., 2000)
, marriage, wife with uterus cervical cancer, transmitting her HPV to the husband
(Lattimer, 1974)
].

LINKS BETWEEN HPV MOLECULAR BIOLOGY AND PROSTATIC CANCER.

There are many connections between HPV and PC : The HPV oncogènes E6 and E7 are inhibiting the tumor suppressors p53 and pRb, precisely those altered in PC (Sellers W.R., 2002)

HPV is integrating upstream of Myc oncogene, which is amplified in 47% of metastatic PC (Kaltz-Wittmer C., 2001). There is a loss of heterozygosity of Bin-1, an anti-myc tumor suppressor, in about half of PC (Sakamuro D., 1996)

We found an Epidermal Growth Factor (EGF) motif in HPV E2 (Tran M.K.G., 1993) and EGF receptor ,which gene is on chromosome 7p, is overexpressed in 33.6% of PC (Inoue K., 1998)

; and Trisomy 7 is correlated with a bad prognosis of PC (Bandyk M.G., 1994)

. There is a " cross-talk " phenomom between EGF and androgen receptor, that can be activated in the absence of the ligand (Cullig Z., 1997 ; Hobisch A., 1997)

. EGF transduction pathway is signalling by Ras, which is frequently mutated in PC (Anwar K, 1992)

. HPV-16 E5 stimulates EGFR (Pim D., 1992).

OBJECTIVE

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As we have found a molecular mimicry between breast cancer virus 3'ORF and PTHrP (parathormone-related peptide) which could explain bone metastasis in breast cancer (*Tran M.K.G., 2003*), similarly we tried to elucidate the HPV-18 role in bone metastases, as HPV-18 was so strongly (80% PC versus 0% controls) (*Anwar K, 1992*)

and specifically associated with the presence of bone metastasis. HPV-18 is known to induce a severe, aggressive cervical cancer in women. HPV-18 has been found also in a metastatic lymph node, and in a seroepidemiological study the OR is 2.88 when antibodies against HPV-18 are present (*Dillner J, 1998*)

. To find a molecular biology explanation would strengthen the role of HPV-18 in the occurrence of a subset of particularly aggressive and lethal PC, that resist to hormonal treatment.

METHOD

Comparison of aminoacids (AA) sequences between HPV-18 E2 protein and 3 proteins of calcic homeostasis : Osteoprotegerin (OPG), PTH (parathyroid hormone) and PTHrP (PTH-related protein). The screening sequence is the tetrapeptide HQLL common to osteoprotegerin and PTHrP.

RESULT

Osteoprotegerin is the most homologous to HPV-18 E2, spanning 8 aminoacids, which is significant. A contrario, histidine (His) is absent in benign HPVs.

| | | | | | | | | | |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| HPV-18 E2 | Ile | Gln | Thr | Leu | Asn | His | Gln | Val | Val |
| Osteoprotegerin | | Glu | Thr | - | Ser | His | Gln | Leu | Leu |
| PTHrP | | | | | Ser | - | Glu | His | Gln |
| PTH | Ile | Gln | - | Leu | Met | His | Asn | Leu | |

DISCUSSION

Owing to the low HPV copy number in prostatic tissue (*Serth J., 1999*), the PCR seemed

the most appropriate method to reveal HPV in prostatic cancer. But the choice of the primer sets is

crucial and can alone determine the PCR positivity

(*Terris M.K., 1997*)

: In the same patient, E6 primer set obtained 11/53 (20.8%), compared to 0/53 (0%) for L1 primer.

Previous numerous negative results have been reported, throwing doubt, and this very important point was analyzed in detail (for review tables, see: *Terris M.K., 1997*

and

Strickler H.D., 1998

): We can now clarify further the debate and try to explain some of these apparent discrepancies, on the basis of 2 criteria (first, the primer sets used, second, the prostatic tissue preparation) as well as the PC heterogeneity.

POSITIVE RESULTS: All positive PCR studies (80%, 75%, 53%, 48.1%, 41%, 21%)

have used HPV

E6 as primers set, and **fresh frozen** (*Z*

ambrano A., 2002)

prostatic tissues (except Anwar K, who used paraffin tissue and E6 primer; like *Sarkar*

who obtained only 13%) .

NEGATIVE RESULTS: Whereas almost all negative (0%) and weak (about 15%)

results employed HPV consensus

L1 and archival

formalin-fixed,

paraffin-

embedded tissues ; these " L1-paraffin " authors were numerous :

Serfling U

(0%),

Effert P.J.

(0%),

Terris M.K.

(0%)

Tu H.

(2.3%),

Ibrahim G.K

. (16%),

Suzuki H.

(16%),

Widerhoff L.

(12.5%) (15.2% in whites).

Wideroff L.
is the only author to obtain no result with E6 primers set, like
Noda T. (1998)
[0/38 (0%)] in paraffin tissue. It seems that paraffin is not recommended for HPV
research, because the majority of results are negative or very weak.
Iwasawa A (1990)
and
Gherdovich S (1997)
have negative results, but their patient number is statistically too low (n=5 only).
Masood S. (1991)
had negative results but used in situ hybridization instead of PCR. There is some
doubt on the results of
Strickler H.D., 1998,
who found zero HPV everywhere (cancer and adenoma controls) : There is no
explanation for their failure (they correctly used E6 and frozen tissue for PCR), except the
PC heterogeneity (they may have examined other PC subsets linked to cadmium,
polyomavirus and genetics). It is unknown why
Strickler H.D.
did not use the same
E6
primers set than for example
Anwar
. A slightly different sequence may be crucial for perturbing the results.

For the discrepancies in seroepidemiological studies, which are less convincing than
PCR studies, the criteria used for discussion is whether they were prospective or
retrospective (retrospective is more subject to errors, because the choice of controls can
always be debated) : The **prospective** cohort studies were positive (*Hisado M., 2000*
; *Dillner J. 1998*)
, whereas the
retrospective
case-control studies generally negative
(*Strickler H.D., 1998 ; Rosenblatt K.A., 2003 ; Hayes R.B., 2000 ; Adami H.O., 2003*)
. However,
Adami H.O.
found negative results with HPV-16 and -18, but positive result with HPV-33 (OR =
2.3).

All these HPV positive results are concerning a subset of PC (about 30-40%), but it
must be kept in mind that non-HPV linked PC exist, for example PC related to tobacco,
cadmium (toxic) or polyomavirus (viral) (*Zambrano A., 2002*) or genetic. So a large
PC heterogeneity can also explain as well negative

(Strickler H.D., 1998)
or weak results.

CONCLUSION

The PC subgroup with bone metastases in Japan is linked by PCR in 80% cases to HPV-18, versus 0% in controls. HPV-18 E2 protein contains an **OPG** motif. This confirms the viral etiology of a PC subgroup, and explains the mechanism of

bone metastases

formation. Cidofovir (Vestide ®) is an active anti-viral against HPV

(De Clerq E., 2003)

and is also used as a 1% gel in cervix intraepithelial neoplasia grade III

(Snoeck R., 2000)

Imiquimod

, a imidazoquinoline immune system stimulator, has been approved for the therapy of genital warts

(Garland S.M., 2003)

. An

anti-HPV-16 vaccine

succeeded against cervical cancer in a clinical trial

(Koutsky L.A., 2002)

. If a subset of PC has to be considered as a

sexually transmitted disease

, it would theoretically follow the same rules as for every STD, i.e. obligatory declaration, systematic viral (HPV, polyomavirus) research in the partner and simultaneous treatment of the partner to avoid any ping pong reinfestation. Obviously, none of these sanitary measures is effectively entered in routine today. There is also a need to develop good and fiable serological tests, alike those used in women cervical cancer (virus-like particles or VLPs) in a cohort prospective seroepidemiological study, and respect the conditions of a highly sensitive nested PCR with specific E6 (not L1) primers set

(Terris M.K., 1997 ; Anwar K, 1992)

on fresh frozen (not paraffin-embedded archival) prostatic tissue, without forgetting to research associated polyomavirus

(Zambrano A., 2002)

. The spectrum of oncogenic HPV types being the most exhaustive as possible.

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