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The role of the tumour suppressor gene PTEN in the etiology of cancers of the female genital tract

by

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Abstrak

Die rol van die tumoronderdrukker geen PTEN in die etiologie van kankers van die vroulike genitale traktus

Fosforilering en defosforilering van die tirosien aminosure in proteine speel ‘n belangrike rol in die regulering van sellulêre prosesse in alle eukariotiese organismes. Dit sluit die regulering van selsikluskontrole, groeikontrole, sellulêre differensiasie sowel as genetiese en sinaptiese oordrag in. Dit word lank reeds gespekuleer dat die fosfatase-gene betrokke is in menslike karsinogenese, maar die PTEN geen is die eerste fosfatase geen wat bewys word om ‘n ware tumoronderdrukker geen te wees. As basiese funksie defosforileer normale PTEN die kinases en inhibeer dit die kinase sinjaal kontrolepaaie wat deur integrien en groeifaktor beheer word.

Die sentrale hipotese van hierdie studie is dat PTEN ‘n belangrike rol speel in tumore van die boonste genitale traktus. Die frekwensie van abnormaliteite in die koderingsareas van hierdie geen is bestudeer in spesifieke ginekologiese tumore en weefsels met die gebruik van polimerase kettingreaksie gebaseerde mutasie-analise. Die maligne tumore sowel as die mees verwante pre-maligne of benigne weefsel- of tumortipes wat beskikbaar was, is gebruik as navorsingsmateriaal om sodoende die verskillende vlakke van PTEN betrokkenheid in die ontwikkeling van neoplasie te demonstreer.

Intieme betrokkenheid van die PTEN geen is gevind in endometriële karsinogenese. PTEN mutasies is in hiperplasie gevind en dit was algemeen in endometroiede karsinoom (54%). Patogene mutasies was baie meer algemeen in kanker as in hiperplasie (10%). Veelvuldige mutasies is in sommige laat stadium tumore aangetoon, wat suggereer dat reeds maligne selle meer genetiese mutasies oor tyd verkry. Alle tumore waar meer as een patogeniese mutasie gevind is het voorgekom by swart pasiënte. Die laaste twee bevindinge is uniek tot hierdie studie.

Selektiewe betrokkenheid van die PTEN geen is gevind in die ontwikkeling van sagte weefsel tumore van die uterus. PTEN mutasies is nie in benigne sagte weefsel tumore gevind nie en geen betekenisvolle betrokkenheid is in leiomiosarkome of endometriële stromale sarkome aangetoon nie. PTEN was egter betekenisvol betrokke in karsinosarkome van die uterus (13%) en veral in tumore met ‘n endometrioiede epiteelkomponent waar mutasies in 17% gevind is. Hierdie bevinding is ‘n hoogs betekenisvolle en unieke navorsingsbevinding wat die hipotese ondersteun dat hierdie tumore uit die endometrium ontstaan. Dit onderskryf ook die indruk dat ‘n sterk band bestaan tussen hierdie geen en endometroiede differensiasie, met morfologie sterk gekoppel aan sellulêre genetika.

Mutasie in die PTEN geen is aangetoon in ovariële endometroiede karsinoom in ~29% van gevalle wat ondersoek is. Die bevinding bevestig PTEN betrokkenheid in karsinogenese in hierdie tumortipe. Weereens toon die resultaat dat PTEN betrokkenheid gekoppel is aan endometroiede morfologie. Die ondersoek van benign of pre-maligne letsels in hierdie orgaan was nie voldoende om kommentaar oor die tydsberekening van mutasie te kan lewer nie.

Met alle tumortipes in ag genome, is daar ‘n tendens aangetoon van minder PTEN mutasies in swart vroue. PTEN mutasies korreleer met endometroiede histologie. In kombinasie bevestig hierdie resultaat ‘n rasse-diskrepansie in die distribusie van tumourtipe of morfologie.

In opsomming is die bevinding van hierdie studie dat daar betekenisvolle dog hoogs selektiewe PTEN geen betrokkenheid in boonste genitale traktus tumore is. ‘n Sterk en interessante verband is bevestig tussen genotipe en histologiese fenotipe. Hierdie resultate verbeter die begrip van karsinogenese en behoort ‘n bydrae te lewer in die soeke na nuwe anti-neoplastiese middels.

Abstract

The role of the tumour suppressor gene PTEN in the etiology of cancers of the female genital tract

The phosphorylation and dephosphorylation of the tyrosine amino-acids in proteins play an important role in the regulation of many cellular processes in all eukariotic organisms, including the regulation of cell cycle control, growth control, cellular differentiation and gene and synaptic transmission. The involvement of the phosphatase genes in human carcinogenesis was long-suspected, but PTEN is the first important phosphatase gene proven to be a true tumour suppressor. The basic function of normal PTEN is the dephosphorylation of the kinases and inhibition of the integrin and growth factor mediated kinase signalling pathways.

The central hypothesis of this study is that PTEN plays an important role in tumours of the upper female genital tract. The involvement of aberrations in the coding regions of this gene was studied in specific gynaecologic tumours and tissues using polymerase chain reaction based mutation analysis. The research model was to study both the malignant tumour and the closest available pre-malignant or benign counterpart to demonstrate different levels of involvement of PTEN in the evolving steps.

The PTEN gene was found to be intimately involved in endometrial carcinogenesis. Involvement was demonstrated in hyperplasia and was common in endometroid carcinoma (54%). Pathogenic PTEN mutations were much more common in cancer than in hyperplasia (10%). Multiple mutations were found in some late stage tumours, suggesting that the already malignant tumour cells accumulate more genetic mutations over time. All tumours with more than one pathogenic mutation occurred in African patients. The latter two findings are unique to the current study.

Selective involvement of the PTEN gene was demonstrated in uterine soft tissue tumours. PTEN involvement was neither found in benign soft tissue tumours nor significantly in leiomyosarcoma or endometrial stromal sarcoma. However, PTEN plays a significant role in uterine carcinosarcoma (13%) and specifically in tumours with an endometroid epithelial component, where mutations were found in 17%. This finding is a highly significant and unique research result which supports the hypothesis of the endometrial origin of these tumours. It also supports the observation of a strong link between this gene and endometroid differentiation, with morphology strongly linked to cellular genetics.

PTEN gene mutation was demonstrated in ovarian endometroid carcinoma in ~29% of cases investigated. This finding confirms PTEN involvement in carcinogenesis in this tumour type. The finding suggests that PTEN involvement is linked to endometroid epithelial morphology. We could not sufficiently test the involvement of the gene in benign or pre-malignant ovarian endometroid lesions and thus cannot comment on the chronology of mutations in this tissue type.

When all tumour types were included, there was a tendency towards a lower frequency of PTEN mutations in African women. PTEN mutations correlated with endometroid histology. In combination, these results confirm the racial disparity in tumour type distribution or morphology.

In summary this study demonstrated significant though highly selective PTEN gene involvement and a strong and interesting association between genotype and histological phenotype was confirmed. The findings enhance our understanding of carcinogenesis and should lead to translational research into new anti-neoplastic drugs.

Short summary

The role of PTEN gene mutation in the evolution of gynaecologic malignancies was analysed using polymerase chain reaction based mutation analysis.

Benign, pre-malignant and malignant tumours of the upper female genital tract were examined. The accumulation of cellular genetic damage during carcinogenesis were studied and compared in the different tissue and tumour types.

The study demonstrated significant though highly selective PTEN gene involvement and a strong and interesting association between genotype and histological phenotype was confirmed.

The findings enhance our understanding of carcinogenesis and should lead to translational research into new therapies.

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