

CRT Licensing Opportunity



Novel Cancer Diagnostics based on OPCML gene

- There is a clear need for early diagnostic tests for malignancies
- OPCML promoter methylation is a widespread phenomenon in cancer tissues
- OPCML behaves as a tumour suppressor gene in *in vivo* models
- Opportunity to develop proprietary diagnostics based on OPCML methylation

DIAGNOSTICS | Discovery

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Introduction

OPCML (also known as OBCAM) is a member of the IgLON family of cell-surface GPI-anchored proteins and has been validated as an epigenetic biomarker for ovarian cancer in the laboratories of Dr Grant Sellar (Cancer Research UK Edinburgh Oncology Unit) and Dr Hani Gabra (Imperial College, London). There is the potential to develop methylation-specific diagnostic assays based on tumour-associated epigenetic modification of OPCML.

Background

Clusters of CpG dinucleotides known as CpG islands are found in the promoter regions of many genes. Aberrant methylation of cytosine residues within these regions leads to gene silencing and in cancer these epigenetic modifications are recognised to contribute to tumour initiation and progression. The fact that methylation patterns are unique to different tumour types and are chemically stable, combined with the availability of tumour DNA in a range of sample types means that cancer methylation markers are ideally suited for the development of sensitive and specific diagnostic tests.

Epithelial ovarian cancer is the most common cause of death from gynaecological malignancy, and a major contributory factor is the trend for late diagnosis. More than 65% of tumours are diagnosed at Stage III or later when the 5 year survival rate is only 20-50%. There is currently no reliable screening method for ovarian cancer. Thus, there is a clear need for novel diagnostic tests that can reliably detect this malignancy at an early stage.

The Technology

Chromosome 11q has been identified as a target for loss of heterozygosity (LOH) in many solid tumour types. Analysis of six polymorphic microsatellite markers in 100 matched epithelial ovarian normal/tumour DNA samples identified neighbouring OPCML and HNT as genes containing the markers frequently subject to LOH. The inventors found that expression of OPCML can be detected by RT-PCR in all normal ovarian tissue samples tested but is abolished in >80% of primary epithelial ovarian tumours (Figure 1).

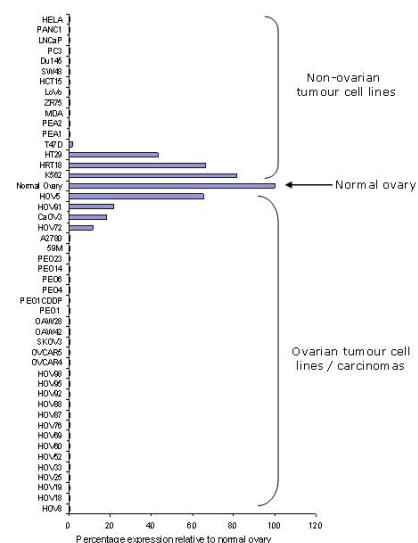


Figure 1. Quantitative RT-PCR analysis of OPCML expression in 18 primary ovarian tumours (HOVs) and 31 ovarian and non-ovarian tumour cell lines, measured relative to normal ovary.

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Methylation specific PCR (MS-PCR) of bisulphite-treated genomic DNA extracted from 69 normal/tumour tissue sample pairs showed that the OPCML CpG island is somatically methylated in 83% of primary ovarian tumours, indicating that in the majority of cases loss of expression is likely to be associated with promoter methylation (Figure 2).



Figure 2. OPCML CpG island methylation demonstrated by MS-PCR assay of tumour (T) and normal (N) matched DNA pairs from endothelial ovarian carcinoma patients, normal ovary (N.Ov1 and N.Ov2) and control methylated DNA (M.DNA). Methylation was observed in 57 of 69 DNA pairs tested.

Furthermore, bisulphite sequencing in 8 primary ovarian tumours confirmed that the OPCML CpG island is extensively methylated across 58 consecutive CpGs, whereas the equivalent region in normal ovarian tissue is essentially unmethylated.

It is now clear that OPCML methylation appears to be a widespread phenomenon in cancer. Subsequent independent studies have confirmed methylation of OPCML in lymphoma as well as ovarian, head and neck, colorectal, breast, cervical, gastric and hepatocellular carcinomas. A recent publication also demonstrated that OPCML is one of five most significantly hypermethylated loci in lung cancer.

In vitro and in vivo functional studies have demonstrated that OPCML expression suppresses tumour cell growth, identifying OPCML as a likely tumour suppressor gene (Figure 3).

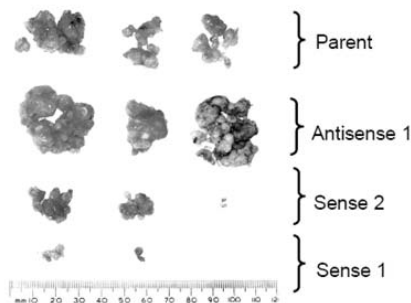


Figure 3. OPCML behaves as a tumour suppressor gene in vivo. Comparison is shown between tumours collected from control, OPCML sense and anti-sense transfected SCOV-3 xenografts.

Commercial Opportunity

An exclusive or non-exclusive multi-territory license is available to develop methylation-based diagnostic tests based on the OPCML and/or HNT genes.

Intellectual Property

Patent application WO03002765 covering the diagnostic and therapeutic applications of this discovery has been filed. The patent family is available for licensing together with associated data.

References

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