

CRT Licensing Opportunity



RKIP: A Prognostic Marker for Colorectal Cancer

- Unmet clinical need for improved stratification of CRC patients
- RKIP expression in primary CRC is an independent prognostic marker for survival
- Useful for identifying early-stage CRC patients at risk of relapse
- Validated by immunohistochemical assessment of four independent patient cohorts

DIAGNOSTICS | Validation

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Introduction

Studies in the laboratory of Professor Walter Kolch (Beatson Institute for Cancer Research) and Dr Fahd Al-Mulla, Kuwait University have demonstrated that Raf kinase inhibitor protein (RKIP) is an independent marker protein in primary colorectal tumours. RKIP expression can predict the risk of early colorectal cancers (CRC's) to relapse and hence guide the therapeutic strategy after surgery. Survival data demonstrate that the level of RKIP expression in primary CRC's is significantly and inversely associated with progression to metastatic disease.

Background

Colorectal cancer is the third most common form of cancer, and accounts for the greatest proportion of cancer deaths in the Western world. Currently, colorectal cancers are graded pathologically by the Dukes scale (A - D) according to the size, invasiveness and spread of the tumour. The long-term outlook for Dukes C and D patients is poor, although adjuvant chemotherapy has been shown to reduce the rate of recurrence after surgery by 40-50% and overall deaths by 16%. In contrast, greater than 85% of Dukes A patients are treated successfully by surgery alone.

The effects of adjuvant chemotherapy for the Dukes B subset of patients have been harder to prove, though small survival benefits have been demonstrated. As such the majority of Dukes B cases are currently treated by surgical resection alone, though greater than 30% of these suffer tumour recurrence and cancer-related death. The ability to identify this high risk

group of Dukes B is of paramount importance because it may allow the identification of patients who should be monitored frequently and who could benefit from adjuvant therapy following surgery.

Duke's staging and lymph node status are the best available clinicopathological markers, but there is an urgent need to define markers that can stratify patients better and earlier according to their risk of CRC recurrence and overall survival.

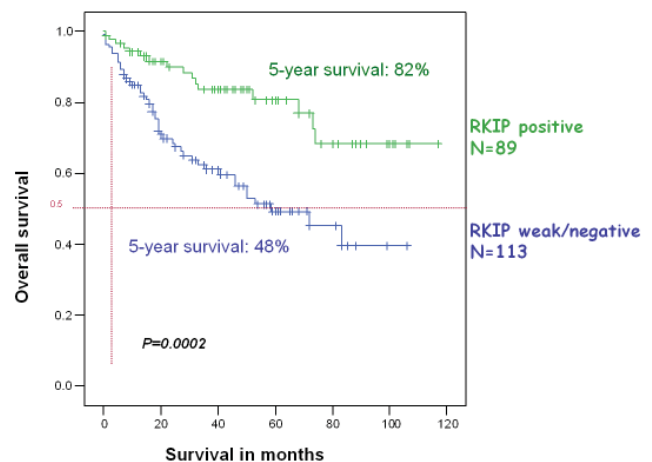


Figure 1: Kaplan-Meier plot of overall survival and mean survival of the Aberdeen cohort of colorectal cancer patients in relation to RKIP expression (1)

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Biological Rationale

RKIP was originally identified as an endogenous inhibitor of the Raf-MAPK kinase (MEK) – ERK pathway, which interfered with the phosphorylation and activation of MEK by Raf-1. Subsequently, RKIP was shown also to suppress the activation of nuclear factor kappa B (NFkB) transcription factor by blocking the inactivation of the inhibitor NFkB, Ikb. Both pathways play an important role in cancer and invasion. Recently, it was suggested that RKIP suppresses metastasis in prostate cancer, breast cancer and melanoma.

Study Data

The Kolch laboratory have examined RKIP expression immunohistochemically in four separate CRC patient cohorts. Overall and metastasis free survival rates were measured in an initial retrospective study of 268 (Aberdeen colorectal tumour bank, Scotland) and 65 (Glasgow, Scotland and Kuwait patient samples) early stage CRC's (1). Further retrospective studies have subsequently been completed in cohorts of 200 patients with Dukes B CRC, and 1050 patients with Duke's A to D (unpublished data)

In each case, the results demonstrate a significant relationship between reduced RKIP expression and disease specific survival. Furthermore expression of RKIP is independent of many of the clinico-pathological indicators which are currently used to stratify patients into risk groups. Patients with Duke's C RKIP positive tumours have similar 5 year survival rates as early stage patients if tumours have equivalent RKIP expression levels. Thus, RKIP protein expression appears to be a suitable and easily determinable marker in the primary tumour that can predict poor outcome in patients, and hence guide strategies for monitoring and therapy.

Two recent publications from an independent laboratory support a case for RKIP being a prognostic marker for survival in CRC patients. Zlobec *et al* identified RKIP as the only independent predictive marker of metastasis among 21 selected tumour markers and concluded that RKIP is highly predictive of distant metastases (2). In a further study, immunohistochemical staining for RKIP was performed on a tissue microarray comprising 1,197 mismatch repair (MMR)-proficient and 141 MMR deficient CRCs (3). Loss of RKIP expression was found to be a marker of tumour progression and distant metastasis in MMR-proficient and MMR-deficient CRCs.

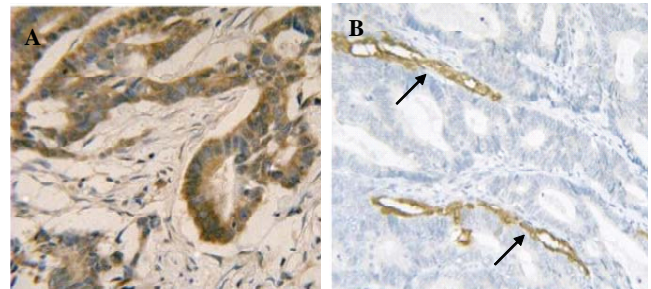


Figure 2: Representative examples of colorectal tumours scored as [A] positive and [B] negative for RKIP protein expression. The arrows indicate the strong RKIP staining of the endothelium of lymphatic vessels used as internal control.

Commercial Opportunity

CRT seeks a commercial partner for collaborative research and/or exclusive licensing related to the metastasis suppressor gene RKIP and its prognostic use in CRC. Proprietary RKIP antibodies have been generated.

Intellectual Property

CRT holds the rights to a patent application covering the prediction of CRC metastasis by determining RKIP expression levels. The patent is available for licensing together with associated data.

References

- (1) Al-Mulla *et al*, Raf kinase inhibitor protein expression in a survival analysis of colorectal cancer patients. *J Clin Oncol*. 2006. 24(36):5672-5679.
- (2) Zlobec I., *et al*. Node-negative colorectal cancer at high risk of distant metastasis identified by combined analysis of lymph node status, vascular invasion, and Raf-1 kinase inhibitor protein expression. *Clin. Cancer Res*. 2008. 14(1):143-148.
- (3) Minoo, P., *et al*. Loss of raf-1 kinase inhibitor protein expression is associated with tumor progression and metastasis in colorectal cancer. *Am. J. Clin. Pathol*. 2007. 127(5):820-827

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