Correspondence

Beckwith-Wiedemann Syndrome, Pancreatoblastoma, and the Wnt Signaling Pathway

To the Editor-in-Chief:

In a recent issue of The American Journal of Pathology, Abraham et al\(^1\) reported frequent alterations in the wnt signaling pathway and chromosome 11p LOH (loss of heterozygosity) in sporadic and familial adenomatous polyposis-associated pancreatoblastomas. The molecular association between pancreatoblastoma and other embryonal tumors such as hepatoblastoma and Wilm's tumor has been previously suggested by the presentation of Beckwith-Wiedemann in children with these tumors.\(^2\)–\(^4\) However, the study of Abraham et al\(^1\) did not describe any case of pancreatoblastoma presenting with Beckwith-Wiedemann syndrome.

Here we report a case of pancreatoblastoma presenting in a four-year-old male with incomplete Beckwith-Wiedemann syndrome, consisting of hemihypertrophy of the right foot and leg (case 1). On examination the tumor was shown to have LOH of 11p, which included the 11p15 BWS gene region and $IGF2$.\(^5\) The genetic mechanism underlying this patient's 11p LOH must be constitutional, although only present in the cells of the limb showing hemihypertrophy. In contrast, all cases of sporadic pancreatoblastoma presented by Abraham et al\(^1\) would have a tumor-specific 11p 15 LOH which has occurred as a somatic event. A second case of pancreatoblastoma presenting in a three-year-old female showed partial LOH of 11p.

Immunohistochemistry showed accumulation of $\beta$-catenin in the cytoplasm and nucleus of both pancreatoblastomas. Case 1 was found to have a missense mutation in exon 3 of the $\beta$-catenin gene (CTNNB1) which caused an amino acid substitution of serine 37 (TCT) to a phenylalanine (TTT). Serine 37 is one of the four threonine-serine phosphorylation sites essential for GSK-3$\beta$-dependent phosphorylation and has been characterized as a ubiquitination-targeting motif. This S37F mutation was found in case P4 of Abraham et al\(^1\). Case P4 also showed 11p LOH, however the parental origin of the lost allele could not be determined. In case 1 described here, LOH of 11p 15.5 was maternal in origin.\(^5\) As stated by Abraham et al\(^1\) maternal allelic loss of 11p 15.5 would be expected based on data from Wilm's tumor and hepatoblastoma. Sequence analysis of exon 3 in the second case of pancreatoblastoma did not reveal a mutation. Large deletions of the $\beta$-catenin NH$_2$-terminal regulatory domain have been previously described in melanoma cell lines and colorectal cancers.\(^6\) Therefore, case 2 was screened for larger deletions using primers that scanned exon 3 and the adjacent introns of CTNNB1. However, a large deletion was not found. In this case nuclear accumulation of $\beta$-catenin without mutation of CTNNB1 could be caused by genetic alteration of down-regulators or negative repressors of the CTNNB1 gene such as APC, PP2A, Tef1, or AXIN1. Genes in the Wnt signaling pathway have been found to be mutated in many types of cancer. As case 2 was of Asian descent, mutation of the APC gene may be likely since the Asian population has been shown to have a high incidence of APC mutations leading to cellular $\beta$-catenin accumulation in hepatoblastoma.\(^7\) These cases provide further evidence that alterations in the wnt signaling pathway play a significant role in the progression of pancreatoblastoma tumorigenesis.

Natalie J. Kerr
Ryuji Fukazawa
Anthony E. Reeve

University of Otago
Dunedin, New Zealand

Michael J. Sullivan

Christchurch School of Medicine
Christchurch, New Zealand

References


Authors’ Reply

We are very pleased to hear of the molecular abnormalities in two new pancreatoblastomas of Kerr et al.1 In our recent study of nine pancreatoblastomas, allelic loss on chromosome 11p15.5 was present in 6 of 7 informative cases (86%), and mutations in the APC/β-catenin pathway in 6 of 9 cases (67%).1 These findings underscore the clinical association between pancreatoblastoma formation and Beckwith-Wiedemann syndrome, as well as a potential association of pancreatoblastoma with familial adenomatous polyposis (FAP).

In the two additional pancreatoblastomas reported by Kerr et al.,2 11p15.5 allelic loss was found in both neoplasms, similar to the very high rate of 11p loss found in our series.1,2 In this regard, case 1 of Kerr et al is particularly exciting because this pancreatoblastoma showed selective loss of the maternal allele, something that we could not document in our pancreatoblastomas for which parental tissue was not available.1,2 This selective loss of the maternal 11p15.5 allele has been previously described in hepatoblastomas3 (neoplasms with clinical and genetic similarity to pancreatoblastomas), but not in pancreatoblastomas, and this strengthens the molecular link of pancreatoblastoma to Beckwith-Wiedemann syndrome.

The finding of Kerr et al2 of an activating β-catenin gene mutation in 1 of 2 pancreatoblastomas is also similar to our rate of β-catenin mutations in 5 of 8 sporadic (non-FAP associated) pancreatoblastomas,1 and underscores the importance of alterations in the APC/β-catenin pathway in pancreatoblastoma development. It is certainly interesting to speculate what alternative molecular alterations in this pathway might be present in those cases that lack demonstrable β-catenin mutations. As noted by Kerr et al.,2 some possibilities would include inactivating APC or AXIN1 mutations. Our series included one patient with FAP whose pancreatoblastoma showed biallelic APC inactivation (a germ-line truncating mutation coupled with somatic 5q allelic loss) rather than β-catenin mutation; we could not detect APC mutations in either of two sporadic pancreatoblastomas that were negative for β-catenin mutations. However, it is certainly possible that the pancreatoblastoma in the Asian patient described by Kerr et al2 might show APC inactivation, since some hepatoblastomas in Asian, but not Western, patients have been shown to contain APC mutations.4

The 11 pancreatoblastomas which to date have been evaluated for molecular alterations in 11p and the APC/β-catenin pathway bear out two important points. First, the occasional occurrence of these tumors in patients with germ-line DNA abnormalities (in this case, Beckwith-Wiedemann syndrome and FAP) provides a clue to the genetic alterations in these tumors themselves. Second, the sporadic variants of these tumors will frequently harbor alterations in the same genes or in related genes of the same molecular pathway.

References


KAI1 Metastasis Suppressor Protein in Cervical Cancer

To the Editor-in-Chief:

We have read with interest the article of Liu et al1 on down-regulation of KAI1-metastasis suppressor protein in cervical cancer.1 This study confirms our results published previously.2 Unfortunately Liu et al1 missed one of our papers on KAI-1 expression in cervical carcinoma, wherein some of the problems discussed in their paper have already been addressed. Liu et al1 suggest that down-regulation of KAI1 might occur early in cervical carcinogenesis, but they did not include any precancerous lesions of the cervix in their study. In contrast, based on immunostaining of various stages of cervical dysplasia, we demonstrated that down-regulation of KAI1 in fact occurs at a very early stage of cervical carcinogenesis, while in 10 cases of cervical intraepithelial neoplasia (CIN) grade I, strong KAI1 expression was found in all cases, no difference in KAI1 expression in CIN II (n = 10) or CIN III (n = 10) and invasive carcinomas (n = 75) was found (P <0.05, Kruskal-Wallis test). Liu et al1 also hypothesize that KAI1 may not have a prognostic influence in cervical cancer, but were not able to perform survival analysis due to the short follow-up time of patients. In our collective of primary irradiated cervical cancers we have demonstrated that KAI1 down-regulation was indeed not associated with prognosis (P >0.05, log-rank test).

In our view, a technical problem of the real time-reverse transcriptase-polymerase chain reaction-based study of Liu et al1 is the fact that KAI1 is also strongly expressed in lymphocytes and macrophages,3 as stated by Liu and colleagues themselves.1 In cervical cancer, inflammatory stroma reaction is a common event, and is even very prominent in many cases.4 To us, mRNA- or protein-based methods for detection of KAI1 expression without reliable separation of tumor cells from the sur-