

## ORIGINAL ARTICLE

# A biological basis for depression in pancreatic cancer

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## Abstract

**Background:** Patients with pancreatic adenocarcinoma frequently present with depression the symptoms of which may precede cancer diagnosis, suggesting that the pathophysiology of depression in pancreatic adenocarcinoma may result from biological changes that are induced by the presence of the tumour itself. The present study was conducted to test a hypothesized relationship with the kynurenine pathway, which has been implicated in both depression and tumour-induced immunosuppression.

**Methods:** 17 patients with pancreatic adenocarcinoma were recruited and completed mood questionnaires (Functional Assessment of Cancer Therapy -Pancreatic Cancer, Beck Depression Inventory and the Beck Anxiety Inventory) and blood testing for serum levels of tryptophan, kynurenine, kynurenic acid and quinolinic acid. Tumour burden was determined from pathology reports (tumour size and nodal involvement).

**Results:** Findings indicated a negative correlation between mood scores and the plasma kynurenic acid : tryptophan ratio in plasma, and a positive correlation between tumour burden and plasma kynurenine level.

**Conclusions:** This study suggests that pancreatic cancer may influence mood via the kynurenine pathway. The relationship of the kynurenine pathway with pancreatic tumour burden should be explored further in large multicentre studies because a better understanding of this physiology might have significant clinical benefit.

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## Introduction

Patients with pancreatic adenocarcinoma often present with new-onset depressive symptoms before they are diagnosed with cancer, as noted in case reports dating from the 1920s and more recent systematic studies.<sup>1</sup> A 1967 series of 46 patients with pancreatic cancer found that 76% had depressive symptoms and approximately half of the depressed patients experienced the onset of depression prior to the diagnosis of cancer.<sup>2</sup> This pattern of psychiatric symptoms is not seen in patients with some other abdominal neoplasms, such as gastric cancer.<sup>3</sup> This onset of depression prior to cancer diagnosis suggests that the depression is not just a grief response to a disease with a poor prognosis. Such findings suggest that the pathophysiology of depression in pancreatic cancer may result from biological changes that are induced

by the presence of the tumour itself.<sup>1</sup> A deficiency in the neurotransmitter serotonin has been linked to major depression; the closely related kynurenine pathway can shunt tryptophan away from serotonin synthesis. Additionally, the kynurenine pathway is implicated in tumour-induced immunosuppression.

The present study was conducted to examine the relationships among mood, tumour burden and metabolites of the indoleamine 2,3-dioxygenase-mediated kynurenine pathway in patients with pancreatic adenocarcinoma. Indoleamine 2,3-dioxygenase (IDO) is an enzyme expressed in pancreatic cancer that catalyses the rate-limiting step in the kynurenine pathway, the conversion of tryptophan to kynurenine. To the present authors' knowledge, this relationship has not been previously studied.

## Materials and methods

The study was approved by the Columbia University Institutional Review Board. Seventeen patients with pancreatic adenocarci-

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noma were enrolled over a 2-year period. Patients with potentially resectable disease were recruited prior to surgery. The Functional Assessment of Cancer Therapy–Pancreatic Cancer (FACT-PA), the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) were administered. The FACT-PA is a self-administered generic (FACT-G) and pancreatic disease-specific (FACT-PA) health status survey in which participants are scored against age- and gender-matched control subjects. The scaled measures are transformed to a scale of 0–100 on which a score of 0 represents the worst quality of life and a score of 100 represents the best. The BDI is a self-report measure of depressive symptoms. The instrument is scored on a scale of 0–63 on which higher scores indicate more severe depression. The BAI is a self-administered measure of anxiety symptoms. The instrument is scored on a scale of 0–63 on which higher scores indicate more severe anxiety. These psychiatric instruments have been validated and used in cancer patient studies.<sup>4–6</sup>

Upon enrolment, 25 ml of blood was collected from each patient by venipuncture. Plasma samples were processed and frozen at  $-56.7^{\circ}\text{C}$ . Plasma levels of tryptophan, kynurenine, kynurenic acid and quinolinic acid were assayed. Tryptophan was measured using a validated, unpublished liquid chromatographic procedure that utilizes the native fluorescence of tryptophan for detection. An internal standard 5-methyltryptophan was added to the plasma sample (0.25 ml), which was then subjected to deproteinization and centrifugation. An aliquot of the supernatant was injected on a column. Using a phosphate buffer (pH 4.7) and acetonitrile as the mobile phase with a reversed-phase octadecylsilane (octadecylsilyl groups) column ( $4\ \mu\text{m}$ ,  $3.9 \times 150\ \text{mm}$ , Nova-Pak C18; Waters Corp., Milford, MA, USA), tryptophan and the internal standard eluted in  $< 12\ \text{min}$ . Fluorescence detection was optimized using an excitation wavelength of 290 nm and analysed at 340 nm. The interassay variability of plasma tryptophan did not exceed 5.1% in the high-quality controls and 7.2% in the low-quality controls ( $n = 22$  samples). Plasma levels of kynurenine, kynurenic acid and quinolinic acid were measured using previously described methods.<sup>7–9</sup>

Tumour burden was determined from surgical pathology reports. Specifically, tumour burden was assessed according to the maximal tumour diameter and the percentage of metastatic lymph nodes in the surgical resection specimen (metastatic nodes/total nodes in specimen). Only lymph nodes with metastases were included; lymph nodes found to be positive as a result of direct invasion by a contiguous primary tumour were excluded.

Patients were excluded if their history included any of the following: treatment within the past month with antidepressant medications that affect serotonin physiology, including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) (benzodiazepine use was permitted); autoimmune diseases such as systemic lupus erythematosus (SLE), multiple sclerosis and rheumatoid arthritis, or congestive heart failure, recent stroke or other major surgery in the past month.

**Table 1** Demographics, mood and pathology results in 17 patients with pancreatic adenocarcinoma

Age, years, median (range)	65 (51–85)
Gender	9 male, 8 female
Race	17 White
BAI score, median (range)	4.2 (0–18)
BDI score, median (range)	7 (0–13.65)
FACT-PA: physical well-being subscore, median (range)	25 (17–28)
FACT-PA: social well-being subscore, median (range)	26 (0–28)
FACT-PA: emotional well-being subscore, median (range)	19 (8–24)
FACT-PA: functional well-being subscore, median (range)	15 (0–27)
FACT-PA: additional concerns subscore, median (range)	29 (14–35)
FACT-G: subscore, median (range)	84.5 (48–106)
FACT-PA: total score, median (range)	109 (64–140)
Lymph nodes positive for metastatic disease, %, median (range)	0 (0–36%)
Diameter of primary tumour, cm, median (range)	2.9 (0.03–4.6)

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; FACT-PA, Functional Assessment of Cancer Therapy–Pancreatic Cancer; FACT-G, Functional Assessment of Cancer Therapy–Generic.

Data were analysed for normality using the Shapiro–Wilks test. For variables that did not satisfy the normality assumption, the non-parametric bivariate rho (Spearman) correlation test was performed. The effects of multiple correlations on potentially related variables were corrected for by performing multivariate partial correlations on variables found to be significant in the bivariate analysis. For the multivariate partial correlation analysis, variables that did not satisfy the normality assumption were transformed using the ranks of the values to achieve normality.

## Results

Demographic information, mood and pathology scores for the study population are shown in Table 1. Multiple IDO metabolites were identified and measured. Median values for metabolites that proved significant were as follows: tryptophan 47 nm/ml (range: 31–76 nm/ml); kynurenine 2.18  $\mu\text{mol}$  (range: 1.25–3.28  $\mu\text{mol}$ ), and kynurenic acid 100 nmol (range: 38–730 nmol). The median plasma kynurenic acid : tryptophan ratio (KATR) was 2.2 (range: 0.8–18.3).

A significant negative correlation was found between the BDI score and plasma KATR ( $P = 0.008$ ,  $\rho = -0.617$ ) (Table 2). Thus, a lower KATR correlated with worse depressive symptoms. In addition, a significant negative correlation was found between the BAI score and plasma KATR ( $P = 0.029$ ,  $\rho = -0.523$ ), whereby a lower KATR correlated with worse anxiety (Table 2). In both cases, the

**Table 2** Bivariate (Spearman  $\rho$ ) correlations between mood score and metabolite level in 17 patients with pancreatic adenocarcinoma

	Correlation with BAI score	Correlation with BDI score
Tryptophan	$P = 0.479$	$P = 0.151$
Kynurenine	$P = 0.493$	$P = 0.356$
Kynurenic acid	$P = 0.060$	$P = 0.059$
Quinolinic acid	$P = 0.910$	$P = 0.914$
Tryptophan : kynurenine ratio	$P = 0.933$	$P = 0.598$
Kynurenic acid : tryptophan ratio	$P = 0.029, \rho = -0.523$	$P = 0.008, \rho = -0.617$
Quinolinic acid : tryptophan ratio	$P = 0.811$	$P = 0.493$

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.

**Table 3** Bivariate (Spearman  $\rho$ ) correlations between tumour burden and metabolite level in 17 patients with pancreatic adenocarcinoma

	Correlation with maximal tumour diameter	Correlation with percentage of positive lymph nodes
Tryptophan	$P = 0.567$	$P = 0.327$
Kynurenine	$P = 0.021, \rho = -0.554$	$P = 0.034, \rho = 0.515$
Kynurenic acid	$P = 0.970$	$P = 0.347$
Quinolinic acid	$P = 0.047$	$P = 0.339$
Tryptophan : kynurenine ratio	$P = 0.083$	$P = 0.796$
Kynurenic acid : tryptophan ratio	$P = 0.779$	$P = 0.800$
Quinolinic acid : tryptophan ratio	$P = 0.132$	$P = 0.915$

**Table 4** Partial correlations: mood score and metabolite level when controlling for tumour burden in 17 patients with pancreatic adenocarcinoma

Control variable		Correlation with BDI score	Correlation with BAI score
Percentage of lymph nodes positive	Kynurenic acid : tryptophan ratio	$P = 0.002, \rho = -0.711$	$P = 0.030, \rho = -0.543$
Maximum tumour diameter	Kynurenic acid : tryptophan ratio	$P = 0.006, \rho = -0.654$	$P = 0.350, \rho = -0.528$

BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

correlation appears to be driven mostly by kynurenic acid; anxiety may also be a component of a major depressive episode in many patients.

A significant positive correlation was found between plasma kynurenine and the percentage of lymph nodes positive for metastatic disease ( $P = 0.034, \rho = 0.515$ ), whereby patients with higher serum kynurenine levels had more metastatic disease in the lymph nodes. There was a significant negative correlation between the maximal tumour diameter and plasma kynurenine ( $P = 0.021, \rho = -0.554$ ). Essentially, a higher plasma kynurenine level correlated with a smaller primary tumour. Bivariate correlations between tumour burden and metabolite level are shown in Table 3.

A multivariate partial correlation analysis was performed to examine the relationship between the significant bivariate correlations (Table 4). The correlations between plasma KATR and scores on the BDI and BAI remained significant after controlling for the percentage of positive lymph nodes and maximal primary tumour diameter.

## Discussion

Tryptophan, an essential precursor for serotonin production, is also a substrate of the kynurenine pathway, which eventually produces NAD<sup>+</sup>, as well as several neuroactive byproducts, including kynurenic acid and quinolinic acid. Interferon- $\gamma$  (IFN- $\gamma$ ), a proinflammatory cytokine, upregulates the expression of the enzyme IDO, which catalyses the conversion of tryptophan to kynurenine. Thus, in the presence of IFN- $\gamma$  and subsequent overexpression of IDO, tryptophan is shunted away from serotonin production toward the kynurenine pathway, leading to increased levels of neuroactive products of kynurenine metabolism, and less serotonin, which may contribute to symptoms of depression.<sup>10,11</sup>

Previous studies of depression have noted that patients with lower levels of kynurenic acid exhibit more depressive symptoms. Specifically, it appears that the ratio of kynurenic acid relative to other metabolites, rather than the absolute level of kynurenic acid,

determines mood.<sup>11</sup> This is consistent with the present finding of a correlation between worse mood and a lower KATR.

In addition to psychopathological morbidities, IDO expression and the kynurenine shunt have also been implicated in tumour-induced immunomodulation. IDO is expressed in a number of tumours, including pancreatic adenocarcinoma.<sup>12,13</sup> The exact mechanism of IDO-induced immunosuppression remains controversial; some authors propose that enhanced IDO expression results in immune tolerance to tumour antigens through modifications of T cell tryptophan catabolism.<sup>12–15</sup> Experimentally, IDO inhibition with the false metabolite 1-methyl-d-tryptophan (D-1MT) has been shown to limit tumour growth; use of D-1MT is currently being evaluated in two National Cancer Institute-sponsored Phase I trials.<sup>15</sup> In an immunocompetent state, the body mounts an inflammatory T cell response against tumour antigens. However, this inflammatory response exerts a selection pressure in favour of tumour cells that express IDO and are therefore capable of inducing T cell tolerogenicity in the local microenvironment or in tumour-draining lymph nodes.<sup>15</sup> The present authors hypothesize that, in pancreatic cancer, a side-effect of enhanced IDO expression is an imbalance in the production of neuroactive kynurenine pathway metabolites and that this may result in symptoms of depression. In animal solid-tumour models, increased IDO expression in the tumour, measured directly by immunohistological analysis, appears to correlate with systemic markers of increased IDO activity, such as kynurenine pathway byproducts.<sup>16</sup>

In line with this hypothesis, a positive correlation was found between kynurenine level and burden of metastatic disease to the lymph nodes. It might be expected that patients shunting more tryptophan to the kynurenine pathway would produce more locally immunosuppressive metabolites with a subsequent increase in metastatic disease. A negative correlation emerged between the maximum diameter of the primary lesion and kynurenine level. The present authors hypothesize that tumours with greater IDO expression and resultant kynurenine shunting metastasize earlier when the primary lesion is smaller, compared with less aggressive tumours with no or lower levels of IDO expression, although this temporal relationship cannot be demonstrated using the current data.

To date, the present authors are unaware of any published data exploring the impact of IDO and tryptophan metabolism on psychopathological morbidity in pancreatic cancer patients. This relationship should be explored in large multicentre studies; data on patients with other gastrointestinal malignancies would be useful as control material. Additionally, direct evidence of IDO metabolite secretion by pancreatic tumours would further support understanding of this important physiology.

#### Conflicts of interest

None declared.

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