



An Increased Level of Aryl Hydrocarbon Receptor in Patients with Pancreatic Cancer

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ABSTRACT

BACKGROUND

Aryl-carbon receptor (AhR), a ligand-activated transcription factor, is best known for its ability to mediate the effects of environmental toxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin. AhR is expressed in several tumor cells and regulates the expression of genes in the signal transduction pathways. In this study, we examined the soluble levels of AhR in patients with pancreatic cancer.

METHODS

123 samples, including 59 (48%) samples of pancreatic ductal adenocarcinoma based on histological evidence and 64 (52%) healthy control samples, were evaluated to determine plasma levels of AhR by Enzyme-linked immunoassay.

RESULTS

The median of AhR among patients was 0.280 ng/mL, which differed considerably from 0.07 ng/mL in the control group ($p < 0.001$). Significant differences of the AhR were observed between the plasma samples of the patients compared with the healthy group, with respect to male sex ($p < 0.001$), age groups ($p = 0.001$), diabetic status ($p < 0.001$), body mass index (BMI) categories ($p = 0.035$), and constantly smokers ($p < 0.001$). We also observed significant differences between the level of AhR expression between men and women ($p = 0.01$) and ever to never smokers ($p = 0.009$) in the case group. In addition, the age of 65 and a BMI of 25 or less were significant factors in plasma AhR levels ([1.61 95%CI 1.08-2.38] and [1.84 95%CI 1.22-2.77], respectively).

CONCLUSION

The results of this study can add diagnostic information to pancreatic cancer involving AhR and the potential efficacy of this receptor in therapeutic strategies.

KEYWORDS:

Pancreatic cancer, Aryl hydrocarbon receptor (AhR), Biomarkers

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INTRODUCTION

The pancreatic ductal cell carcinoma is the fourth leading cause of cancer death worldwide.^{1,2} Despite many efforts, the causes of pancreatic cancer are unknown and the recognition of biomarkers helps in early diagnosis and treatment.^{3,4} Aryl hydrocarbon receptor (AhR) has been introduced as a regulator of carcinogenesis induced by xenobiotics. Recent data have shown that the knockdown of the AhR gene is associated with fewer proliferations and invasions of carcinogenic cell lines. AhR is interesting for its functional roles



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in mediating the toxicity of xenobiotic metabolism and cellular processes such as energy metabolism, immune function and tumorigenesis.^{5,6} It plays a role in the promotion and progression of tumors and may be present as a new target for pharmacological interference with cancer.⁶

AhR belongs to the basic subgroup helix-loop-helix-*PER-ARNT-SIM* (bHLH-PAS) of the bHLH superfamily of transcription factors, which is phylogenetically conserved from invertebrates to vertebrates. Following binding to the ligand, AhR in the form of a cytoplasmic complex with co-chaperone is transferred into the nucleus and produces dimerism with the aryl hydrocarbon nuclear translocation (ARNT).^{7,8} This receptor was initially recognized for its high affinity by binding to the more toxic products and to the tumor promoter ligand of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).⁵ However, various ligands from dietary compounds and endogenous synthetic materials (L-Kynurenine) and environmental chemicals are also involved in the activation of AhR.⁹ AhR is involved in the detoxification of environmental pollutants through binding to the sensitive xenobiotic element (XRE) in the promoters of the target genes.^{5,10} AhR activates genes that encode enzymes for the phase I drug, in which cytochrome P450 mono-oxygenases, dependent on cytochrome CYP1A1 and CYP1A2, are more important.¹¹ The AhR also induces metabolic phase II enzymes, mainly transferase and glutathione peroxidase, and phase III enzymes related to conjugation and transport processes.⁹

These enzymes are related to adaptation between host and environment and expressed in many tissues, such as the liver, intestine, kidney, and brain and are also essential in the metabolism, elimination, and detoxification of xenobiotics introduced into the human body.^{10,12,13-15} In addition to drug metabolism, AhR plays an important role in modulating the activity of numerous signaling pathways and in regulating chronic inflammatory and immune processes. Furthermore, it was considered that AhR-mediated enzymes play a key role in tumor initiation processes following the transformation of lethal carcinogens into active genotoxins.^{7,16} The AhR is constitutively expressed with very different levels in the liver, lungs, spleen, heart, and kidneys,^{7,13} however it has been defined that AhR is highly upregulated in the lung, prostate, and pancreatic cancers.^{5,17} The increase in AhR levels in human tumors has approved the involvement of AhR at

the beginning of the tumor progression and metastasis.⁶ However, few studies have thoroughly studied the level of AhR expression in pancreatic cancer.¹⁴

Despite the crucial role of AhR in human tumors and the exploration of AhR ligands in pharmaceuticals investigations, there are no reports of AhR expression in patients with pancreatic cancer. So in this study we determined the amount of circulating AhR in patients with pancreatic cancer compared with the healthy group and in association with their clinical features.

MATERIALS AND METHODS

Patients

Fifty nine consecutive patients with pancreatic cancer were enrolled at the Department of Gastroenterology, Shariati Hospital, Tehran, Iran. The patients were new incident cases with a histopathological diagnosis of adenocarcinoma and their tissues were achieved directly from the pancreas.¹⁸ Inclusion criterion of the patients was confirmed diagnosis of pancreatic cancer confined to the pancreas both histologically and clinically. In order to provide a matched control cohort, 64 individuals without cancer were included by a random sampling of a health examination cohort. Both cases and control subjects were recruited between the years 2012 and 2015. All individuals completed a valid and reliable questionnaire and venous blood samples from all the participants were collected in evacuated tubes containing EDTA anticoagulant.¹⁸ Plasma samples were prepared after centrifugation of blood samples and stored at -70°C until tested according to certified procedures.¹⁹ The Ethics Committee of the Shariati Hospital, Tehran University of Medical Science, approved all procedures of this study.

Quantification of AhR in the patients' plasma

The patients' plasma levels of AhR were measured using an ELISA (enzyme-linked immunosorbent assay) kit (Abbexa Ltd., United Kingdom), following the manufacturer's instructions. Reproducibility were assessed by the intra-assay CV (%) and inter-assay CV (%). The linearity of the AhR assay has been demonstrated in the range of 0.05-4 ng/mL. The samples of patients containing more than the 4 ng/mL dose range were diluted with one or two parts of deionized water. The results were multiplied by the dilution factor. The sensitivity of the test was 0.01 ng/mL.

Table 1: Clinical features of 59 patients with pancreatic cancer compared with 64 healthy control

Characteristics		Case	Control	P value	Total
Sex N (%)	Male	29 (49.2%)	32 (50%)	1.00	61 (49.6%)
	Female	30 (50.8%)	32 (50%)		62 (50.4%)
Age N (%)	≤ 65 years	28 (47.5%)	32 (50%)	0.46	60 (48.8%)
	> 65 years	31 (52.5%)	32 (50%)		63 (51.2%)
Diabetes status N (%)	Yes	18 (30.5%)	12 (18.8%)	0.09	30 (24.4%)
	No	41 (69.5%)	52 (81.3%)		93 (75.6%)
Body mass index N (%)	≤ 25 kg/m ²	38 (64.4%)	31 (48.4%)	0.05	69 (56.1%)
	> 25 kg/m ²	21 (35.6%)	33 (51.6%)		54 (43.9%)
Cigarette smoking N (%)	Ever	40 (67.8%)	40 (62.5%)	0.33	80 (65.0%)
	Never	19 (32.2%)	24 (37.5%)		43 (35.0%)

Table 2: Association between plasma level of AhR and baseline characteristics of all participants

Characteristics		AhR (ng/mL)		P value
		Mean ± SD	Median	
Sex N (%)	Male	0.533 ± 1.41	0.100	0.68
	Female	0.346 ± 0.67	0.100	
Age N (%)	≤ 65 years	0.230 ± 0.48	0.100	0.012
	> 65 years	0.639 ± 1.44	0.150	
Diabetes status	Yes	0.179 ± 0.17	0.100	0.49
	No	0.523 ± 1.25	0.100	
Body mass index	≤ 25 kg/m ²	0.588 ± 1.36	0.170	0.009
	> 25 kg/m ²	0.249 ± 0.58	0.095	
Cigarette smoking	Ever	0.303 ± 0.51	0.150	0.27
	Never	0.692 ± 1.71	0.100	

AhR, Aryl hydrocarbon receptor

Statistical analysis

The descriptive analysis was conducted from the case-control state using Chi-square statistics. The associations between the patients' characteristics and AhR expression were evaluated using Mann-Whitney U test. The hypothesis of normality was evaluated using the Shapiro-Wick test. The determinant of AhR was calculated from a simple linear regression with log-transform on AhR. Odds ratios (ORs) were calculated using unconditional logistic regression models with a 95% confidence interval (CIs) adjusted for sex, age (upper and lower compared with the age of 65 participants), body mass index (below or above the WHO limit point (= 25 kg/m²), diabetes status, and cigarette smoking. *P* values of < 0.05 were considered as statistically significant. These analyzes were performed using the STATA software, version 12.0 (Stata Corp., College Station, TX, USA).

RESULTS

Clinical Characteristics of the study participants

Clinical features of a total of 123 participants were studied for age, sex, body mass index (BMI), and history of diabetes and smoking. The mean age and BMI of all participants were 65 ± 10 years and 24.5 ± 5.1 kg/m², respectively. 61 (49.6%) of the patients were men. At enrollment in the study, 63 (51.2%) participants were over 65 years old. Almost 24 (37.5%) of the controls did not have a smoking history. This was 19 (32.2%) in the patients group. Overall there were no statistical differences in the basic characteristics between the cases and the controls. The characteristics of the patients and healthy volunteers were presented in table 1.

Correlation analysis between the clinical features of all participants with AhR

The association between AhR and characteristics of the participants is summarized in table 2. As can clearly

Table 3: Association between AhR and baseline characteristics due to the case-control group

Characteristics	AhR (ng/mL)						P value	
	Case (n = 59)			Control (n = 64)				
	Mean ± SD	Median	P value	Mean ± SD	Median	P value		
All participants	0.713 ± 1.59	0.280	-	0.371 ± 1.23	0.070	-	0.000	
Sex N (%)	Male	0.713 ± 1.59	0.280	0.010	0.371 ± 1.23	0.070	0.171	0.000
	Female	0.326 ± 0.57	0.100		0.365 ± 0.76	0.095		0.377
Age N (%)	≤ 65 years	0.329 ± 0.68	0.180	0.228	0.143 ± 0.17	0.080	0.384	0.001
	> 65 years	0.685 ± 1.51	0.260		0.593 ± 1.40	0.085		0.036
Diabetes status	Yes	0.206 ± 0.20	0.135	0.078	0.138 ± 0.11	0.085	0.842	0.000
	No	0.652 ± 1.41	0.260		0.421 ± 1.12	0.080		0.200
Body mass index	≤ 25 kg/m ²	0.687 ± 1.46	0.190	0.272	0.465 ± 1.24	0.090	0.134	0.035
	> 25 kg/m ²	0.207 ± 0.12	0.250		0.277 ± 0.75	0.070		0.007
Cigarette smoking	Ever	0.420 ± 0.67	0.260	0.009	0.187 ± 0.25	0.075	0.439	0.000
	Never	0.719 ± 1.88	0.100		0.670 ± 1.60	0.085		0.614

Table 4: Determinants of AhR with 95% confidence interval (CI) from pancreatic cancer and corresponding control subjects using multivariate logistic regression

Characteristics	Coefficient* (95% CI)	P value
Sex		
Male / Female	1.09 (0.72-1.64)	0.657
Age group		
> 65 / ≤ 65	1.61 (1.08-2.38)	0.018
Body mass index		
≤ 25 / > 25	1.84 (1.22-2.77)	0.004
Smoking		
Ever / Never	1.03 (0.68-1.56)	0.868
Diabetes, N (%)		
Yes / No	0.65 (0.40-1.02)	0.065

*Exact value of coefficients was calculated

be seen from the table, the plasma level of AhR has a direct correlation with age ($p = 0.012$) and inverse association with BMI ($p = 0.009$). People over the age of 65 years had a significantly higher mean of AhR than the younger group (0.230 vs 0.639 ng/mL). And the mean plasma level of AhR decreased in subjects with BMI above 25 kg/m² compared with those with less than 25 (0.249 vs 0.588). There were no significant differences in AhR between male and female subjects and also never to ever smokers, however never smokers had higher level of AhR. Table 3 presents the association between the expression of AhR and the potential correlated factors between the cases and controls. The median of AhR among patients was 0.280 ng/mL, which significantly differed from 0.07 ng/mL in the control group ($p < 0.001$). Fur-

thermore, there were significant differences between AhR plasma level of the case and control groups, in respect to male sex ($p < 0.001$), age ≤ 65 years ($p = 0.001$), diabetic status ($p < 0.001$), BMI categories ($p = 0.035$) and ever smoking ($p < 0.001$). We also observed significant differences between the level of AhR expression between male and female sex ($p = 0.01$) and ever and never smokers ($p = 0.009$) in the case group.

Determinants of AhR level

Table 4 shows the coefficients of the determinants derived from the linear regression for the plasma level of AhR from the patients with pancreatic cancer and corresponding control subjects. Subjects over 65 years of age and with a BMI of 25 or less had significant coefficients

Table 5: Crude and adjusted ORs for pancreatic cancer and 95% CI in relation to AhR by logistic regression analysis for several models

Model	AhR	Crude OR (95% CI)	Adjusted* OR (95% CI)
1	Continuous scale	1.13 (0.80, 1.59)	1.15 (0.81, 1.65)
2	Quartile scale		
	1	1	
	2	4.43 (1.47, 13.35)	4.39 (1.41, 13.61)
	3	8.28 (2.68, 25.30)	8.39 (2.64, 26.65)
	4	6.40 (2.07, 19.51)	6.08 (1.84, 20.01)
3	Linear trend of quartiles	1.02 (1.01, 1.03)	1.02 (1.01, 1.04)
4	Dichotomous scale		
	Below the median	1	
	Above the median	3.44 (1.62, 7.19)	3.40 (1.55, 7.45)

* Adjusted for age, sex, body mass index, smoking, and diabetes status.

on AhR level (1.61 IC 95% 1.08-2.38), (1.84 IC 95% 1.22-2.77), respectively. However, due to weight loss in patients with cancer, the significant coefficient may not be valid in this situation.

Pancreatic cancer in association with plasma level of AhR

Table 5 shows the crude and adjusted ORs and 95% CIs for pancreatic cancer risk in relation to the levels of AhR in scales of continuous, quartile, and dichotomous. The adjusted ORs and 95% CI for pancreatic cancer in relation to AhR levels in continues scale was 1.13 (0.80,1.59). However there was a trend of higher median of AhR in patients with pancreatic cancer in conditional regression models. The risk of pancreatic cancer in quartile 2, 3, and 4 of AhR compared with quartile 1 was 4.43 (95% CI 1.47–13.35), 8.28 (95% CI 2.68–25.30), and 6.40 (95% CI 2.07-19.51), respectively, which were statistically significant. The association persisted when adjusted for the covariates that are shown in the table footnotes. Finally, considering the AhR as a dichotomous scale in the model, this significant relationship was still well kept with pancreatic cancer (3.44, 95%CI 1.62-7.19).

DISCUSSION

Some studies have indicated the underlying mechanisms caused by AhR in the development of cancer and the association between irregular expression of AhR and tumors.²⁰ AhR is produced mainly in different adult tissues, especially in the liver, kidneys, lungs, and heart,^{10,12,13-15}

however the presence of AhR in the circulatory system in patents with pancreatic cancer has not been evaluated.

Our finding revealed the increased level of AhR in patients with pancreatic cancer compared with healthy conditions. Meanwhile, an increase in plasma AhR occurred in participants over the age of 65 and BMI below 25 kg/m². Subsequently, the age of 65 and the BMI of less than 25 were significant determinants of AhR. These results are consistent with previous studies that examined the association between age and AhR. The study by Eckers and colleagues revealed a positive association between AhR expression of red blood cells and vascular rigidity as an index of vascular aging in healthy human subjects.¹³ Age is a crucial cause of the development of a series of cancers and probably increases the risk of pancreatic cancer in over 60 years.^{1,21} However, very few data concerning AhR and BMI are available. The methylation of the AhR repressor (AHRR) gene from cord blood was positively associated with maternal BMI.²² The AHRR protein inhibits the AhR function by stopping the AHR/ARNT complex. Pancreatic tumors tend to be diagnosed at a later stage when patients are progressive in association with weight loss. Thus a significant relationship between the AhR plasma level and the BMI below 25 in this study is interfering with the patients' weight loss. Koliopanos and co-workers showed high levels of AhR human expression in pancreatic cancer tissues and suggested the potential role of AhR modulators as novel chemotherapeutic agents.¹⁴ Furthermore, it has been shown that patients with high AhR expression may be more susceptible to active therapy with AhR.²³

The possible reasons for elevated plasma levels of AhR in patients with pancreatic cancer can be explained by different approaches that could increase our knowledge on the role of AhR in tumorigenesis. P450 enzymes that have been shown to be stimulated due to environmental dioxins and dioxin-like compounds, are able to induce oxidative stress and the production of reactive oxygen species (ROS).²⁴ Furthermore, oxidative stress contributes potentially to the dioxin-induced mitochondrial toxicity,¹¹ DNA damage and lipid peroxidation. Alternatively, it is known that AhR activation is important in the promotion of the tumor that metabolizes xenobiotics and converts inactive carcinogens into active genotoxins. Furthermore, the activation of AhR by endogenous ligands such as kynurenine inhibits autoimmunity and immune responses to pathogens in tolerance system. Kynurenine is produced in tryptophan dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) pathways and plays a role in the development of regulatory T (Treg) cells. However, a large amount of AhR kynurenine ligands are generated by the tumor cells to their own advantage in immune tolerance to cancer to facilitate tumor progression. A positive correlation between high TDO expression and the CYP1B1 that is regulated by AhR has been reported in human cancer.²⁵

In conclusion, this study revealed significant associations between plasma levels of AhR and pancreatic cancer, which suggest that AhR could be an effective target in the therapeutic strategies of pancreatic tumors through AhR antagonists.

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Authors and Contributions

All authors participated in the conception of the work, experimental and clinical analysis, and interpretation of data and writing of this paper. They have seen and approved the final manuscript and come across the criteria for authorship.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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