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DISTRIBUTION OF DUFFY ANTIGEN RECEPTOR FOR CHEMOKINES (DARC) AND RISK OF PROSTATE CANCER IN BARBADOS, WEST INDIES

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Abstract

Background—Blood typing across different racial groups has revealed that Caucasians predominantly test positive for the Duffy Antigen/Receptor for Chemokines (DARC), while 70–95% of African-origin populations lack expression of DARC on their erythrocytes. Since men of African descent are known to have higher rates of prostate cancer (PC) and some animal studies have indicated anti-angiogenic effects associated with Duffy-positive mice, DARC-negativity may help to explain some of the racial differences in prostate tumorigenesis.

Methods—The Prostate Cancer in a Black Population (PCBP) study, a large case-control investigation including 1,007 incident PC cases and 1,005 controls, performed DARC testing on a subset of 1,295 participants (641 cases, 654 controls). The relationship between DARC expressivity and PC risk was evaluated using logistic regression models and findings are presented as odds ratios and 95% confidence intervals.

Results—More than three-quarters (76.5%) of African-Barbadian men lacked DARC expression, whereas almost three-fifths (59.3%) of White participants tested positive for the Duffy a and b alleles. DARC-negativity was not found to be associated with PC risk in the present investigation (OR=1.04, 95% CI (0.78, 1.37)), regardless of tumor grade.

Discussion—Findings from the PCBP study indicate that the majority of African-Barbadian men do not express DARC on their erythrocytes, yet absence of expression does not appear to be associated with PC development in this population.

Keywords

African ancestry; prostate cancer; Duffy blood group; Duffy Antigen Receptor for Chemokines (DARC)

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INTRODUCTION

The Duffy Antigen/Receptor for Chemokines (DARC) is a blood group antigen that is commonly expressed among European-derived populations, whereas approximately 70% of African-American and 95% of endemic African populations lack expression of DARC on their red blood cells (1–3). The Duffy antigen is thought to be a malaria parasite receptor. The lack of expression of this binding protein in African populations is believed to result from an evolutionary selection process providing increased resistance to malaria infection (1, 4).

DARC-negativity has been shown to exhibit angiogenic properties, which have been implicated in mediating prostate tumorigenesis in some animal models (5–6). It has further been suggested that Duffy-positive antigens may buffer against the development of prostate tumor growth by acting as a sponge and removing the angiogenic chemokines (2). In one transgenic mouse model, DARC appeared to clear angiogenic CXC subclass chemokines produced by PC cells and resulted in an overall reduction of the disease (6). Likewise, tumors from DARC-deficient mice in the same study had increased angiogenesis, higher tumor vessel density and more advanced carcinogenesis. If the Duffy antigen/receptor also provides a protective mechanism against tumor growth in humans, its reduced expressivity among westernized African populations might help to explain their increased incidence and mortality of PC. Furthermore, the development of drugs to modulate Duffy antigen/receptor expression might provide additional opportunities for the treatment and prevention of PC in DARC-negative men of African descent.

The Prostate Cancer in a Black Population (PCBP) study was a large, population-based case-control study designed to evaluate genetic and epidemiologic contributors to PC in Barbados, West Indies, an Afro-Caribbean nation with relatively low admixture (7). The purpose of this investigation is to describe the distribution of the DARC phenotype and evaluate the relationship between Duffy antigens and PC among men in the PCBP study.

MATERIALS and METHODS

Eligible cases for the PCBP study included all male citizens of Barbados with newly diagnosed and histologically confirmed PC identified between July, 2002 and January, 2011. Controls were residents of the island who were randomly selected from a national database, frequency age-matched (by 5-year age groups) to the cases, and free of PC at the time of the study visit. Controls received PSA testing and those with high PSAs were referred for follow-up. If subsequent biopsies were positive, these men converted to cases. All study participants provided informed consent and the protocols conformed to the Declaration of Helsinki.

The design and methodology of the PCBP study have been described in detail elsewhere (8) and are summarized below. A standardized and comprehensive questionnaire was administered by certified nurse-interviewers and included sections relating to demographic and lifestyle characteristics, anthropometric and other measures, medical and family history information, and specific prostate-related factors. Venipuncture was performed to obtain

blood samples for the testing of PSA, HbA1c and selected genetic variants. Beginning in January, 2005, the study protocols were revised to include DARC expressivity testing for all subsequent participants and Duffy antigen data were ultimately collected on a total of 1,295 study participants (641 cases, 654 controls).

The Duffy (Fy) locus, located on chromosome 1q near the centromere, is comprised of two co-dominant alleles, Fy^a and Fy^b, and is denoted by four mutually exclusive phenotypes: Fy(a+b+), Fy(a+b−), Fy(a−b+) and Fy(a−b−). Individuals who express either Fy^a or Fy^b on their erythrocytes are classified as DARC-positive, whereas those who lack expression on both alleles are considered DARC-negative. Screening for DARC included testing for the presence of antibodies to Fy^a and Fy^b using the DiaMed-ID Micro Typing System (Switzerland).

Statistical Analyses

Characteristics of the study participants are described as means ± standard deviations (sd) and median values for continuous variables and percentages for categorical variables. Logistic regression models were used to evaluate the relationship between the Duffy-negative phenotype and PC. Multivariate models were adjusted for demographic and other factors shown to be associated with PC, including age, marital status, religion, occupation, waist-hip ratio, and family history of PC (8–9). The regression results are presented as odds ratios and 95% confidence intervals and are additionally stratified by tumor grade, defined by Gleason Score <7 (low-grade) and ≥7 (high-grade). The Statistical Analysis System (SAS Institute, Cary NC) was used for these analyses.

RESULTS

The PCBP study included 1,007 men with PC and 1,005 controls, representing 80% and 75% of those eligible, respectively. A consecutive subset of these participants (n=1,295) received testing for DARC and the age and case-control status distributions for this subset were similar to the group of PCBP participants who were not tested. Of the 641 cases and 654 controls evaluated for DARC expressivity, 595 cases and 588 controls self-reported their race as African-Barbadian. Table 1 presents the characteristics of these 1,183 participants typed for the Duffy antigens. The mean (±sd) ages for the cases and controls were 67.3 (±9.0) and 66.5 (±9.1) years, respectively, and approximately three-fifths of participants reported being married or living with a partner. Cases had significantly larger waist-hip ratios than controls (mean (± sd): 0.93 (±0.07) vs. 0.91 (±0.06), respectively) and were almost twice as likely to report at least one family member with PC (25.2% vs. 13.3%).

The phenotype distribution of the Duffy Blood Group among healthy men (controls unaffected with PC), stratified by race, is presented in Table 2. The distribution of Fy^{a+} was significantly different between Black and White controls (11.9% vs 70.4%, respectively). The percentage of Mixed race men expressing the a+ phenotype (42.9%) was found to be intermediate to the expression levels demonstrated by the other two races. A similar distribution was noted for the Duffy b allele, with 13.6% of Black, 35.7% of Mixed and 88.9% of White controls exhibiting the b+ phenotype. With regard to DARC expressivity, 100% of the White men were DARC-positive, with almost three-fifths exhibiting the Fy(a+b

+) phenotype. In contrast, more than three-quarters of Black men were found to be DARC-negative (Fy(a−b−)), with only 2% having the Fy(a+b+) phenotype. Approximately one-third of the Mixed race controls were DARC-negative.

To determine the relationship between DARC-negativity and PC, we restricted the analyses to men who self-reported their race as Black. Among the African-Caribbean PC cases, 29 had missing data on Gleason Score, yielding a total of 595 cases and 588 controls for this subgroup investigation. The logistic regression results are presented in Table 3. The percent of Duffy-negativity was almost identical for all PC cases (76.8%) and controls (76.5%), with crude OR close to unity (OR=1.02, 95% CI (0.78, 1.33)). The multivariate-adjusted OR (95% CI) for all PC cases was 1.04 (0.78, 1.37), suggesting that there is no association between lack of DARC expression and PC. The results were similarly null for both low-grade (OR=1.04, 95% CI (0.71, 1.50)) and high-grade tumors (OR=1.11, 95% CI (0.79, 1.55)) evaluated independently.

DISCUSSION

Due to a predominance of DARC-negative expression among men of African descent, as well as the notably high rates of PC in this group, DARC negativity may be associated with prostate carcinogenesis in men of African heritage. This hypothesis was explored in the PCBP, which represents the largest population-based case-control study of incident PC among men of African origin to date. Findings indicate that more than three-quarters of African-Barbadian men are DARC-negative, with only 2% found exhibiting Fy(a+b+), a phenotype that is predominant among Caucasians. However, DARC-negativity was not related to PC in the PCBP, regardless of tumor grade.

Distribution of the Duffy Phenotype

African- and European-descent populations are known to have notably different distributions of Duffy blood group phenotypes. The distribution of Fy(a+b+), Fy(a+b−) and Fy(a−b+) has been reported to be 49%, 17% and 34%, respectively, in Caucasians compared to 1%, 9% and 22%, respectively, in African-Americans (10). Duffy-negativity predominates in populations of African descent with approximately 70% of African-Americans and 95% endemic Africans shown to carry the Fy(a−b−) phenotype (2). Additionally, a small study evaluating the relationship between DARC and PC in Jamaica found that 78% of Jamaican men did not express DARC (11). The percentage of DARC-negative men found in Barbados (76.5%) was similar to that reported in Jamaica and indicates that DARC expressivity in African-Caribbean populations appears to be intermediate between the expression exhibited in African-American and West African populations.

DARC and PC

Chemokines (also known as chemotactic cytokines) are divided into four subgroups: CXC, CC, CX_3C and C. The CXC subgroup is further stratified into ELR^+ (angiogenic) and ELR^- (mostly angiostatic) motifs and has been implicated in several biological processes, including angiogenesis and PC tumor progression (12). It has been suggested that

tumorigenesis is the result of a disturbance in the equilibrium of angiogenic and angiostatic influences, with increases in angiogenesis promoting tumor growth by providing a mechanism to deliver nutrients and oxygen to existing cancer cells.

DARC is a chemokine receptor that can be expressed on red blood cells (erythrocytes) and endothelial cells. Expression on the two cell types may not necessarily be concordant, as some individuals expressing DARC on their endothelial cells have lacked expressivity on their erythrocytes (13). Some animal studies have suggested that lack of DARC expressivity may contribute to PC tumor angiogenesis as a result of the inability of DARC-negative individuals to remove the build-up of angiogenic chemokines believed to contribute to carcinogenesis (5–6). Shen et al demonstrated that DARC-negative mice had higher concentrations of angiogenic chemokines, increased tumor vessel density and increased PC tumorigenesis (6), thus supporting the theory that DARC may have anti-angiogenic properties. It should be noted that the mice in this latter investigation lacked DARC expression on both erythrocyte and vascular endothelial cells. As such, findings from that study make it difficult to differentiate the effect of DARC expression on PC based on cell type.

As a result of a small number of animal studies, it has been proposed that African-American men who lack erythroid DARC may have a higher mortality from PC because angiogenic chemokines produced by the tumor are unable to be cleared (6). If this were true, the development of therapeutic drugs to modulate DARC expression would provide an opportunity to inhibit tumor growth. To this end, Moore et al showed that human PC cell lines can produce angiogenic CXC chemokines in mice and that neutralizing antisera to interleukin-8 (IL-8) can successfully inhibit such tumor growth (5). However, evaluations of these findings in human populations have been limited and inconsistent.

A comprehensive search of the literature revealed one small bench-side study of 25 tissue specimens from men undergoing radical prostatectomy and found that CXC chemokines were present in PC cells in vivo, with increased levels in tumors of men with PC compared to those with BPH and normal prostate cells (14). To our knowledge, the only investigation to date including human subjects and designed to evaluate the relationship between DARC expressivity and PC was a small hospital-based case-control study in Jamaica, including 81 men with PC and a similar number of age-matched males without the disease (11). The Jamaican investigation found DARC expressivity in 22% of both groups with no association reported between erythrocyte DARC expression and PC risk (11). It should be noted that 40–45% of the controls in that study were diabetic (recruited from the hospital's phlebotomy laboratory) and if diabetes was inversely associated with DARC expression, the selection of a significant number of diabetic controls would result in a bias towards the null, thereby explaining the observed lack of association. In the current PCBP investigation, diabetes history was similarly observed in cases and controls (24% and 25%, respectively). Additionally, among those with diabetes, Duffy negativity was expressed in 81.7% of cases and 80.1% of controls. Among those without diabetes, negative expression was found to be 75.2% and 75.4% for cases and controls, respectively. Findings from the PCBP are consistent with those reported in the Jamaican study and indicate that DARC negativity does not appear to increase the risk of PC.

Strengths and Weaknesses

The PCBP represents the largest, nationwide study of incident, histologically confirmed PC among men of African ancestry to date. The study is further strengthened by its standardized and comprehensive protocols and high participation rates. Although the present investigation does not support a relationship between the Duffy blood group and PC, there continues to be interest in DARC as an explanatory variable for malignancy (15). The function and role of this antigen with regard to PC specifically and tumorigenesis in general requires further investigation.

CONCLUSIONS

DARC binds to a wide range of chemokines, a subset of which, the CXC class, has been shown to influence prostate tumor growth in some animal models. It has been suggested, therefore, that lack of DARC expression, which is common in populations of African origin, may be partly responsible for the higher rates of PC in this group. Findings from the PCBP, a large nationwide case-control study of PC in Barbados, indicate that more than three-quarters of African-Barbadian men are DARC-negative, yet there does not appear to be an association between DARC expressivity and PC risk in this predominantly African-origin population. To date, the cellular functionality and possible anti-angiogenic properties of DARC cells remain unclear. Additional research is necessary to disentangle the underlying molecular mechanism(s) promoting prostate tumorigenesis and to elucidate how discordant expressivity on erythrocyte and endothelial cells may influence the relationship between DARC expressivity and PC risk.

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Table 1

Characteristics of African-Barbadian Study Participants by Case-Control Status

Characteristics	Cases (n=595)	Controls (n=588)
Age (years), mean sd (median)	67.3 9.0 (68.0)	66.5 9.1 (67.0)
Religion, % Anglican	47.7 (n=284)	41.7 (n=245)
Marital Status, % Married or living together	62.4 (n=371)	57.1 (n=336)
Occupation, professional, %	21.7 (n=129)	16.2 (n=95)
Waist-hip ratio, mean sd (median)	0.93 0.07 (0.92)	0.91 0.06 (0.91)
Family history of prostate cancer	25.2 (n=150)	13.3 (n=78)

Table 2

Phenotype Distribution of Duffy Blood Group by Self-reported Race (Controls from the PCBP)

	Self-reported Race*		
Duffy phenotype	**African-Barbadian (n=588)**	**Mixed (Black/White) (n=28)**	**White (n=27)**
Fy^{a+},%	11.9	42.9	70.4
Fy^{b+},%	13.6	35.7	88.9
Positive Expression	*23.5*	*67.8*	*100.0*
Fy(a+b−)	9.9	32.1	11.1
Fy(a−b+)	11.6	25.0	29.6
Fy(a+b+)	2.0	10.7	59.3
Negative Expression	*76.5*	*32.1*	*0.0*
Fy(a−b−)	76.5	32.1	0.0

* excluding 11 participants with “other” self-reported race

Table 3

The Relationship between Duffy-Negative Phenotype and Prostate Cancer among African-Barbadian Men in the PCBP Study

	Cases† %	Controls† %	Crude OR (95%CI)	Multivariate-adjusted* OR (95% CI)
All PC (n=595)	76.8	76.5	1.02 (0.78, 1.33)	1.04 (0.78, 1.37)
Low-grade PC (n=243)	77.4	76.5	1.05 (0.73, 1.50)	1.04 (0.71, 1.50)
High-grade PC (n=323)	77.7	76.5	1.07 (0.77, 1.48)	1.11 (0.79, 1.55)

OR=odds ratio; CI=confidence interval

† 29 had missing data on Gleason Scores; n=588 for controls

* Based on logistic regression models adjusting for age, marital status, religion, occupation, waist-hip ratio and family history of PC