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Commentary

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Mitochondrial alterations may underlie race-specific differences in cancer risk and outcome

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African Americans are at increased risk of cancer and associated mortalities compared with European American populations. Socioeconomic, cultural, and biological factors have been implicated in this discrepancy. In this issue of the *JCI*, Piyarathna et al. identify a set of genes that are upregulated in a number of tumor types in African American cancer patients as compared with European American patients. These genes were associated with enhanced oxidative phosphorylation and upregulation of transcription factors that promote mitochondrial biogenesis, resulting in greater numbers of mitochondria in tumor samples from African American subjects. Together, these results indicate that mitochondria dysfunction may underlie the increased cancer incidence and poor outcomes observed in African American patients.

Racial disparity in cancer outcome

The observed disparities for both risk and survival among African Americans and European Americans continue for the vast majority of cancers to be both a serious concern for the medical community and a complicated problem for researchers seeking to understand the fundamental causes of the disparities. The higher incidence of disease and poorer outcomes experienced by African Americans diagnosed with cancer may be explained in part by socioeconomic and cultural differences that influence not only the distribution of important cancer risk factors, but also access to quality medical care that includes screening for early detection, choice and uptake of treatment, and adequate follow-up (1). There is also strong evidence to suggest that the underlying biology of cancer, related to both the initiation and progression of disease, differs by race (2). Yet to date, the investigations focused on genetic and

epigenetic events contributing to racial disparities are typically conducted in a tumor-specific fashion.

OXPHOS and mitochondrial dysfunction linked to disparity

In this issue of the *JCI*, Piyarathna et al. (3) have identified distinct race-specific differences in tumor gene expression profiles using an in silico approach in a pan-cancer setting with data available through The Cancer Genome Atlas (TCGA) database. Specifically, the authors discovered that a set of genes encoding mitochondrial complexes involved in oxidative phosphorylation (OXPHOS) are upregulated to a greater extent in tumor specimens from African American patients compared with those from European American patients. In subsequent analyses, the authors identified estrogen-related receptor 1 (ERR1) and peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC1 α) as the most commonly enriched transcrip-

tion factors within the OXPHOS pathway in tumors from African American patients. Because these two genes act in concert to regulate mitochondrial biogenesis, Piyarathna et al. hypothesized that mitochondrial content would be higher in tumors from African American subjects compared with tumors derived from patients of European American descent. This hypothesis was supported in an experiment using tissue microarrays constructed from prostate, laryngeal, and oral cancer specimens.

The potential impact of the findings of Piyarathna and colleagues is considerable, not only in furthering our knowledge of the biological basis of cancer health disparities, but in moving the needle with respect to personalized medicine. Primarily responsible for cellular respiration and energy production, mitochondria have been shown to play an important role in oxidative stress, cell signaling, and cell death; therefore, it is logical to conclude that these organelles may be important in carcinogenesis (4). A better understanding of the role of mitochondria and the impact of their dysfunction in cancer initiation and progression will be critical in developing the next generation of cancer therapeutics and for exploiting the full potential of existing mitochondrial inhibitors, such as metformin and phenformin (5).

Moreover, the work of Piyarathna et al. contributes to a growing body of literature that supports a role for mitochondria in cancer health disparities. Prior studies have been mixed and focused on specific cancers. For example, previous research in prostate cancer found that mitochondrial content measured by immunohistochemistry positively correlated with clinical characteristics associated with aggressive disease, including pathologic stage, Gleason score, and early evidence of prostate-specific antigen recurrence following treatment (6). This study was conducted in a large European cohort, so the potential

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Conflict of interest: JLB is a consultant for The CUSP Group, LLC., a uro-oncology trials management organization. KAC is coinventor on a patent (no. 9,593,380) related to the discovery of HOXB13 as a prostate cancer susceptibility gene.

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association of mitochondrial content and race could not be addressed. Koochekpour et al. (7) observed mitochondrial DNA depletion in prostate tissue from African American patients and suggested that lower mitochondrial DNA content contributes to differences by race in prostate cancer incidence and progression. Additional research has focused on both germline and somatic mutations in mitochondrial DNA in prostate cancer and other malignancies with variable findings (8). Finally, use of metformin as a prostate cancer chemopreventive has shown some promise, as it has been linked to reduced risk of recurrence, metastatic disease, and death in men with concomitant type 2 diabetes (9). However, whether or not there are differences by race and/or ethnicity in sensitivity to drugs such as metformin requires further study.

Future considerations and conclusions

While the findings of Piyarathna et al. are intriguing, there are some points that merit further consideration. The tumor types used for the initial discovery work were selected because at least ten African American patients were enrolled in TCGA for that particular cancer. Race was obtained by self-report, and the number of African American cases (overall 12.7% in TCGA) compared with European American cases was likely small. In addition, individuals typically report their race based on skin color rather than ancestry, thereby creating an opportunity for misclassification (10). Furthermore, African Americans can have differing amounts of African and

European ancestry, and we concur with the recommendation by Piyarathna et al. that future studies focus on use of ancestry-informative genetic markers to more accurately classify individuals in studies of biological contributions to cancer disparities. Additionally, the overall number of cancer cases in the Piyarathna et al. report is small and the enrichment of OXPHOS appears to be variable across tumor types and should be further explored. Finally, the potential role(s) of mitochondria in cancer incidence and aggressiveness are complex; therefore, mitochondrial function, in addition to total number of these organelles, merits investigation.

In summary, studies that focus simultaneously on multiple cancer types may help identify signals that will lead to recognition of common biological mechanisms that contribute to increased cancer incidence and/or aggressiveness in African American individuals. For example, while PGC1 α has been extensively studied in cancer (11), to our knowledge this is the first report of its potential contribution to cancer disparities. Future studies of OXPHOS-associated genes in well-annotated clinical series of racially diverse patients characterized with ancestry-informative markers are warranted.

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