Deciphering Ancestral Clues to a Subset of Metastatic Cancers

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Introduction: Racial Differences in Calcium Metabolism

African-Americans show an unusually high susceptibly to Metastatic Prostate Cancer (PCa) with a mortality rate 250% higher than that of their White counterparts. This ethnic population also has more than twice the mortality rate of Whites from Triple Negative Breast Cancer (TNBC), Ovarian and Colorectal Cancer. What these malignancies have in common is the tell-tale upregulation of mRNA from the TRPV6 calcium ion channel, which correlates with the advanced stages of prostate, colon, breast and ovarian carcinomas. The study of black vulnerability to these aggressive cancers uncovers their shared etiology and thus offers potential therapeutic targets that can be applied to patients of all ethnicities.

African-Americans are an admixed genetic population composed primarily of 75% Niger-Kordofanian West Africans, 24% Northern Europeans and 1% Native Americans. It is the African portion of this genetic ancestry that offers new insights into metastatic cancers. This is because of the oncogenic hypersensitivity to excess calcium of the African TRPV6a calcium ion channel variant when placed under environmental stresses. Because this allele is far more calcium-absorbent than the non-African//European TRPV6b variant, what might be the triggering mechanisms for such "stress"?

The Niger-Kordofanian (NK) genetic ancestors of Black Americans inhabit a vast swathe of West Africa infested by the parasitic tsetse fly (Glossina), the carrier of Trypanosoma brucei. Its presence represented for millennia a barrier to the introduction of pastoralism and dairy farming into these regions of the African continent. However, the NK populations maintained strong bones and low rates of osteoporosis on a 200-400 mg daily intake of dietary calcium, because the African TRPV6a variant absorbed more Ca2+ than the non-African TRPV6b variant.

While adaptive for NK populations inhabiting a low-calcium homeland, this TRPV6a variant may, however, have become more problematic, or even oncologically maladaptive for African-Americans in the high calcium, dairy food culture of the U.S. Even though this ethnic group is generally lactase non-persistent (lactose intolerant), the availability of popular low-lactose dairy products, such as ice cream, butter, yogurt and cheese in the diets, triples Blacks' calcium intake over that of their ancestors. A chronic flooding of excess free-calcium ions into prostatic and breast and among tissues that cannot be excreted in the urine, might in fact trigger the carcinogenic reaction of the more calcium-absorbent TRPV6a variant. This is because it works in concert with another variant. The African A563T Single Nucleotide Polymorphism found on the TRPV5 located in the kidneys retains excess calcium rather than expelling it in the urine, which occurs as a function of the non-African variant.

TRPV6-Expressing Cancers

Even apart from the high African-American risk of Metastatic PCa, an increasing number of reports have identified the over-consumption of calcium as a possible trigger for this disease. TRPV6 mRNA becomes a veritable biomarker for these malignancies as it proliferates in the prostate, breast or other organs and metastasizes. Recent investigations of ionized calcium at the cellular level have shown that a chronic excess can lead to disturbances in organelles, including the initiation of nuclear DNA mutations. The greater the exposure of the TRPV6 intestinal channel to Ca2+ (in the absence of alleles blocking its intestinal absorption), the higher the risk of producing mutagenic changes in the prostatic TRPV6 calcium ion channel.

Black women find themselves at an even more serious disadvantage. Because white females in the U.S. consume 43% more calcium than their African-American counterparts, the latter group is seen in contrast as "calcium deficient". No allowance is given to the fact that black women have strong bones and the lowest rate of osteoporosis of any American ethnic group. All American women are given the same public health message, which is to take supplemental calcium to strengthen their bone health. The nutritional guidelines do not take into consideration the fact that this ubiquitous advice might trigger metastatic cancers in females who carry the more calcium-absorbent TRPV6a gene variant.

A Potential Therapeutic Target

Even though the focus of this research is the TRPV6 calcium ion channel, the aim here is not to over-simplify the complex mechanism of calcium homeostasis. TRPV6 expression is also linked to the Vitamin D receptor (VDR). In addition, the "African" Q1011E allele (rs1801726 SNP) is found on the Calcium Sensing Receptor (CaSR) Gene, which modulates extracellular calcium homeostasis through secretion from the parathyroid hormone. This variant has also been linked to the bony metastases of

breast and prostate cancer. In short, it is not known which of these gene variants might independently or in concert with the TRPV6a variant contribute to blacks' higher susceptibility to these metastatic cancers. However, the TRPV6 channel has been singled out in this study because:

a. it represents the first step in the absorption of free-calcium ions into the small intestine;
b TRPV6 mRNA is dramatically over-expressed in metastatic tumors
c. this calcium ion channel can be blocked without interrupting cardiac and other vital functions.

At present, there is only one peptide TRPV6 inhibitor that successfully completed a phase I clinical trial in February 2016 to evaluate safety and tolerability. It is in the process of initiating phase II testing of the efficacy of the drug on solid tumors. The drug being tested, SOR-C13, is a compound derived from the venom of the northern short-tail shrew.

While lidocaine is commonly known as a local anesthetic, researchers at Chongqing Medical University in China announced their initial success in using the drug as a TRPV6 calcium channel blocker. The experiment was conducted in 2016, treating human breast cancer MDA-MB-231 cells, prostatic cancer PC-3 cells and ovarian cancer ES-2 cells with lidocaine in a concentration-dependent manner between 1 and 10 mM. Lidocaine decreased cell viability, and inhibited migration and invasion in all these cell lines. Since then, several new investigations have been launched and await results regarding the use of lidocaine to suppress lung cancer, hepatocellular carcinoma, bladder and prostate cancer.

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