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Racial disparity in metabolic regulation of cancer

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1. ABSTRACT

Genetic mutations and metabolic reprogramming are two key hallmarks of cancer, required for proliferation, invasion, and metastasis of the disease. While genetic mutations, whether inherited or acquired, are critical for the initiation of tumor development, metabolic reprogramming is an effector mechanism imperative for adaptational transition during the progression of cancer. Recent findings in the literature emphasize the significance of molecular cross-talk between these two cellular processes in regulating signaling and differentiation of cancer cells. Genome-wide sequencing analyses of cancer genomes have highlighted the association of various genic mutations in predicting cancer risk and survival. Oncogenic mutational frequency is heterogeneously distributed among various cancer types in different populations, resulting in varying susceptibility to cancer risk. In this review, we explore and discuss the role of genetic mutations in metabolic enzymes and metabolic oncoregulators to stratify cancer risk in persons of different racial backgrounds.

2. INTRODUCTION

The underlying genetic diversity among different human populations that stratifies genomes in various ethnic groups can also manifest resistance or susceptibility to complex polygenic diseases. The skewed distribution of measures of disease frequency such as incidence, prevalence, and mortality, confers differential disease susceptibility risk in these ethnic populations (1). In the post-genomic era, genome-wide meta-analysis of human genome sequences and genome-wide association data sets have led to the identification of multiple disease susceptibility loci associated with an increased risk of complex diseases like type-2 diabetes, obesity, Crohn's disease, allergies, and cancer across various ethnic populations (2, 3). These trans-ethnic, genome-wide studies have enhanced understanding of the complex and heterogeneous genetic architecture of diseases, including cancer.

Cancer is a complex disease of multicellular origin, characterized by rapid, unregulated

proliferation of cells that invade normal tissues and may metastasize to distant organs (4). Although various cancer pathologies are differentiated based on the site of origin, their risk factors differ based on the ethnic background of those who contract the disease (5). Cancer etiopathogenesis is an outcome of the complex interplay between genetic mutations, epigenetic alterations, and environmental risk factors (6). Genetic alterations in cancer cells are of paramount significance since they dictate the onset and progression of the disease (7). Cancer mutations are acquired and somatic, fixed by natural selection and evolution. Further, they may be inherited in varying frequencies in different populations (5). Recent genetic studies and quantitative population-genetic analyses suggest genetic diversity in ethnic populations as a classifier for cancer risk that is population-specific and has shared risk mutations in different populations (8).

Cellular metabolic reprogramming, a key hallmark of cancer, is critical for the survival, progression, and malignant transformation of cancer cells and occurs under an altered micro-environmental state. Metabolic rewiring in tumors benefits host cells by enhancing macromolecular biosynthesis, regulation of redox balance, and rapid ATP generation to meet the requirements of rapidly dividing cells (9). Although the Warburg effect is a key metabolic adaptation known to exist in cancer cells, recent studies indicate metabolic symbiosis, glutamine addiction, and a reverse Warburg effect as newly understood, associated metabolic features (10-12). Mutations in these oncogenic signaling pathways are known to cause differential activation of downstream signaling cascades that further translates to altered metabolic regulations (13). Therefore, in this review, we explore whether genetic mutations in metabolic enzymes or metabolites themselves serve as discriminatory criteria for racial stratification.

3. RACIAL DISPARITY IN INCIDENCE, MORTALITY AND RISK FACTORS IN CANCER

Cancer is a complex group of diseases that consist of anatomically distinct pathophysiologies, and that differ in their genesis and manifestation (14). Although cancer is the leading cause of mortalities worldwide, notable differences are observed in disease incidence, prevalence, and mortality rates depending on the ethnic or racial backgrounds of patients (15). In this review, we focus on lung, breast, colorectal, and pancreatic cancer, since these accounts for the majority of cancer incidences and related mortalities. Recent data from the National Cancer Institute on these four most lethal cancers demonstrate prominent differences in incidence and mortality rates among different racial populations. African-Americans, for example, have relatively higher age-adjusted incidence rates for all four cancer types than Caucasians based on combined data for both sexes. The same trend is reflected in mortality rates, indicating late diagnosis and absence of effective therapeutic modalities, for reasons discussed below (Figure 1). The second-highest mortality rates are found among Caucasians and followed by other three racial populations (15). Nevertheless, in a study conducted on breast cancer over a period of three decades, it was surprising to see a 40 percent higher mortality rate in females of African-American descent than Caucasian, despite having low overall incidence rates (16). It was also interesting to note that non-Hispanic populations overall showed significantly higher incidence and mortality rates in comparison to Hispanic populations (15).

Socioeconomic status, obesity, basal metabolic index (BMI), smoking, type-2 diabetes, exposure to sunlight and carcinogens, dietary factors such as vitamin intake and nutrient density of foods consumed, and family history are major predictors of cancer risk in all races (17-20). A disproportionately high incidence and mortality rates in African-Americans can be attributed to their genetic architecture, specific environmental influences, or risk factors associated with lifestyle habits (21). Also of note is that males from all five racial populations are at higher risk for lung, colorectal, and pancreatic cancer than are females, as reflected in epidemiological trends. Lung cancer is the leading cause of cancer-related deaths in the United States, and the majority of those deaths are associated with cigarette smoking (22). Based on smoking patterns, African-Americans and Native Hawaiians are more susceptible to lung cancer (23). In females, breast cancer is the second leading cause of cancer-related deaths; however, the severity of the disease is directly correlated with a lack of expression of oncogenic receptors. Triple-negative breast cancers are aggressive tumors with poor prognostic potential, and these also show very high incidences among African-American women (24).

Another example of a notable racial disparity is found in colorectal cancer, where African-American patients also present with skewed incidence and mortality rates compared to the U.S. Caucasian population (25). Colorectal cancer, apart from being third leading cause of cancer-related deaths, demonstrates remarkable stage-dependant physiological and cellular changes during disease progression (26). Vitamin D deficiency which is widely prevalent in African-American populations is associated with increased risk of diabetes and colorectal cancer (25). Type2 diabetes mellitus and obesity are other risk factors associated with the difference in the racial stratification of disease (27, 28). Pancreatic cancer, one of the leading causes of cancer mortalities in developed countries, has a low survival rate which is primarily attributed to the sudden onset of disease, rapid metastatic rate, and limited therapeutic interventions (29). A 32% higher

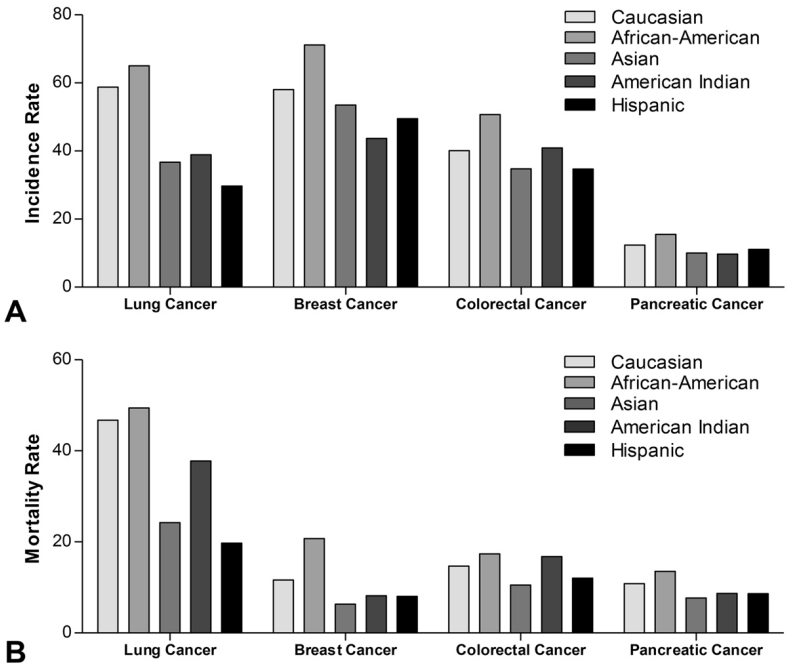

Figure 1. Racial disparity in incidence and mortality rates of cancer. The graph represents age-adjusted (a) incidence rates and, (b) mortality rates of lung, breast, colorectal and pancreatic cancers in different races in the United States from the year 2009-2013. The data is taken from Surveillance, Epidemiology, and End Results report released in 2016 by National Cancer Institute.

pancreatic cancer death rate is recorded in African-Americans compared to Caucasians from the United States. The majority of racial disparity in pancreatic cancer patients is accounted for by cigarette smoking, long-term diabetes mellitus, and family history of pancreatic cancer (in females, alcohol consumption and high BMI are additional risk factors) (30-32). While some differences in the incidence of cancer related to race can be attributed to various risk factors, a differential distribution of natural variations in ethnic and racial populations can account for unexplained inequalities. Therefore, we here focus on a population-based stratification of cancer risk based on genetic alterations in metabolic genes and regulators.

4. METABOLIC REPROGRAMMING IN CANCER

Tumor cells are rapidly proliferating cells that demand different metabolic requirements to support their unusually high rates of cell growth and proliferation. To meet these challenges, the tumor cells exhibit active metabolic reprogramming by enhancing the glycolytic flux to lactate in the presence of oxygen (Figure 2). This phenomenon, known as the ‘‘Warburg effect,’’ or “aerobic glycolysis,” is firmly established as a hallmark of cancer where ATP is preferentially generated through aerobic glycolysis instead of oxidative phosphorylation (33). Such metabolic transformation results in the rapid yet inefficient production of ATP per unit of glucose consumed and therefore, impose an atypically high rate of glucose uptake by tumor cells to convene the enhanced anabolic requirements (34).

The cellular uptake of glucose is mediated by glucose transporters (GLUTs) (35). Subsequent to the uptake, the glucose undergoes a series of metabolic reactions to produce glycolytic intermediates which are channelized to secondary metabolic pathways resulting in the generation of macromolecules such as lipids, nucleotides, amino acids and reducing equivalents such as NADPH indispensable for tumor cell survival and progression (36, 37). In glycolysis, glucose is catalyzed by hexokinases (HK2) to produce glucose-6-phosphate which is sequentially acted upon by glucose-6-phosphate isomerase (GPI) and phosphofructokinase1 (PFK1) to produce fructose-1,6-bisphosphate. Fructose-1,6-bisphosphate is converted to glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, which is further shunted to synthesize triacylglycerols and phospholipids, the precursors for cell membrane (38). The glucose-6-phosphate can also be redirected to the oxidative arm of pentose phosphate pathway (PPP) to generate NADPH, which is critical for the maintenance of redox status in tumor cells. Meanwhile, the non-oxidative arm of PPP is involved in the synthesis of ribose-5-phosphate, required for *de novo* synthesis of nucleotides within the cell (39).

The high glycolytic flux in cancer cells is maintained in a multipronged manner. Key regulatory

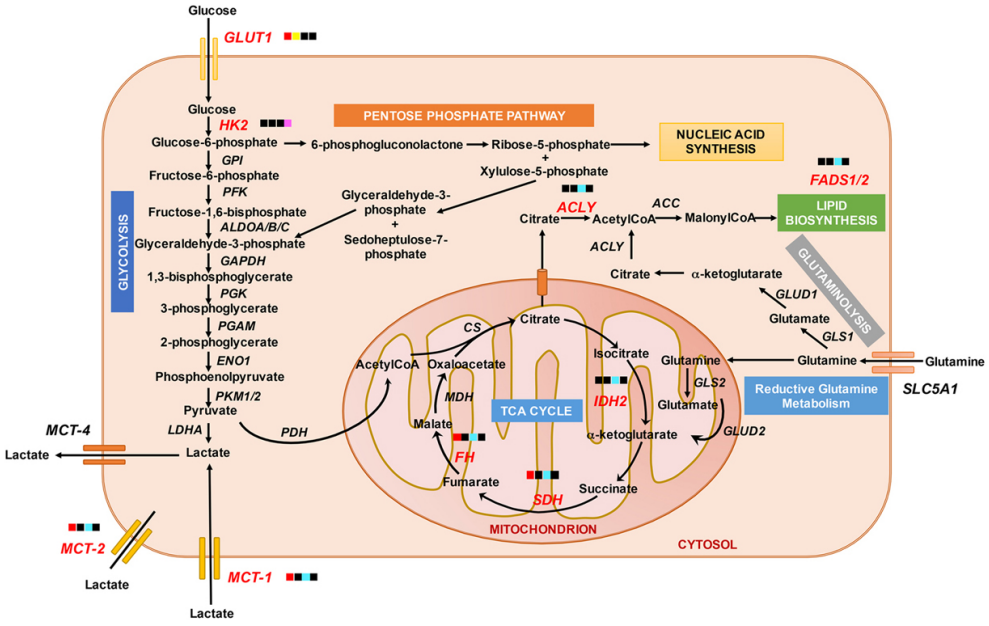

Figure 2. The mutational landscape of metabolic pathways in cancer. Mutation in key metabolic enzymes regulating metabolic reprogramming in cancerous cells is highlighted in red. Colored square boxes represent the presence of mutations in different forms of cancer (red=lung cancer, blue=breast cancer, yellow = colorectal cancer, pink=pancreatic cancer and black= absence of mutation).

enzymes such as phosphofructokinase-2 (PFK-2), lactate dehydrogenase (LDH) and pyruvate kinase (PK) play a critical role in maintaining the increased glycolytic flux in cancer cells by regulating the levels of fructose-2,6-bisphosphate, NAD^+/NADH ratio, and pyruvate respectively (40-42). Approximately 90% of the pyruvate generated from glucose is channelized to form lactate by LDH-A (33). The lactate produced is readily secreted into the extracellular environment by monocarboxylate transporters (MCTs) rather than being completely oxidized. LDH-A catalyzes pyruvate to lactate conversion to recover NAD+ required for maintaining glycolysis (41). The constitutively activated uptake and metabolism of glucose in cancer cells is accompanied by major metabolic reprogramming, thus leading to the production of a vast repertoire of cellular ATP that even supersedes the production rate from oxidative phosphorylation (43).

Around 10% of the pyruvate generated from aerobic glycolysis enters the tricarboxylic acid cycle (TCA). However, the pyruvate is extruded from the TCA cycle as diverse metabolites which are utilized for various biosynthetic processes. Pyruvate is catalyzed by pyruvate dehydrogenase (PDH) to form acetyl-CoA which condenses with oxaloacetate to form citrate (44). The citrate formed is transported from the mitochondria to the cytosol where it is converted back to acetyl-CoA by ATP citrate lyase (ACL). ACL has been demonstrated to be critical for tumor cell proliferation and glucose-dependent lipid biosynthesis (45).

Depletion of TCA cycle intermediates has been shown to alter mitochondrial integrity. The utilization of citrate for lipid synthesis results in depletion of oxaloacetic acid (OAA) which accepts acetyl-CoA to maintain the levels of TCA cycle metabolites (46). This is accomplished by the stepwise oxidation of glutamine in proliferating cells, another major substrate on which the cancer cells have a metabolic dependency. Glutamine uptake in cancer cells is carried out by the glutamine transporters SLC5A1 and SLC7A1 (47, 48). The glutamine acquired by the cancer cells is transformed into biomass, 60% of which is converted to alanine that is further secreted as cellular waste. Recent studies have established that malignant transformation results in the conversion of glutamine to lactate by glutaminolysis which utilizes the cytosolic form of malic enzyme 1 (49). This process of partial oxidation provides cells with NADPH for the reductive reactions of fatty acid and nucleotide biosynthesis. Glutamine participates in various anapleurotic processes as well. Glutamine is acted upon by glutaminase to produce glutamate which is converted to alpha-ketoglutarate (α-KG) and enters the TCA cycle. The condensation of carbon molecules from glucose-derived acetyl-CoA and glutamine-derived OAA permits the production of fatty acids (50). A recent study has also shown the utilization of isocitrate dehydrogenase-1 (IDH1)-dependent pathway-mediated reductive metabolism of α-KG to synthesize acetyl-CoA for *de novo* lipogenesis under hypoxia (51). Reversal of major canonical reactions of the TCA cycle using glutamine as a precursor leads

to the generation of TCA cycle intermediates during dysfunctional mitochondrial metabolism (52). The reprogramming of glutamine metabolism has been elegantly demonstrated to be regulated by KRAS in pancreatic cancer (53). This process of anaplerosis provides the carbon input such as OAA required for the TCA cycle to function as a biosynthetic 'hub' wherein the mitochondria are transformed into apparatuses to sustain rapid cell division (54, 55). In addition to its anaplerotic function, glutamine plays a critical role in the maintenance of cellular redox homeostasis. Glutamate derived from glutamine is catalyzed by the enzyme glutathione cysteine ligase to form glutathione (GSH). This reduced form of GSH is a major antioxidant found in mammalian cells that maintain the cellular redox state of all sub-cellular compartments (56).

5. ENZYMATIC GENE MUTATIONS AS MEDIATORS OF METABOLIC REWIRING

Genetic polymorphism in metabolic genes is tightly associated with altered metabolic profiles resulting in diverse clinical outcomes during cancer pathogenesis (Figure 2). Single nucleotide polymorphisms (SNPs) identified in Glucokinase (GK IVS1+9652C→T) and HK2 N692N homozygous variants are associated with reduced overall survival (OS) in 154 pancreatic adenocarcinomas patients (57). In addition, genetic polymorphism in the GLUT1 (2841A→T) exhibited significant correlation with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose-uptake in the squamous cell type of non-small cell lung cancer (NSCLC) (58). Of interest, many of the mitochondrial genes harbor mutations that can directly contribute to carcinogenesis. Recent studies have indicated genetic defects in many of the TCA cycle enzymes that include isocitrate dehydrogenase (IDH2), succinate dehydrogenase (SDHA and SDHC), and fumarate hydratase (FH) (59-62). Genetic variations in metabolic oncoregulators such as SDH, FH, and IDH, are associated with prognosis of patients with NSCLC. Genetic mutations in SDH and FH results in activation of HIF-1α-mediated glucose utilization (63). Hypoxia-inducible factor-1α (HIF-1α) is a central transcription factor that controls major regulatory nodes of the glycolytic pathway leading to enhanced glycolysis. It is reported that mutations in SDH and FH results in the accumulation of succinate and fumarate, that may further inhibit the prolyl hydroxylases (PHDs), a class of α-ketoglutarate-dependent enzymes, known to hydroxylate HIF-1α (64). Hydroxylation of HIF-1α leads to its degradation by the von Hippel-Lindau-mediated ubiquitination pathways. Thus, germline mutations in SDH and FH can mark the stabilization of HIF-1α during carcinogenesis (65). IDHs have been extensively studied in human glioblastoma multiforme, acute myeloid leukemia, and chondrosarcoma. IDH2 catalyzes the conversion of isocitrate to α-KG. Genetic analysis has revealed the IDHs to harbor point mutations that impart new enzymatic activity wherein α-KG is converted to 2-hydroxyglutarate (2-HG), an oncometabolite. In addition to the productions of 2-HG, mutant IDH also results in the reduction of α-KG and thus leads to stabilization of HIF-1α with a concomitant upregulation of glycolysis (66). In two independent studies performed in NSCLC and colorectal cancer (CRC), three SNPs identified in MCT1 and MCT2 genes were associated with clinical outcomes in patients that could be utilized as predictors of response to adjuvant chemotherapy (67, 68). SNPs are also identified in the lipid biosynthetic pathways of the cancer cell as well. Moreover, two other SNPs found in ACLY gene are associated with high risk of death in colorectal cancer patients (69). In a recently conducted genome-wide association study, two SNPs in the fatty acid desaturase 1 (FADS1) and FADS2 genes were found to have a strong correlation with their expression in colon tumor tissue as compared to normal tissue (70). Together these findings, advocate the possibility of exploiting genetic variations in metabolic genes as prognostic markers to determine cancer risk.

6. MUTATIONAL CONTROL OF METABOLIC REGULATIONS

6.1. Oncogene-directed metabolic rewiring

Metabolic pathways functional in proliferating tumor cells are distinctly regulated by multiple intracellular signaling cascades. These are altered by mutations in known oncogenes and tumor suppressor genes. Such regulatory mutations result in the re-engineering of the entire metabolic machinery to promote survival and growth (Figure 3) (13), but the proliferation of cells is highly dependent on the rate of uptake of nutrients from the microenvironment, a phenomenon dependent on growth factors. The acquisition of genetic mutations in oncogenes leads to altered receptor-initiated signaling pathways in cancer cells, which can result in an increased uptake of nutrients, such as glucose, to compensate for the increased bioenergetic requirements of cancer cells (71).

Mutations in KRAS, p53, Myc, BRCA1, or BRAF have been extensively studied and have been implicated as orchestrators of metabolic reprogramming in multiple cancers. Oncogenic mutations in KRAS and BRAF have been shown to drive the EGFR pathway, a signaling cascade critical for promoting tumor proliferation and survival (72, 73). In a recent study in colorectal cancer, mutations in KRAS and BRAF were shown to increase the expression of the glucose transporter, GLUT1 (74). Activating KRAS point mutations are associated with single-point mutations in exon 12, 13, or 61 and are most prevalent in pancreatic cancer (61%), colon cancer (33%), and lung cancers (17%) (75). Lung

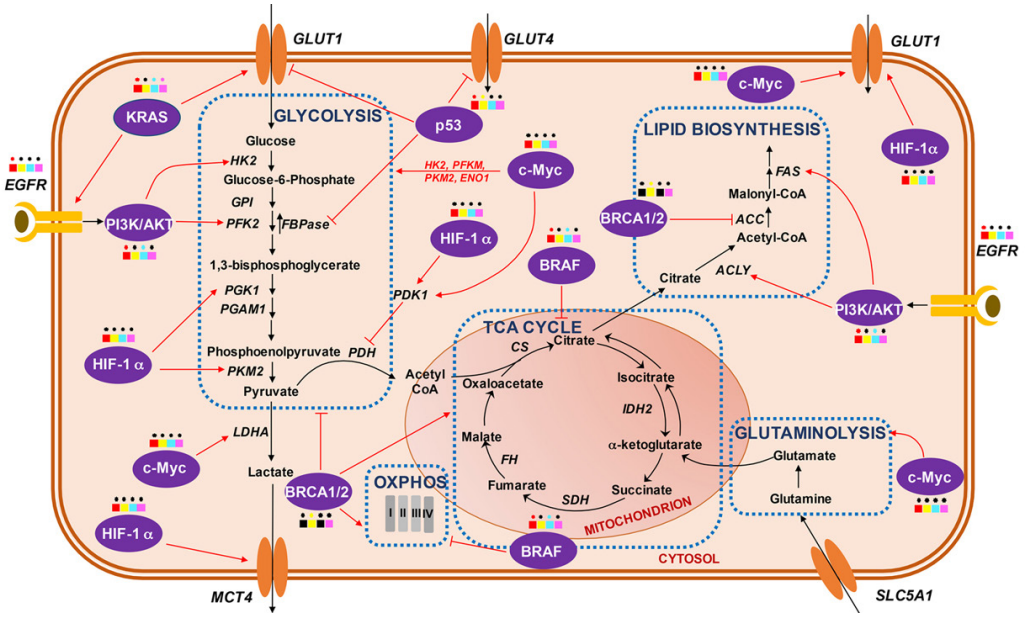

Figure 3. Racial disparity in the mutational profile of metabolic oncoregulators. The figure depicts various metabolic interactions regulated by oncoregulatory genes in cancer. Colored square boxes represent the presence of mutations in different forms of cancer (red = lung cancer, blue = breast cancer, yellow = colorectal cancer, pink = pancreatic cancer and black = absence of mutation). Red colored arrows indicate interactions regulated by metabolic oncoregulators. Star marked above the square box represents the cancer type in which race-specific genetic mutation frequency is reported.

cancer cells homozygous for the KRAS-activating mutation ($Kras^{G12D}$/ $Kras^{G12D}$) exhibit a glycolytic switch wherein the glucose-derived metabolites are shunted into the TCA cycle and glutathione biosynthesis, which assist in enhanced glutathione-mediated detoxification (76).

BRAF mutations were identified in varying frequency in 43 different cancer cell lines including 20 of 34 (59%) melanomas, 7 of 40 (18%) colorectal cancers, 4 of 38 (11%) gliomas, 4 of 131 (3%) lung cancers, 5 of 59 (9%) sarcomas, 1 of 26 (4%) ovarian carcinomas, 1 of 45 (2%) breast cancers, and 1 of 7 (14%) liver cancers (77). The BRAF V600E mutation is prevalent in melanoma cells, colorectal, and thyroid cancer cells where point mutation leads to a reduction in the expression of TCA cycle enzymes and mitochondrial oxidative phosphorylation (78). Also, the BRAF gene mutations were identified in 1% to 3% of all NSCLC samples (79).

The “transcription factor triad,” p53, c-Myc and HIF-1α, actively orchestrates the energy metabolism of cancer cells (80). p53 is a critical and well-studied tumor suppressor protein involved in the regulation of cell cycle, apoptosis, and cell growth and development. Both p16 (Ink4a) and p19(Arf)-p53 pathways have been shown to constrain the progression of pancreatic adenocarcinomas in mouse (81). p53 not only responds to metabolic changes but influences metabolic processes by controlling various regulatory nodes. A variety of metabolic enzymes are downstream targets of p53. The commonly regulated glucose metabolizing enzymes include the glucose transporters GLUT1, GLUT4, and FBPase, which promote the degradation of fructose-2,6-bisphosphate (F-2,6-BP) (82). In cancerous cells, reduction in F-2,6-BP enhances the formation of fructose-6-phosphate, which is converted to metabolic intermediates channelized to PPP (83). In different cancers, inactivation of the p53 tumor suppressor is a common phenomenon, with a mutation rate ranging from 38-50% in ovarian, colorectal, esophageal, lung, and larynx cancers to around 5% in primary leukemia, malignant melanoma, and cervical cancer (84-86). Such oncogenetic changes encompass amplifications, mutations, and gene deletions, giving rise to a mutated yet stable p53 protein that loses tumor-suppressive functions but gains additional oncogenic roles. Such mutations in tumor suppressor genes endow cells with growth and survival advantages (87).

The amplification of c-Myc proto-oncogene is frequently observed in different tumor forms mediated through multiple mechanisms; initial studies indicate the major role of c-Myc in self-renewal capacity of stem cells and tumorigenesis (88). An alternative concept is emerging that suggests the primary functions of activated oncogenes and inactivated tumor suppressors as mediators of cellular rewiring. An increased expression of LDHA upon c-Myc activation emphasized the role of c-Myc in the regulation of glycolysis (89). Subsequent studies have shown that various genes indispensable for glucose metabolism such as GLUT1, HK2, PFKM, PKM2, PDK1, and ENO1 are also found to be regulated by c-Myc and

directly contribute to aerobic glycolysis (90, 91). It is interesting that activation of c-Myc also induces glutaminolysis (92).

Another class of tumor suppressor genes, critical for regulating cell proliferation in a controlled manner in breast cancer, is BRCA, which repairs damaged DNA to maintain the integrity of the genetic material (93). BRCA1 contributes to various metabolic modifications in cancer cells including inhibition of glycolysis and activation of TCA cycle and oxidative phosphorylation (94). BRCA1 is also known to inhibit energy-consuming anabolic processes such as lipid biosynthesis in cancer cells by interacting with the phosphorylated form of acetyl coenzyme A carboxylase alpha (ACCA), the rate-limiting enzyme that catalyzes *de novo* fatty acid biogenesis (95). This altered metabolic programming allows the cells to maintain a low energy status and controls the excessive proliferation that is a hallmark of cancer cells. A recent report also indicates crosstalk between BRCA1 and SIRT1, known to modulate energy metabolism (96). BRCA1 mutations are also the major hereditary factors responsible for a large fraction of inherited breast cancers; they account for a 40-85% lifetime risk of female breast cancer (97). BRCA1 has been shown to mediate its effects by interacting with a multitude of key cellular proteins such as p53, c-Myc, Akt (98), HIF1α (99, 100), and acetyl-CoA carboxylase (ACCA) (101) and by controlling the turnover of these target proteins, including p-ACCA, HIF1α, and p-Akt.

6.2. Signaling pathway-mediated metabolic reprogramming

6.2.1. EGFR signaling in cancer

Growth factor-mediated signaling has been extensively implicated in tumorigenesis, EGFR being a central mediator. EGFR signaling is reported to reprogram the metabolic machinery of cancer cells so as to augment the production of glycolytic intermediates that favor tumor growth (102). A recent report indicated that EGFR signaling simultaneously results in activation of the first step (HK2) and impedes the last step of glycolysis (PKM2), to result in accumulation of glycolytic intermediates in TNBC cells (102). Fructose-1,6-bisphosphate, one such intermediate, functions as an activator of EGFR and provides feed-forward signaling to maintain the shift in the metabolic pathways in cancer cells (102). Constitutive activation of EGFR signaling is driven by mutations in the EGFR tyrosine kinase domain (103).

6.2.2. PI3K/AKT signaling

The PI3K/Akt signaling pathway is inappropriately activated in many cancers. Mutations in growth factors have been implicated in the hyperactivation of Ras in cancer cells that further results in activation of effector pathways such as the PI3K/Akt pathway (104, 105). The PI3K/Akt pathway is also activated by two major mechanisms including receptor tyrosine kinases and somatic mutations in the signaling pathways (106, 107). Activation of Akt results in the major metabolic reprogramming in tumor cells necessary for tumor cell proliferation and progression. The PI3K/Akt pathway promotes glycolysis through multiple mechanisms. Akt enhances the membrane localization of GLUT1 (108), phosphorylates and activates PFK-2 (109), and it increases the translocation of hexokinase to mitochondria, which elicits glycolytic flux (110). PI3K/Akt/MAPK has also been implicated in lipid biosynthesis by phosphorylation and regulation of ACLY and fatty acid synthase (FAS) enzymes (111, 112).

6.3. Metabolic reprogramming mediated by the tumor microenvironment

The tumor microenvironment undergoes a series of biochemical changes such as hypoxia, depletion of glucose, high levels of lactate, and acidic pH (113, 114). Of these changes, hypoxia is widely established as a hallmark of the tumor microenvironment. The cellular adaptive response to low oxygen tension, such as activation of gene expression programs controlling glucose uptake, metabolism, cell proliferation, and differentiation, is largely regulated by HIF-1α and HIF-2α (115, 116). The targets of hypoxia-mediated metabolic regulation include the glucose transporters GLUT1 and GLUT3, 6-Phosphofructo-2-kinase (PFKFB1), a key regulator of fructose-2,6-bisphosphate (Fru-2,6-BP), which regulates glycolytic flux (117-119). The glycolytic enzymes, phosphoglycerate kinase 1 (PGK 1) and pyruvate kinase M2 (PKM2) are known to be regulated transcriptionally by HIF-1α (120). HIF-1α also regulates the monocarboxylate transporter, MCT4 required for lactic acid efflux from cancerous cells (121). In addition to its trans-activating role, HIF-1α actively suppresses metabolism by directly trans-activating the gene-encoding pyruvate dehydrogenase kinase 1 (PDK1); this kinase prevents the pyruvate oxidative decarboxylation to acetyl-CoA and reduces pyruvate entry into the TCA cycle (122). The controlled transactivation of these genes by HIF-1α reprograms the intracellular fate of glucose (123). Clearly, then, the initiation and progression of tumorigenesis is promoted by HIF signaling. HIF-1α is activated in cancer cells by loss of function of tumor suppressor (e.g., VHL) and gain of function (leading to PI3K/AKT/mTOR activity) and mediates the metabolic alterations that drive cancer progression (124, 125). In addition to the signaling pathways, HIF-1α is also methylated by SET7/9 methyltransferase, and lysine-specific demethylase 1 reverses its methylation (126). Systematic meta-analysis based on 40 case-control studies has revealed that polymorphisms in HIF-1α

Table 1. Racial disparity in oncomutations found in metabolic enzymes and regulators

Cancer	Population	No. of Subjects	Molecular Marker	Patient/Tumor Characteristics	References
Breast	Asian, Caucasian	50, 49	BRCA1 and BRCA2	BRCA1 mutations more in Caucasians and BRCA2 more in Asian	(132)
Lung	African-Americans, Native Hawaiians, Whites, Latinos, Japanese Americans	331–709 from each ethnic group	GSTT2	Mutation in GSTT2 correlated with PheT	(149)
Colorectal	Asian, African-American, Caucasian	83, 149, 195	BRAF	Lower mutation frequency in Asians	(130)
Lung	African-American, Caucasian	513	EGFR and KRAS	Association of race with EGFR mutation in NSCLC	(141)
Lung	African-American, Caucasian	53, 102	EGFR	Caucasians had more activation mutations in NSCLC	(142)
Lung	Hispanic American, Non-Hispanic American	40, 43	EGFR	Similar mutation rate in adenocarcinomas from both groups	(143)
Breast	European, African	1307(658 cases), 1365(621 cases)	Estrogen pathway	SNPs in ESR1 gene associated with Europeans	(134)
Breast	Ashkenazic Jews, Icelandic	138, 662	BRCA1 and BRCA2	Founder mutations	(129)
Colorectal	African-American, Caucasian	67, 237	KRAS, BRAF, PIK3CA	KRAS mutation more common in African-Americans	(138)
Lung	Caucasian	403	HER2	HER2 mutation higher in female adenocarcinomas	(144)
Lung	Chinese	239	LKB1, EGFR, KRAS	LKB1 mutation in 6.9.% adenocarcinoma patients	(145)
Lung	African-American, Caucasian	116 lung tumors	KRAS	More serine mutations	(137)
Pancreatic	African-American, Caucasian	166, 244	KRAS	African-Americans had high rates of KRAS mutations to Valine	(190)
Pancreatic	Chinese	37	KRAS	Mutation rates different than Caucasians	(139)
Lung	African-American, Native Hawaiian, Caucasian , Latino, Japanese American	364, 311, 437, 453, 674	UGT2B10	Nicotine metabolism associated with variant alleles	(150)
Lung	Caucasian, African-American, Asian, Latino	5838, 60, 48, 28	10 oncogenes	Difference in prevalence of oncogenic drivers	(135)
Lung	Asian, Caucasian, African-American	141, 76,66	MET, EGFR, KRAS, TP53	Germline MET mutations in East Asians	(140)
Colorectal	Chinese	697,256	TCA enzymes	TCA enzyme mutations associated with Chinese population	(148)
Breast and Lung	15 Populations	75	p53	Higher frequency of all transition type mutations in African-Americans	(147)
Breast	African-American, Caucasian	47	p53	Higher incidence of A:T→G:C	(146)
Breast	African-American, Caucasian	60	Metabolites	High level of fatty acids in plasma from TNBC patients	(169)
Colon	Asian, African-American, Caucasian	3305	KRAS, BRAF	Lower mutation rate in Asians	(180)

at C1772T and G1790A may contribute to increased cancer susceptibility in breast cancer, lung cancer, pancreatic cancer, and oral cancer (127, 128).

7. METABOLIC GENE MUTATIONS AS DIFFERENTIAL PREDICTORS OF CANCER RISK

Racial disparity in allele frequency attributed to cancer risk can arise either from acquired somatic mutations or inherited germline mutations. While somatic mutations are a result of complex environmental interactions, germline mutation, such as founder mutations, determine in part the selective enrichment of mutant alleles in related populations (Figure 3 and Table 1) (5). Founder mutations in oncogenes are passed on from ancestors to descendants in specific populations, rendering them at greater risk of cancer. For example, founder mutations

of BRCA1/2 genes found in Ashkenazic Jews and Icelandic populations account for approximately 3-10% of all breast cancers in the general population, and it has been demonstrated that founder germline mutations impart differential cancer susceptibility in different racial groups. The prevalence of the BRCA2 999del5 mutation in the Icelandic population, for example, is 20 times greater than in that of the general population (129). In another study conducted on colorectal cancer, it was discovered that a lower mutational load appeared in Asians compared to African-Americans and Caucasians (60% vs. 79 and 77%) upon investigation of 385 mutations across 33 known cancer genes. BRAF mutations were more prevalent in Caucasians, with the highest frequency observed for the BRAF V600E mutation (130).

The molecular subtypes in breast cancer are stratified, based on heterogeneous expression of signaling receptors. As noted above, racial disparity in different sub-types of breast cancer is well established, with maximal disease risk being observed in African-Americans. In a study conducted in 11 immigrant populations from different geographical locations, it was demonstrated that recent immigrant populations had higher disease risk for ER-negative/PR-negative tumors (131). The BRCA gene, associated with breast cancer risk, shows contrasting trends in Asians and Caucasian populations. Mutations in the BRCA1 gene are more prevalent in Caucasians (67 vs. 42%), while BRCA2 mutations are more in Asians (58 vs. 37%) (132). Estrogen receptor signaling is crucial in the development of breast cancer. High levels of circulating estrogens and their metabolites have been shown to correlate with an increased risk of breast cancer among postmenopausal women (133). A comparative analysis of patients of European and African descent showed significant association in SNPs of ESR1 gene (rs1801132, rs2046210, and rs3020314) in ER-positive breast cancers in European women. GWAS studies conducted in Asian population show association of SNP rs2046210, although its association in African-American population has not been investigated (134).

Racial disparity in the stratification of cancer risk is well associated with mutations in key oncoregulators. According to the Lung Cancer Mutation Consortium 1 database, an analysis of 10 key oncogenes revealed higher rates of oncogenic drivers in Asian patients, while frequent mutations of KRAS and EGFR genes were found in African-American patients (135). KRAS mutations have also been associated with different stages in the progression of lung adenocarcinomas. KRAS transcripts from the minor allele for KRAS-1 and -6 polymorphisms severely affected oncogenic signaling than those having the major allele (136). Genetic mutations in the different populations not only vary at different positions in the gene but can also vary in insertion types. Approximately 27% of mutations in KRAS genes are found at either codon 12 or 13. The majority of these mutations result in the insertion of cysteine; however, rare insertions of valine, glycine and serine were observed in African-Americans at a higher rate than Caucasians (137). KRAS mutations in colorectal cancer are more frequently found in African-Americans than Caucasians (37% vs. 21) and were associated with advanced stage (odds ratio = 3.3.) and tumor grade (odds ratio = 5.6.0) in African-Americans (138). Higher mutation rates in KRAS gene were also observed in pancreatic neuroendocrine tumors of Chinese patients than Caucasian (139). EGFR mutations are well associated with different races in non-small cell lung cancers (140). The lower frequency of EGFR mutations are reported in African-American patients compared to Caucasians; however, no difference is observed in the frequency of L858R mutations (141). Activating EGFR mutations are also critical indicators for response to therapy. Higher rates of EGFR mutation frequency are observed in East-Asian patients along with the relatively higher frequency of exon 19 deletions and L858R mutation (142). EGFR mutations were also observed in US Hispanic and Non-Hispanics, although their rates were similar between both the groups (143). Association of oncogenic KRAS and EGFR mutations with somatic mutations in the LKB1 and HER2 genes have been addressed in various racial populations. The mutational hotspot in the HER2 gene at 776–779 bases was found to exist differentially in Asian and Caucasian patients. Further, EGFR, HER2, and KRAS mutations were mutually exclusive in Caucasian lung adenocarcinoma patients (144). LKB1 mutations were also found in different frequencies in Caucasian and East Asian populations; however, no significant associations were established among these populations due to small sample size (145).

PIK3CA and BRAF mutations can also influence colorectal cancer risk with significantly higher rates of PIK3CA mutations being associated with higher mortality rates in African-Americans (138). Mutations of the tumor suppressor gene, p53, are used to study the effects of carcinogens in the development of cancers. Mutations resulting in A:T→G:C transitions were more prevalent in African-Americans than Caucasians (146). The prominent diversity in the p53 mutational landscape was also reflected in 15 geographically and ethnically diverse populations (147).

Mutations in metabolic enzymes can also be linked with stratified cancer risk. Genetic alterations in metabolic enzymes of TCA cycle were recently linked to risk and overall survival various in cancers. Mutations found in two key enzymes SDHC (rs4131826) and FH (rs12071124) were significantly associated with the survival time of colorectal cancer patients (148). Cigarette smoking, the major risk factor for lung cancer, is also associated with differential risk

in smokers from different racial backgrounds. Cancer risk in African-American patients is associated with higher levels of the two phenanthrene metabolites, 3-hydroxyphenanthrene (3-PheOH) and phenanthrene tetraol (PheT) found in cigarette smoke, as compared to other populations. Further, polymorphism in the GSTT2 gene was associated with PheT levels; however, the mutation was not significantly associated in different racial groups (149). In another study on similar lines, the proportion of nicotine metabolic pathways (C-oxidation, N-glucuronidation, and N-oxidation) upon correlation with UGT2B10 genotype demonstrated different metabolic patterns in five ethnic populations. The UGT2B10 splice variant (rs116294140) was associated with low levels of nicotine and N-glucuronidation in the African-American persons studied (150). These two studies lay the foundation for conducting integrative metabolic and genetic studies to unravel informative differences between diverse ethnic groups in future.

8. METABOLIC PROFILES AS DISCRIMINATORS OF CANCER RISK IN DIFFERENT RACIAL GROUPS

Different genetic mutational signatures are associated with various forms of tumors; however, the regulation of core metabolic machinery is a central feature of all of them. Metabolomic hallmarks of cancer include Warburg effect, enhanced glycolysis, glutaminolysis, and gluconeogenesis along with suppression of Krebs cycle and lipid catabolism (9). Advances in metabolomics research have enabled the possibility of using metabolomic profiles as biomarkers of early detection, tumor characterization, and clinical outcome prediction. Global metabolic profiles of paired tumor samples from liver, breast, and pancreas identified metabolites unique to each tissue and cancer type with significant differences observed in lipid and amino acid pathways (151). Colorectal tumor tissues exhibit significantly higher levels of C16 and C24 ceramides and endocannabinoid compared to adjacent non-tumor tissues (152).

Metabolomic signatures can also distinguish different disease states based on an analysis of serum metabolites. Blood plasma or serum has been extensively used in different cancer types, such as breast, colorectal, pancreatic, and lung cancers to delineate metabolic markers (153, 154). Metabolic profiling of sera from pancreatic cancer patients and healthy subjects showed alterations in levels of 206 metabolites capable of discriminating disease states (155, 156). Further, metabolomic analysis of the pancreatic cancer patient's serum from Japanese and Caucasian populations demonstrated lower levels of serum phospholipids and ultra-long-chain fatty acid, PC-594 (157). Another study on metabolomic analysis of 38 pancreatic cell lines discriminated all pancreatic ductal adenocarcinoma into three distinct metabolic subtypes, characterized by reduced proliferative capacity and glycolytic and lipogenic profiles (158). Metabolic differences in benign and metastatic pulmonary nodules also discriminated different stages of lung cancer (159). In another study, metabolite profiling of lung carcinomas distinguished lung adenocarcinomas from squamous cell carcinoma by a metabolic signature consisting of 13 metabolites. Adenocarcinomas demonstrated elevated phospholipid metabolism and protein catabolism, whereas stronger glycolytic and glutaminolytic profiles were observed in squamous cell carcinomas (160). Further, phospholipidomic analysis of malignant and non-malignant lung tissues from 162 non-small cell lung cancer patients identified 91 differentially expressed phospholipids with prominent changes detected in sphingomyelins and phosphatidylinositols (161). Serum metabolomic profiles from colorectal adenocarcinoma patients were also able to distinguish different stages of metastases (162). Metabolic changes in colonic tissues, including tumor, polyps, and adjacent matched normal mucosa from 26 patients investigated during colorectal cancer progression, revealed elevated levels of amino acids and lipids, especially carnitine metabolites in the polyps and tumors (26).

Metabolic studies on breast cancers subtypes show different profiles based on growth factor receptor expression. Triple-negative breast cancers (TNBC) are the most aggressive tumors with no effective therapeutic intervention (163). Metabolite choline, which is associated with cell proliferation and oncogenic signaling, was found to be significantly altered, as was glutaminolysis in triple-negative and triple-positive breast cancer patients (164). Furthermore, a metabolomic comparison of TNBC with estrogen receptor-positive breast carcinomas in African-American patients identified significant differences in 133 metabolites involved in increased methionine uptake and transmethylation reactions resulting in elevated levels of methylated nucleic acids and amino acids. Also, elevated levels of oncometabolites (sarcosine and 2-hydroxyglutarate) were detected, though their significance in breast cancer is not understood (24). Another metabolomic study conducted on 204 estrogen receptor-positive and 67 estrogen receptor-negative breast cancer tissues found 19 altered metabolites with significant changes in beta-alanine, 2-hydroyglutarate, glutamate, xanthine, and glutamine (165). African- American women have shown higher incidences of more aggressive TNBC with poor survival rate as compared to Caucasian women. To understand the differences in the prevalence of breast cancer in different races, microarray profiling done in 23 African-American and 34 Caucasian triple-negative breast cancer women revealed no drastic difference in expression of genes except CRYBB2P1 pseudogene (166).

Genic mutations in oncoregulators can modulate metabolite levels by differentially regulating signaling cascades. Since the genic mutational frequency is differentially associated with various races, this frequency can translate to differences in oncometabolite levels. Mutations in KRAS oncoregulators are frequently found in pancreatic, colon, and lung cancers. KRAS mutations found in codon-12 (G12C, G12D, G12V) are associated with different metabolomic profiles compared to the KRAS WT gene and have lower amounts of glutamine, asparagine, and proline. Mutant G12C had the largest number of specific unique metabolites, with KRAS G12C showing a significant increase in L-alpha-aminobutyric acid, a precursor metabolite associated with oxidative stress (167). Of interest, it was found that genetic variations in humans can only account for 12% of the observed variation in metabolic homeostasis (168). While genetic factors can partly explain the racial disparity in the heritability for cancer risk, metabolite profiling can be an alternative approach for dissecting this anomaly. A case-control study conducted on 60 breast cancer patients found 78 discriminatory metabolites belonging to amino acids, fatty acids, and lysolipids in both the racial groups compared to healthy controls (169). As opposed to earlier research on cancer metabolism focused on the regulation of core metabolic pathways, shifting research focus on understanding the role of metabolic oncogenes and metabolic regulation in different races can unravel novel metabolic markers.

9. RACIAL DISPARITY IN GENETIC REGULATION OF CANCER PROGNOSIS AND THERAPY

Genetic variation in different populations, confer differential susceptibility to risk or prevention of cancer, and therefore clinical outcomes for common cancers are also determined by the genetic backgrounds of racial and ethnic groups (170). With emerging statistics detailing the disparities in cancer prevalence among different races, particularly African-Americans (some reasons for which are poorly defined) (23, 171), it is critical to understand the underlying mechanisms for racial groups to best apply therapeutic interventions. Genome-wide mutation analysis studies have enabled the identification of the differential incidence of somatic gene mutations in key oncogenic drivers and metabolic enzymes in cancer pathogenesis. The temporal differences in survival of cancer patients can be attributed to observed variation in modified genetic make-up of cancer cells. A promoter polymorphism of the myeloperoxidase gene MPO (463G→A), a key enzyme in tobacco-induced carcinogenesis, was shown to decrease lung cancer susceptibility in small cell lung cancer (172, 173). In another instance, analysis of Stage II and III breast cancer patients clearly demonstrated a poorer survival outcome in African-American patients compared to other racial groups. Further investigation revealed the genetic composition of susceptible African-American patients to involve $ER^+/PR^+/HER2^-$, the presence of which resulted in diminished survival among African-American women patients (174).

Differences in susceptibility to the effects of chemotherapy, commonly termed as pharmacoethnicity, among racial and ethnic groups, can also regulate therapeutic outcomes in the administration of anti-cancer drugs. Recent advances in clinical research have explored predictive clinical and molecular factors for cancer therapies in patients with diverse cancer phenotypes. Genetic polymorphism studies have revealed a plethora of such candidate genes. Somatic mutations in the EGFR gene were examined in NSCLC patients from Japan and United States with a prevalence rate of 26% and 1.6.% respectively (175). The genetic polymorphism of the hENT1 gene 706G →C has been associated with reduced response to gemcitabine chemotherapy and with the prognosis of NSCLC (176). Remarkably, metabolomic studies in breast cancer have revealed that patients with allelic variations in CYP2D6, SULT1A2, $UGT1A4^{48Val}$ and $UGT2B7^{268Tyr}$ as best candidates for the optimal therapeutic response to tamoxifen, a chemotherapeutic prodrug, the hydroxylated and non-glucuronidated form of which exerts anti-estrogen effects during the treatment of estrogen-dependent breast cancer (177). These examples distinctly indicate a link between inherited genetic differences to therapy responses by specific drugs.

In addition to genetic polymorphisms in drug metabolizing enzymes, inherited variations in genes involved in metabolism, DNA repair, and drug transport may also contribute to differential outcomes of cancer treatment (175, 178). Mutation spectrum analysis of samples from metastatic colorectal cancer undergoing a phase III clinical trial for the VEGF inhibitor cediranib indicated the association between glycolytic and hypoxic gene expression profiles with improved clinical outcome in patients treated with cediranib (179).

A detailed analysis of oncogenic driver mutation in KRAS and BRAF genes was performed in node-positive colon cancer patients of different races including Asians, African-Americans, and Caucasians. Association of the race with clinicopathological characteristics revealed that the BRAFV600E mutation frequency was almost twice that of Asians and African-Americans. However, KRAS mutation rates were highest in African-Americans (44.1.%). Moreover, the wild type forms of KRAS and BRAF were most common among Asians (180). Typically, the BRAFV600E mutations forecast adverse prognosis and the KRAS mutations predict resistance to EGFR inhibitors in advanced disease. Detailed analysis of BRAF mutations in 697 patients with lung adenocarcinomas has shown the prevalence rate to

be approximately 2.5.8%. The identified mutations were V600E, G469A, and D594G and intriguingly, all the patients carrying the mutations were Caucasians (181). In a Chinese colorectal cancer patient cohort study, high frequency of KRAS mutation (31%) was observed which in turn altered the clinical efficacy of the EGFR-TK inhibitor therapy using cetuximab (182). KRAS mutation prevalence analysis in Chinese NSCLC patients revealed relatively lower mutation rate as compared to Caucasian patients (3.8.-8% vs. 18-26%) (142, 183-186). Thus, understanding of the mutations in KRAS are critical for selection of optimal drug therapies in distinct patient groups.

Mutations in oncogenes like Myc and tumor-suppressor genes like p53 drastically alter cancer physiology and survival by reprogramming cellular metabolism and mitochondrial biogenesis (80). An unbiased metabolomics approach to elucidate metabolic signatures and differences between African-American and European-American breast cancer patients was conducted. Of note, prominent elevation in the levels of 2-HG; which is linked to Myc activation and glutamine dependence, was observed in the African-American population (187).

Along with the incidence of oncogenic mutations, the efficacy of cancer targeting approaches is strikingly affected by metabolic heterogeneity of mutant cells. It was recently demonstrated that advanced lung tumors acquired a mutant copy of Kras ($Kras^{G12D/G12D}$ homozygotes) pertinent to malignant progression of tumor cells. $Kras^{G12D/G12D}$ homozygotes exhibited a glycolytic switch and were highly sensitive to the glucose analog, 2-deoxy-D-glucose compared to early stage lung tumors ($Kras^{G12D/WT}$ heterozygotes), which displayed increased sensitivity to low glutamine. Clearly, the mutant KRAS lung tumor is heterogeneous in nature, exhibiting bivariate metabolic profiles and prognosis, and demanding unique drug therapies to selectively target hostile tumor cells based on the differences in mutant allelic content (76).

We believe that genetic mutations observed within different racial and ethnic groups can also identify treatment responses to chemotherapeutic and radiotherapeutic interventions and prognosis of cancer. With the advent of molecularly targeted therapies for diverse cancer treatments, it is rational to consider racial differences in specific genetic and genomic alterations that have implications in the choices of therapeutics and subsequent development of drug sensitivity/resistance profiles.

10. SUMMARY AND PERSPECTIVE

Race and ethnicity are subjective matters, since they are determined or accepted based upon declared racial and ethnic status, patterns of human migration and admixture of populations. Populations are classified into different groups on the basis of common ancestral pedigree and geographical barriers. Populations belonging to different geographical locations are exposed to similar environmental cues and carcinogens, and thus present a high probability of harboring an induced mutation (188). Recent studies in the field of cancer suggest a very strong association of genetic polymorphisms with differential rates of cancer incidence, prevalence, and mortality (189). Racial differences in natural genetic variations can be used as a classifier of cancer risk. However, very few studies have addressed the connection between metabolic pathways and genetic mutations in metabolic enzymes and their regulators. Metabolic reprogramming in cancerous cells is critical for tumor progression and metastasis (9). This review summarizes how mutations in proto-oncogenes and tumor suppressor genes alter the regulation of signal transduction pathways to reprogram cellular metabolism required to support anabolic growth. Furthermore, the oncogenic roles of metabolites have also been demonstrated to alter signaling pathways and regulate cellular differentiation. Apart from mutations in metabolic enzymes and regulators, metabolites themselves can serve as discriminators for cancer risk in different races. This review also suggests the potential of population-specific candidate mutations and metabolomic differences, whether explored or unexplored, in discriminating cancer risk, prognosis and predict efficacy of therapeutic interventions in different human races. Clearly, there is a need to conduct focused studies on metabolic profiling in conjunction with genome-wide mutation analysis in different human races so as to unravel novel molecular determinants of cancer risk and chemotherapeutic susceptibility.

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