Pathogen-Induced Epigenetic Modifications in Cancer in Africa

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Cancer remains a global burden with multiple causality. Over the years, studies have linked various infectious pathogens with various cancer. Nonetheless, precise mechanism(s) by which pathogens induce or enhance cancer development remains largely obscure. Since cancers are almost invariably associated with genetic alterations, pathogen-induced cancers are likely to be linked with genetic alterations, including epigenetic modification, a change in gene expression without changes in the DNA sequences. Indeed, studies have reported associations between some infectious pathogens can induce epigenetic changes. This implies that pathogens could be involved in cancer development through the modification of host epigenetic factors. With the high burden of infectious pathogens, Africa is at a higher risk of pathogen-mediated cancers. To tame a potential rise of such cancers, there is the need for thorough understanding of the role of tropical infectious pathogens in regulating epigenetic modifications that could be associated with cancer development.

epigenetics tropical pathogens cancer

1. Introduction

Globally, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 alone. It is projected that by 2040, the burden will rise by 47%. The relative expected magnitude of the increase is most striking in low Human Development Index countries, like Africa, where the burden is likely to rise by 95% [1]. Many of those cases are preventable or treatable at early stages. However, achieving early cancer diagnosis and efficient treatment remains challenging owing to the multiple causalities of the disease and the high infrastructural costs [2] required for cancer diagnosis and management.

Infectious pathogens are a major cause of cancer, especially in low-and middle-income countries, which are ill-equipped to manage the disease. Therefore, the focus should be directed towards the prevention of infections, as this could reduce the development of pathogen-related cancers. It is estimated that in 2018, 2.2 million out of a total of 18 million new cancer cases worldwide were caused by infectious pathogens [3]. In low-income countries mostly in Africa, over 60% of diseases are attributed to infectious pathogens in contrast to high-income countries where less than 5% of diseases are linked to pathogens [4]. The proportion of infection-mediated cancers varies greatly by geographical region [5]. In Africa, 24.5% of cancers are attributed to infectious pathogens [6]. This may be an underestimation considering the limited cancer diagnosis infrastructure in most African countries.

The involvement of infectious pathogens in carcinogenesis poses a serious threat to the fight against cancer, especially in tropical regions, which have a disproportionately high burden of infectious pathogens. Africa harbors several tropical pathogens, including *Plasmodium* spp., *Leishmania*, *Schistosoma* spp., *Trypanosoma* spp., *Brugia* spp., Dengue virus, Chikungunya virus, *Wuchereria bancrofti* and *Onchocerca volvulus*. Generally, the etiological role of many of these pathogens in carcinogenesis remains unclear. Several studies have suggested that *Helicobacter pylori* and Human papillomavirus (HPV) involved in gastric cancer and cervical cancer, respectively, induce carcinogenesis by altering gene expression through epigenetic mechanisms (reviewed in [7]). Furthermore, some of the endemic tropical pathogens, such as *S. mansoni* [8], *O. volvulus* [9] and *P. falciparum* [10], induce inflammation, a key driver of carcinogenesis (reviewed in [11]). Due to their unique diets and lifestyle, Africans tend to have a distinct set of microbiomes [12]. The increasing evidence of microbiome-associated cancers via alteration of the local immune system, systemic deregulation and dysregulation of antitumor immunity [13] suggest that Africans may be at elevated risk of pathogen-associated cancers. Detailed studies aimed at understanding the precise role of tropical pathogens in cancer development could inform on cancer prevention, early diagnosis and pharmacogenomically aided therapy.

2. Epigenetics in Cancer Development and Progression

Epigenetics is a term that describes reversible heritable changes in gene expression without variations in the DNA sequence [14]. Epigenetic deregulation has been recognized as a key player in carcinogenesis [15][16][17]. Observed epigenetic alterations include changes in DNA methylation, histone modifications, and nucleosome positioning [18]. Changes in the epigenome disrupt gene regulation, resulting in cancer-promoting gene expression patterns. Known epigenetic mutations include genome-wide hypomethylation and regional hypermethylation, particularly in promoter-associated CpG islands [19][20][21], universal changes in histone modification marks [21][22] and deregulation of non-coding RNAs [21][23][24].

Adding to the growing knowledge on epigenetics and its role in cancer biology, several studies have demonstrated how deregulation in different epigenetic mechanisms is associated with cancer [25][26][27][28]. It was also demonstrated that the epigenetic alterations leading to carcinogenesis were caused by infectious pathogens; for instance, a proposed mechanism of gastric carcinogenesis by *H. pylori* is the silencing of miR-490-3p, which reactivates the Chromatin Remodeler, SMARCD1 [29]. Moreover, higher methylation rates of *RARbeta2* and *APC* genes have been observed in Schistosoma-associated bladder cancer compared to non-Schistosoma bladder cancer patients [30].

DNA methylation changes, which involve both hypomethylation and hypermethylation, have received the most attention in epigenetic studies, as aberrations in this modification are common in virtually all cancers [31]. In cancerous cells, DNA hypermethylation has mostly been reported at promoter CpG islands of key genes involved in processes such as cell cycle regulation, DNA repair, apoptosis and differentiation [32]. Moreover, high-throughput analyses of genome-wide DNA methylation have demonstrated distinct epigenetic signatures that correlate with tumor stage and type are reproducibly found in nearly all cases of specific types of cancers [20][33].

Histone modification changes in cancers are less well understood compared to DNA methylation changes. Histone modification enzymes have been shown to exhibit distinct patterns of expression depending on the tissue of origin and can discriminate tumors from their matched normal tissues, clustering them according to cell type [34]. This indicates that abnormal expression of histone modification enzymes is involved in cancer-specific neoplastic transformation [34].

Histone mutations have recently been associated with various cancers. For example, mutations in histone H3 have been reported with high genetic penetrance in rare pediatric gliomas and sarcomas [35][36][37]. These histone mutations have led to the coining of the term “oncohistones”, with several mutations being associated with cancers. For instance, oncohistone H3K27M and H3G34V/R have been identified in diffuse intrinsic pontine gliomas and pediatric glioblastomas, respectively [35][36]. Other studies have shown that the histone H3 variant H3.3 is modified at lysine 36 (H3.3K36M) in 95% of chondroblastomas and at glycine 34 (H3.3G34W/L) in 92% of giant cell tumors of the bone [37]. Oncohistones have also been observed in diffuse large B-cell lymphomas (histone H1), head and neck cancers (H3K36M) and carcinosarcomas (H2A and H2B) [38][39][40]. In some cases, the histone mutations are found to be the only recurrent mutation identified in the tumor, suggesting that they are not only associated with cancer development but also act as initiators [35]. A distinct feature of these common oncohistone mutations is their occurrence at or near key regulatory post-translational modifications in the histone tails, implying a potential interference with the ‘reading’, ‘writing’ and/or ‘erasing’ of these regulatory marks [41].

The frequent genetic alterations in epigenome regulating genes suggest their centrality in carcinogenesis. As shown in **Figure 1**, our analysis of a few epigenetic regulating genes, such as *SETD2*, *HDAC1, TET2* and *EZH2*, using The Cancer Genome Atlas (TCGA) Pan-Cancer dataset on cBioPortal for Cancer Genomics (https://www.cbioportal.org/, accessed on 8 November 2021) revealed that these regulatory genes are frequently altered in different cancer types. Thus providing supporting evidence implicating epigenetic regulation as a mechanism underlying tumor development and progression.

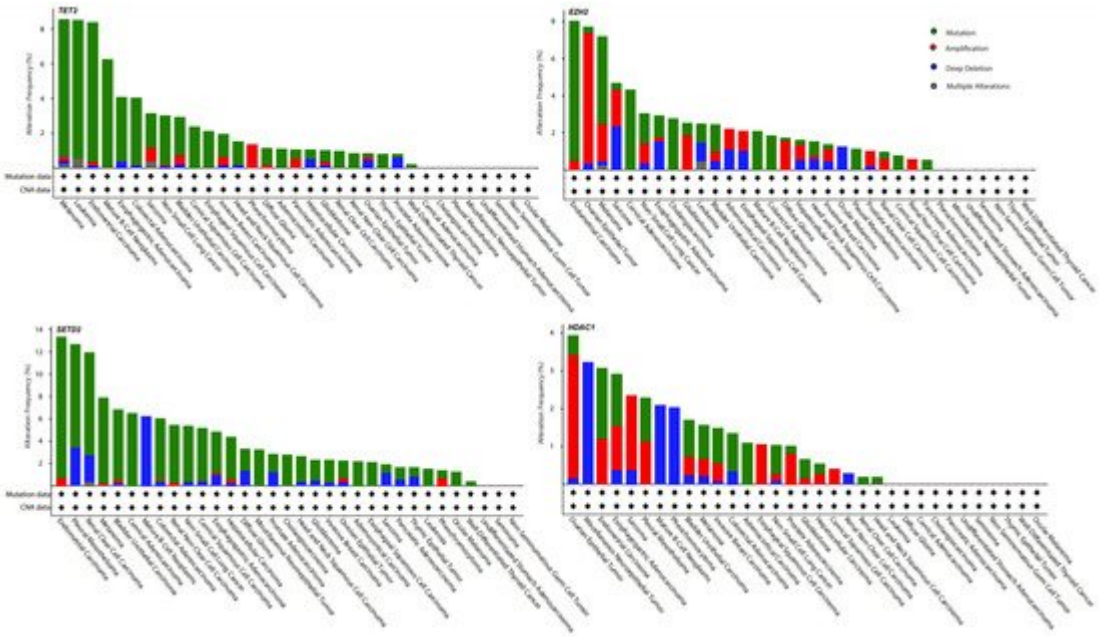

Figure 1. Genetic alteration in epigenetic regulating genes across various tumor types. TCGA Pan cancer data from 32 studies were analyzed on cBioPortal for Cancer Genomics. The bars represent the genetic alteration (mutations, amplifications, deep deletions, etc.) frequencies of *TET2*, *SETD2*, *EZH2* and *HDAC1* across different cancers. The analysis was performed as detailed previously [42][43].

Non-coding RNAs play an integral role in gene expression regulation. Their deregulation as a result of amplification, deletions and mutations as well as through other regulator genes have been associated with a growing number of cancers through aberrant functioning of their specific targets [44]. Non-coding RNAs can act as oncogenes or tumor-suppressors. In chronic lymphocytic leukemia (CLL) patients, deletion at the 13q14 region that encodes miR-15 and miR-16 is common [45]. The miR-15 and miR-16 miRNAs are implicated in apoptosis through their targeting of B-cell lymphoma 2 (*BCL*-2) [45]. Another example of non-coding epigenetic regulation is seen in B cell lymphoma, where the miR-17~92 cluster (13q31-q32) is amplified and acts with *MYC* to promote tumor development in hematopoietic malignancies [46].

3. Overview of Cancer Epigenetic Studies Conducted in Populations of African Descent

Africa is a region of considerable genetic, cultural, geographical and phenotypic diversity [47][48]. These variable factors among Africans, especially genetic, environmental and dietary are critical for understanding the genetic risk factors for disease, gene-environment interactions and epigenetic basis of human diseases [47]. However, most studies have focused on non-African residents; hence, the interplay between these factors and human genetic diseases is scanty. Studying the epigenome is important, as alterations in epigenetic processes drive many diseases, including cancer [31].

Ethnic disparities in cancer measures such as incidence, prevalence, mortality, survival and morbidity have been reported and epigenetic modifications could be contributing factors. However, while studies on the epigenetic basis of different types of cancers have mainly focused on mostly Caucasians and African Americans to a lesser extent [49] as summarized in **Table 1**, cancer epigenetics studies on people residing in Africa are largely lacking.

Table 1. Epigenetic modifications in African Americans and the genes implicated.

Type of Cancer	Epigenetic Modification	Genes/miRNA Involved	Differences between African Americans and Caucasians	Link with Disease Progression	References
Prostate	Hypermethylation	*CD44*, *GSTP1*	Higher frequency of CD44 hypermethylation in African Americans	Not indicated	[50]
	Hypermethylation	*Nkx2-5*, *TIMP3* *AR*,	Higher methylation in African	Yes	[51]

Type of Cancer	Epigenetic Modification	Genes/miRNA Involved	Differences between African Americans and Caucasians	Link with Disease Progression	References
		RARβ2, *SPARC*	Americans		
	Hypermethylated	*miR-152*	Higher methylation in African Americans	Yes	[52]
Colorectal	Hypermethylation	*CHL1*, *NELL1*, *GDF1*, *ARHGEF4*, *ITGA4*	Higher methylation in African Americans	Not indicated	[53]
	Hypermethylation	*miR-9*, *miR-124*, *miR-137*, *miR-548*, *miR-663*, *miR-2682*, *miR-6130*	Higher methylation in African Americans	Not indicated	[53]
Breast	Hypermethylation	*CDH13*, *HIN-1*, *TWIST*, *RAR-β*, *RASSF1A*	Higher methylation in African Americans	Not indicated	[54]
Thyroid	miRNA Upregulation	*miR-31*, *miR-221*	Upregulated in Caucasians downregulated in African Americans	Yes	[55]
Endometrial	RNA Down-regulation	*miR-337*	Downregulated in Caucasians compared with African Americans	Not indicated	[56]
Lung	Hypomethylation	*SHISA4*, *RAD1*	Decreased DNA methylation in African Americans	Yes	[57] [58]

Hence, it ome [49]. Consequently, resident Africans are more exposed to pathogenic infections compared to non-resident Africans. However, knowledge on the role of epigenetics in cancer in Africa is usually drawn from studies conducted among African Americans, which should not be extrapolated to native Africans due to admixture [59][60] and the higher genetic diversity in extant Africans. Epigenetic therapy is a rapidly advancing field of cancer research, since targeting epigenetic aberrations offers remarkable promise as a potential anti-cancer therapy, given the reversible nature of epigenetic changes [61]. Therefore, the lack of cancer epigenetics studies in Africa might have negative implications for people residing in Africa, as treatment development from studies in other ethnicities might not be effective for people of African descent. This calls for African-tailored cancer-related epigenetic studies to inspire African-specific cancer diagnostics and therapies. Advances in scientific research approaches, such as sequencing technologies, enabling the characterization of tumor phenotypes on a large scale, have highlighted epigenetic changes as a hallmark of cancer [61] and are promising solutions to overcome longstanding limitations in cancer

epigenetics research [62]. While sequencing technologies are being applied in cancer epigenetic research in other parts of the world, their usage in Africa is relatively low, partly due to limited resources and technical know-how [63]. Therefore, more initiatives such as the Human Heredity and Health in Africa (H3Africa) consortium, a platform for collaboration and capacity building, should be created to focus on cancer epigenetics in Africa. Such initiatives will be invaluable in generating funds, training younger researchers and capacity building in cancer epigenetics research and development of cancer diagnostics and therapeutics.

4. Correlating the Prevalence of Tropical Pathogens and Cancer Prevalence

Besides causing infectious diseases, the role of infectious agents in non-communicable diseases including cancers is increasingly being appreciated. Currently, infections collectively account for 25–50% of all human cancers [64].

Infectious carcinogens affecting humans span all classes of microbial pathogens—viruses, bacteria, fungi and parasites. Among viruses, the Epstein-Barr virus (EBV), hepatitis C virus (HCV), hepatitis B virus (HBV), Kaposi's sarcoma herpesvirus (KSHV), human immunodeficiency virus type-1 (HIV-1), human T cell lymphotropic virus type-1 (HTLV-1) and high-risk HPV (HR-HPV) genotypes are well-linked to cancer [65]. Notably, HR-HPV, HBV and HCV accounted for 690,000, 360,000 and 160,000 new cancer cases worldwide, respectively, in 2018 [3]. Most of these viral pathogens have been reported in Africa. For instance, the prevalence of HBV and HCV among the general population in the World Health Organization's African Region is estimated at 7.5% and 1.0%, respectively, while for HIV, the prevalence is 3.6% among adults [66][67]. In Africa, EBV has been associated with endemic Burkitt's lymphoma and other cancers such as nasopharyngeal carcinoma [68].

There are relatively fewer bacteria known to cause cancer. Thus far, *Helicobacter pylori,* a gastric ulcer-associated pathogen, is the only bacterium that has been clearly shown to be oncogenic. *H. pylori* causes both gastric cardia and gastric non-cardia adenocarcinoma [69], as well as non-Hodgkin lymphoma of gastric location [70]. Globally, *H. pylori* was the leading cause of infection-related cancer in 2018, being responsible for 810,000 new cancer cases [3]. Limited epidemiological evidence indicates a sexually transmitted bacterium, *Chlamydia trachomatis*, in ovarian cancer [71] and as a cofactor of HPV-associated cervical cancer [72]. This evidence is further supported by the extensive host DNA damage and depletion of the tumor suppressor p53 observed during *Chlamydia* infection [73]. Furthermore, a nationwide cohort study in Taiwan has associated genitourinary tuberculosis with urothelial cancer [74]. Together, these observations underscore the need for more studies to explore the role of bacteria in human cancers.

Three parasites, namely, *Schistosoma haematobium*, *Opisthorchis viverrini* and *Clonorchis sinensis*, are also considered oncogenic pathogens [75]. A link between *S. haematobium* and bladder cancer has long been established [76]. Globally, a total of 550,000 new cases of bladder cancer were reported in 2018 with *S. haematobium* accounting for about 1.1% [3]. The role of *S. haematobium* in bladder cancer is likely to be higher in Africa, where about 90% of those requiring treatment globally for schistosomiasis reside [77].

In addition to *S. haematobium,* three foodborne liver flukes, *Opisthorchis viverrini, Opisthorchis felineus* and *Clonorchis sinensis*, have been linked to hepatic cancers [78][79][80]. Although these parasites have not been reported in Africa, chronic infection by these parasites has been linked to cholangiocarcinoma, a bile duct cancer, in other parts of the world [81]. In 2018, *O. viverrini* and *C. sinensis* together accounted for 3500 (2.7%) of the 130,000 new cases of cholangiocarcinoma reported globally [3].

Aspergillus flavus, a fungus that is more prevalent in tropical regions, produces mycotoxins, particularly B1 aflatoxins, which are known to cause hepatocellular carcinoma (HCC) [82][83], as well as lung cancers [84]. Similarly, two other mycotoxins, ochratoxin and sterigmatocystin produced by fungi of the genus *Aspergillus*, have been implicated in some malignancies such as breast and testicular cancers [85]. In addition, a recent study by Aykut et al. demonstrated that in animal models and humans, mycological dysbiosis of the gut favoring infiltration of the pancreas by *Malassezia* species promotes pancreatic ductal adenocarcinoma [86]. Collectively, these findings highlight the role of fungi or their metabolites in many malignancies.

The involvement of infectious pathogens in carcinogenesis poses a serious threat to cancer prevention, especially in tropical climates, where the burden of infection is high. Unfortunately, many aspects of this involvement such as the mechanism of infection-induced carcinogenesis, have not been elucidated. Hence, further studies are needed to unravel the links between infection and cancers to help accelerate diagnostics, drug and vaccine development.

5. Conclusions

Despite the steady surge of cancers in Africa, significant progress in curbing the disease is still far from realization. Whereas epigenetic studies are a promising avenue for cancer detection and management, there is a significant paucity of data from the African continent. Infectious pathogens mediate epigenetic alterations associated with carcinogenesis, and Africa carries the highest burden of infections. This suggests a predisposition to pathogen-induced epigenetic changes that may lead to cancer development among native Africans. Thus, detailed studies on the patterns of epigenetic deregulation, as well as the role of tropical pathogens in infection-associated cancer in Africa are crucial. Such studies are likely to identify targets for African-specific prevention, diagnosis and therapeutic strategies that could ultimately tame the rising tide of cancer cases and mortalities in Africa.

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