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Letter to the Editor

Cancer and Immunology-the Homeostasis Dance

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Abstract

The human body is made up of not only tissues and blood, but also microbiota on the surfaces of the skin, mucosal membrane of the intestine, urogenital, lungs, and mouth, to form ecological niches. Some of these niches have been well studied, while some are understudied, due to the unknown presence of these microbiota in such systems. The T cell response by the immune system is one step of the cancer-immunity cycle, that maintains the prevention of autoimmunity. Cancer cells have T cell inhibitory signals, including programmed death-ligand-1, which have been identified for the development of new immunotherapies that are specifically responsible for hindering immune effector inhibition, thereby reinvigorating, and enhancing pre-existing anticancer immune response. Previous activity in immune therapies has always considered suppressive factors in the tumour microenvironment without consideration to other factors such as the genetic basis of the immune system. Attention to the immune system has always been on the response to the pathogens, or the threatening foreign target, but not on the genes responsible for regulating the immune system. The immune system is a concert of interactions between existing microbes and host. One of the major tools of cellular interaction is epigenetics. Epigenetic information regulates differentiation and development, thus can impact on pathological condition. Therefore, it is vital to understand the resident parties (constituents) in an ecosystem, the basic system behind the ecosystem and epigenetics interaction within the ecosystem (microbes and host) is vital in cancer development and treatment.

Keywords: irAE, immunotherapy, cancer, microbiota, glutathione, immunity

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Cancer cells have fundamental characteristic trait of genomic and epigenomic DNA alterations. Genetic and epigenetic alterations are essential factors responsible for initiation and progression of cancers[1]. These alterations alter cellular and molecular processes of the cell; and in association with other host and microenvironmental factors, regulate clinical behaviour of both pre-cancer and cancer cells; thereby presenting as biomarkers for determination of cancer risk, prevention, early detection, prognosis, and responses to therapy. Immunotherapy has gained Food and Drug Administration approval since 2017; however, immunotherapy is associated with immune related-adverse event (irAE) and this is common in gastrointestinal, endocrine, dermatological, hepatic and other system including renal, hematologic, pulmonary and

neurological[2]. Although irAEs are mostly managed with corticosteroids, but occasionally, refractory to multiple lines of immunosuppressive agents and fatal at times; the emerging combination therapy in advanced cancer is associated with higher incidence of irAEs[3]. Incidences of irAE includes the occurrence of "pruritis in 15-20% of patients receiving treatment with anti-programmed death 1 (PD-1)/PD-L1 monotherapy, compared to 40% in patients treated with anit-PD-1 + anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy; and the occurrence of diarrhoea and colitis in 10-20% of anti-PD1/PD-L1 versus 44% in anti-PD-1 + anti-CTLA-4"[4]. Resistance in patience with colorectal cancer (CRC) is seen in patience with lack of tumour-infiltrating lymphocytes, tumour mutational burden, interferon gamma expression and low PD-1. The DNA mismatch repair/high microsatellite instability (dMMR/MSI-H) which are 15% of CRC, and MMR/MSI-low are poor responders[5]. The accumulating evidence of the utilization of faecal transplant attracts the focus on the genetic implication of microbes in host phenotypic microenvironments. Although, now understood and accepted that the human system has microorganism (microbiota) as legal residents of the human body; there is limited understanding of the factor responsible in sustaining these legal residents, thus impacting on the understanding of the irAE and its mechanisms. Microbes are specific to host; microbes are extension of self. Gut microbiota are extension of self (individual) and this together with genetic make-up, are determinant of metabolism and physiology of an individual[6]. The tissues of individuals are presented with specific resident microbes, which is referred to as self. "The cancer-immunity cycle which also involves the presentation of antigens[7], relies on presentation of native intracellular proteins or neoantigens produced by cancer cells to effector CD8+ T cells"-Ekine-Afolabi (unpublished). Major histocompatibility complex class 1 (MHC-1) is the key player in the presentation process. Therefore, defects in the presentation process can disrupt check point inhibitors' response. Ekine-Afolabi (unpublished Springer Book chapter) provides in-depth understanding in cancer & immunology book series. Recent evidence has shown the implications of mutations in human leukocyte antigens-human leukocyte antigen (HLA)-A and HLA-B in patients' outcome. Zaretsky et al.[8] demonstrated the decrease in response to PD(L)-1 blockade with loss of MHC-1 expression, indicating that the expression of HLA-A and HLA-B are associated with activation of T cell. Although T cell activation has been associated to glutathione availability and glutathione-S-transferase (GST) functionality; with the polymorphism which occurs in GST which impacts on the T cell functions, there is possibility of association of GST polymorphism with the mutations in MHC-1. Additionally, consideration of the role of microbiota in the immune system is vital. Microbes upregulate the expression of PD(L)-1 in epithelial tumours to enhance the escape from host' immune response or promote immune tolerance[9]. Melanomas show high expression of PD-L1 in about 50% patients[10]. Evidence of expression and function of PD-1 being influenced by glutathione, vitamin D3 and activated protein kinase in hypoxic cell signals, have been reported[11]. The understanding of the function of glutathione and its conjugating element (GST) shows that the immune system cascade which includes antigen presenting cells and the surface proteins, including CTLA-4 that is present on T cells' surfaces are impacted by dysfunction and GST polymorphism. Recently, exosomes involvement has been reported[12]. Although controversial, exosomal PD-L1 expression decreased in patients responding to treatment. Certain cells are dose-dependently influenced by the occurrence of microbes in the niche[13]. The relationship between microbiota and immune cells such as hepatic γδT cells in liver[14], informs on the importance of microbiota in the human ecology, and could inform on the biomarkers for diagnosis, and prognosis. However, the epigenetic control by microbes in these functionalities is yet to be elucidated.

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Conflicts of Interest

The author declared no conflict of interest.

Author Contribution

Conception, design, development, and methodology, as well as, data collection, data analysis, writing and reviewing are all performed by Ekine-Afolabi B.

Abbreviation List

CRC, Colorectal cancer
CTLA-4, Anti-cytotoxic T-lymphocyte-associated protein 4
GST, Glutathione-S-transferase
HLA, Human leukocyte antigen
irAE, Related-adverse event
MHC-1, Major histocompatibility complex class
MMR, Mismatch repair
MSI-H, High microsatellite instability
PD-1, Programmed death 1
PD-L1, Programmed death-ligand-1

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