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REVIEW

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Men's mutagenomic applications and advances in malignancies treatment: a narrative review

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Abstract

Cancer has higher incidence and mortality rates in men compared to women because of the sex genetics. Tumors and malignant diseases such as gallbladder, pancreas and liver cancers have poor prognosis which threaten the human lives. Conducive treatment strategies are thus required to improve men's health. Herein, phenotypic screening of strains, bacteria and microbiomes by the mutational genomics is presented as novel therapeutic strategy. Mutant genomes can reduce toxicity, negative stress and sensitivity of the human body through genomic resetting and recombination. However, studies are lacking on microbial or genome-related therapeutics from the pharmacological perspective. This paper thus presents new strategies and directions in anticancer therapy including mutant genome-based human epidermal growth factor receptor 2 (HER2)/neu, vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR), mitogen-activated protein kinase (MAPK) rat sarcoma/rapidly accelerated fibrosarcoma/MAPK/ERK Kinase/extracellular signal-regulated kinase (RAS/RAF/MEK/ERK) pathway, phosphoinositide 3-Kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, programmed death-1/programmed death-ligand 1 (PD-1/PD-L1), high tumor mutational burden (TMB) and immune checkpoint inhibitor (ICI) therapy. They are all relevant to human physiology. Moreover, strategies for treating aggressive tumors and preventive cancer are discussed along with the clinical case studies for future therapeutic applications.

Keywords

Mutagenomic; Malignancies; HER2/neu; VEGR; Men's health

1. Introduction

Men are more exposed to health risks compared to women because of the differences in sex hormones [1]. Prostate, esophageal, liver, bladder, and melanoma are particularly affected by the gender difference. Men have 34% higher death rates compared to women [2, 3]. It is thus believed that disease susceptibility differs between sexes. The genetic and molecular differences between men and women contribute to the cancer prevalence, where men are more exposed to cancers than women [4, 5]. Sex differences are also evident in the chemotherapeutic anticancer activity. The efficacy and toxicity differences of drugs cannot exclude sex-related responses [6, 7]. Pharmacogenomic improvements between the sexes are thus important for personalized medicine. Gender affects the pathophysiology, clinical presentation, and treatment outcomes. It has vital role in developing future chemotherapeutics and treatment strategies [8].

Malignant patients' samples are analyzed for the microbial host genetic material, *i.e.*, DNA and RNA. It can positively impact patient care and public health [9]. Mutagenesis is a potential therapeutic and defined as the applied mutant breeding required for desired mutations. It originated in plants and used in addressing the resistance to disease or abiotic stress. Furthermore, the linkage map of genetic modifications, biochemical traits and markers is reconstructed for reducing the anti-nutritional factors or enhancing the antioxidants, dietary fiber, nutrients, and medicinal and aromatic values [10]. Strategies for malignancies' treatment via the targeted therapies have emerged in recent years and include gallbladder cancer with poor prognosis. It also refers to new treatments for aggressive tumors and cancers like pancreatic and liver. It includes human epidermal growth factor receptor 2 (HER2/neu), vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR), epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK) or RAS/RAF/MAPK/ERK kinase (MEK)/extracellular-signal-regulated kinase (ERK) pathway, phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB, AKT)/mammalian target of rapamycin (mTOR) pathway, programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1), microsatellite instability-high (MSI-High), high tumor mutational burden (TMB), immune checkpoint inhibitor (ICI) therapy, and DNA damage repair (DDR) deficiency [11].

Phenotypic stripping of strains, bacteria, microbiomes, *etc.* by mutagenesis involves the genome resetting and recombination. It allows for the biological screening to reduce virulence, activate stress sensitivity, and restore gene function against infections and fungi at the earlier disease stages [12]. Microorganisms in human body can affect human physiology as the therapeutic drugs, antibiotics and diet-derived bioactive compounds. However, research lacks on microorganisms and their genomes from pharmacological perspective. It is thus necessary to study the potential therapeutic mutagenomic applications which demonstrate the revival of interaction-based microbial biotransformation in environmental biology [13]. The applications and advances of genomic and mutagenomic technologies in tumor therapy are summarized in this review.

2. HER2/Neu

Human epidermal growth factor receptor-2 (HER2/neu) regulates cell growth and proliferation via the signal transduction pathways. It belongs to the family of four transmembrane receptor tyrosine kinases. HER2/neu has emerged as a novel therapeutic target for treating tumors like the male breast cancer. HER2/neu network has role in the breast cancer regarding cell survival and growth [14]. HER2/neu can predict chemotherapeutic response in breast cancer and used as a predictor of drug response toward hormonal therapy and cytotoxicity. It may also have role in determining potential mechanisms of resistance and sensitivity to various drugs [15]. HER2/neu expression from cell surface to nucleus is blocked by the exogenous blocking antibodies such as trastuzumab which interferes with the ligand activation signal and heterodimerization of HER2/neu on 2C4. Immunological responses are induced by anti-HER2/neu vaccines and overexpression by intracellular single-chain antibodies, transcriptional inhibitors of HER2/neu promoter such as E1A and antisense oligonucleotides or ribozymes, and tyrosine kinase inhibitors of HER2/neu or other EGFRs [16]. Trastuzumab molecularly controls the aggressive behavior in HER2/neu pathway. It is a recommended therapeutic choice for HER2/neu-positive cancer patients with recurrence and used in the targeted therapy [17] as shown in Fig. 1.

3. VEGF/VEGFR

VEGF is a widely secreted homodimeric protein having role in immune regulation and inhibiting T-cell infiltration [18, 19].

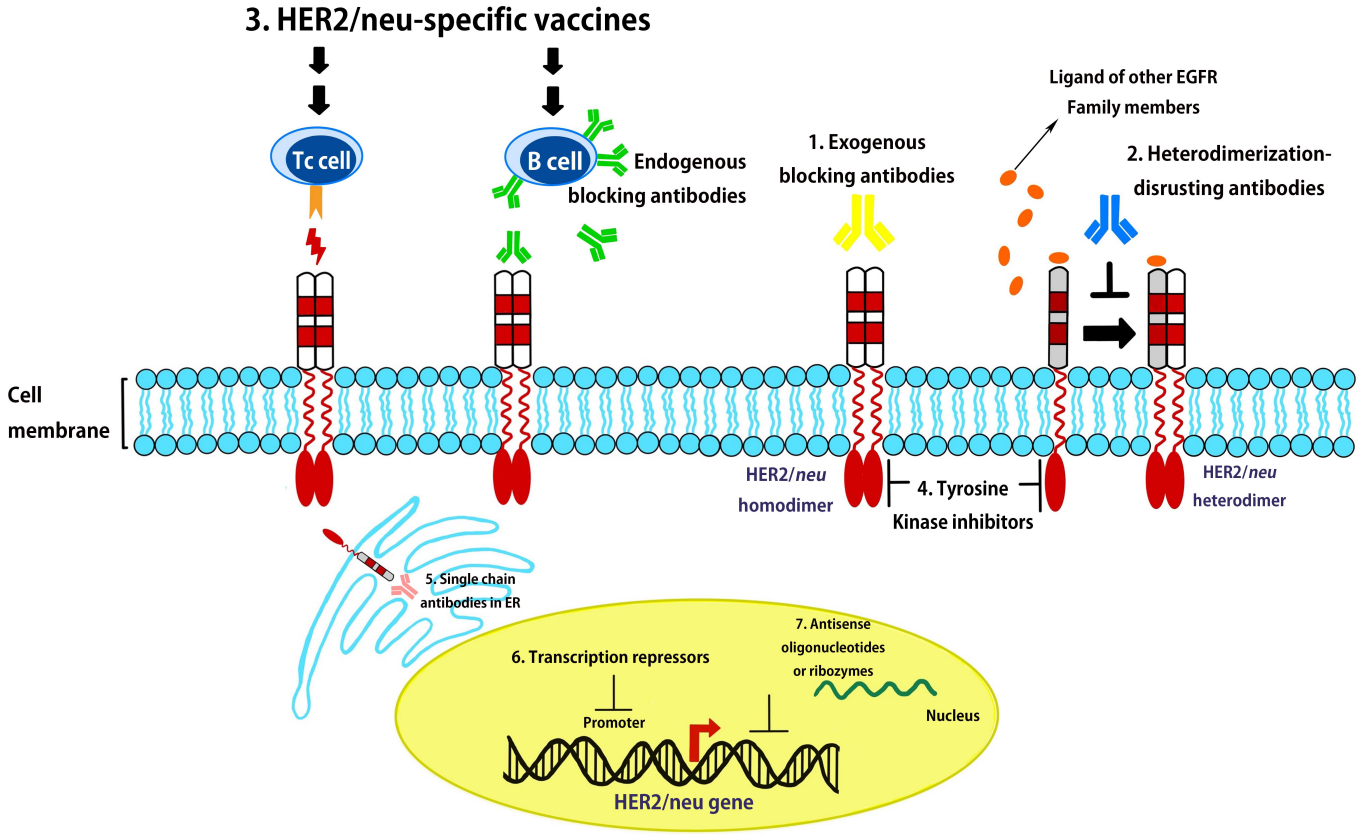

FIGURE 1. Targeting strategies in HER2/neu-overexpressing cancer cells. Targeting strategies for HER2/neu overexpressing cancer cells. Overexpression of HER2/neu, from the cell surface to the nucleus, can be inhibited by (1) exogenous blocking antibodies, such as trastuzumab; (2) antibodies that interfere with ligand activation signaling and heterodimerization of HER2/neu, such as 2C4; (3) immunologic responses induced by anti-HER2/neu vaccines; (4) tyrosine kinase inhibitors of HER2/neu and/or other EGFR receptors; (5) intracellular single-chain antibodies in the ER; (6) transcriptional inhibitors of the HER2/neu promoter, such as E1A; and (7) antisense oligonucleotides or ribozymes. HER2: human epidermal growth factor receptor 2; EGFR: epidermal growth factor receptor.

It is the placental growth factor (PIGF) with range of cellular sources in physiological and pathological settings, and includes VEGF-B, VEGF-C, VEGF-D and placenta. VEGF-A is an important factor in regulating endothelial cell germination, mitosis, cell migration, vasodilation and vascular permeability. VEGF-B activates embryo and is associated with angiogenesis and increased cell coverage. VEGF-C and VEGF-D regulate lymphangiogenesis. PIGFs perform multiple functions including angiogenesis, inflammation and wound healing. VEGF induces positive biological functions by binding to VEGFR and expressed in tissues such as blood vessels, blood, and lymphatic vessels [20, 21].

The lung tumor marker enzymes aryl hydrocarbon hydroxylase (AHH), adenosine deaminase (ADA) and lactate dehydrogenase (LDH) increase the serum levels of inflammatory mediator nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and decrease the total antioxidant capacity (TAC). They are linked to the levels of tumor angiogenesis marker vascular endothelial growth factor (VEGF) and the lipid peroxidation marker malondialdehyde (MDA) which upregulate tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) expressions and anti-apoptotic gene B-cell lymphoma 2 (Bcl-2) [22]. VEGFR regulates the angiogenesis and lymphangiogenesis by binding to VEGF and promotes endothelial quiescence and cytoplasmic attenuation of basal resting or activated VEGFR. VEGF/VEGFR functions make it conducive for range of applications regarding therapeutic usage against human diseases [23]. Furthermore, VEGFA, sVEGFR, TNF-α, IL-1, IL-2 and IL-6 expression levels are increased in the peritoneal fluid of rats. This is superior to gestrinone [24].

4. MAPK (RAS/RAF/MEK/ERK) pathway

MAP kinase (MAPK) catalyzes the phosphorylation of microtubule-associated protein 2 (MAP-2) in insulin-treated 3T3-L1 adipocytes [25]. MAPK is a major signaling pathway regulating several cellular processes including proliferation, differentiation, apoptosis and stress response [26]. MAPK pathway involves kinases, MAPK kinases and MAPKs. It transmits and regulates cell signaling in intracellular and extracellular pathological conditions. RAS/RAF/MEK/ERK pathway is a cascade of all MAPK signaling pathways having role in the survival and development of tumor cells. ERK/MAPK signaling pathway involvement in tumor cell-matrix degradation and tumor angiogenesis is large [27]. Kinases activated by MAPK pathway regulate the migratory functions of cell growth, differentiation, proliferation and apoptosis. This is the RAS-RAF-MEK-ERK-MAPK (RAS-MAPK) pathway which begins its involvement in human cancer because of the abnormal activation of receptor tyrosine kinases and mutations in RAS or RAF genes. This pathway can thus be utilized as an anti-cancer agent. RAS-MAPK molecular mechanism in malignant cells may serve as a combination therapeutic agent in novel anticancer therapies [28].

5. PI3K/AKT/mTOR pathway, PD-1/PD-L1

Immunotherapy against PD-1/PD-L1 is among the popular adjuvant therapies in recent years which treats various tumors including non-small cell lung cancer (NSCLC). However, there are problems like the side effects and drug resistance after using ICIs, which can be modulated by PI3K/AKT/mTOR pathway via PD-L1 expression regulation. Abnormal PI3K/AKT/mTOR pathway activation increases the PD-L1 protein translation, however PD-L1 overexpression can reverse PI3K/AKT/mTOR pathway activation. The combination of therapeutic modalities has greater value in achieving therapeutic efficacy and survival quality. PD-1/PD-L1 inhibitors are employed in studying the intracellular interaction between PD-1/PD-L1 and PI3K/AKT/mTOR pathway [29]. PD-L1 expression is an independent factor of poor prognosis in gastrointestinal stromal tumor (GIST) and depleted T-cells in TILs population or blood. PI3K/AKT/mTOR levels in cluster of differentiation 8 positive ($CD8^+$) T cells as rescued by PD-1/PD-L1 blockade are higher compared to the non-treated [30]. Increased cell-death-ligand (PD-L1) expression in lung diseases such as GIST and pulmonary fibrosis with no effective therapies implies an effective mechanism for treatment and disease development via anti-PD-L1 monoclonal antibodies. This modifies the monoclonal antibody (anti-PD-L1 mAB) for treating pulmonary fibrosis models through histopathological, molecular and functional roles. This potential therapy operates via the downregulation of PI3K/AKT/mTOR signaling pathway. Anti-PD-L1 mABs with autophagy-activating properties have important role in disease treatment, particularly the pulmonary fibrosis [31].

6. High TMB and ICI therapy

The molecular signatures of high tumor mutational burden (High TMB) have the diversity. They are caused by a combination of mutations because of the random errors in DNA replication, and environmental and endogenous factors influencing the mutations. They improve the immune system as shown by the clinical trials. TMB acts as a potential mutation-based biomarker across cancers, particularly in the melanoma. It may enhance the neoantigen formation in cancers such as renal cell carcinoma (RCC) or work in conjunction with immune system in biliary tract cancer, SCLC and mesothelioma [32, 33]. Advances in RNA sequencing (RNA-seq) have an impact on TMBs calculation. Genomic methods have revealed the relationship between TMBs and their impact on patient prognosis. TMB characterization can thus be merged with biomarkers to improve the monitoring and practicality in clinical settings [34]. TMB has emerged as a biomarker for patients receiving immunotherapy in certain solid tumor types. This has been confirmed in a clinical trial of 2767 patients receiving ICI therapy. TMB assists in exploring the cutoffs for survival prediction and identifies universal optimal cutoffs in 8 cancer types [35]. TMB cannot be converted to cobalt (COB) T-cells unless the cancer immune cycle of immune cells, T-cells, is intact. A link is thus required to represent the non-direct relationship between TMB and CD8

T-cell infiltration pertaining to the barrier between immunity and COB T-cells. The modulator of TMB-associated immune infiltration (MOTIF) has therefore been proposed [36].

Biomarkers are essential for the precision immunotherapy in treating advanced non-small cell lung cancer (NSCLC). Tissue-based PD-L1 expression and TMB are employed as the biomarkers to select patients for immunotherapy [37]. However, tissue samples are difficult to access and cannot overcome the spatial and temporal heterogeneity. ICI therapies have reshaped the lung cancer therapeutics by improving patient response, prognosis, and overall survival [38]. However, the variability in treatment response and drug resistance demand predictive biomarkers to select individualized and efficient therapeutic approach. The identification of such biomarkers is on the rise. TMB is the leading predictive biomarker for ICIs efficacy in NSCLC among other tumors. Anti-PD-1/PD-L1 and anti-CTLA-4 antibodies have been clinically utilized. However, the efficiency of these drugs remains unsatisfactory. It has prompted the investigations of novel inhibitors such as LAG-3, TIM-3, TIGIT and VISTA for using them as monotherapy or synergistically with PD-1/PD-L1 or CTLA-4 blockers. In addition, PD-L1^{+} immunohistochemistry (IHC), microsatellite instability/deficient mismatch repair (MSI/dMMR), tumor infiltrating lymphocytes (TILs), microbiome, and circulating tumor DNA (ctDNA) can serve as additional potential biomarkers in lung cancer response to immunotherapy [39–41].

7. DNA damage repair (DDR) deficiency

DNA damage occurs the whole life. It can promote the developmental disorders and lead to chronic diseases like metabolic syndrome, cardiovascular disease and neurodegeneration. Genotoxic stresses on genome contribute to human health and disease. DNA-based mechanistic therapeutic approaches are thus important [42]. The somatic and germline mutations and DDR gene methylation are associated with tumor neoantigenesis and immune infiltration. DDR deficiency is thus involved in the immunotherapy across cancers [43]. DNA damage allows the DNA repair, however severe genotoxic interventions cause the cell apoptosis or necrosis. This can be repaired by autophagy or ultimately by organelle removal. DNA damage response can thus prevent negative prognosis by the progression of cell cycle phases. The DDR system pathways include direct reversal/repair (DR), base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), non-homologous end-joining (NHEJ), and homologous recombination repair (HRR) [44–46]. These are shown in Fig. 2.

The response to DDR or repair of DNA damage promote the normal human development with genomic stability and immune system functioning across the clinical spectrum. It mediates variety of processes such as the functional interplay between DNA damage response and cell cycle checkpoints. It serves as a therapeutic target for rare genetic disorder called microcephaly osteogenesis primitive dwarfism

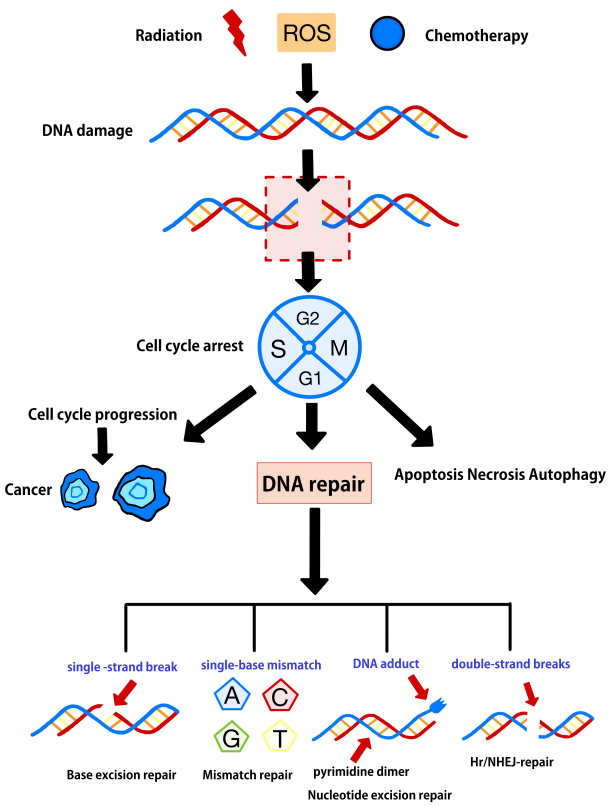

FIGURE 2. DNA damage and main DNA repair pathways. Endogenous reactive oxygen species (ROS) are induced by normal cellular metabolism and can threaten genomic integrity. Exogenous anti-cancer therapies, including ionizing radiation and chemotherapy, can cause DNA damage. When DNA damage occurs, DNA activates mechanistic recruitment activities. However, it can also be subjected to severe genotoxic insults in the cell, leading to cell death or necrosis.

type [47]. DDR maintains genomic stability for the survival and reproduction of all the cells. The sustained instability promotes cancer development based on the cell biological processes. Modifications to the genomic stability-related signaling pathways can be used in preventing the accumulation of DNA genomic stability. These pathways include the signaling cascades of ATM (ATM serine/protein kinase), ATR (ATR serine/threonine kinase), and DNA-dependent protein kinase catalytic subunit (DNA-PKcs). They refer to the molecular mechanisms by which cells maintain genomic stability, and effects of genomic instability are linked to the cancer prevention [48]. DDR interacts with the immune response via a detailed mechanism that correlates with androgen receptor (AR) signaling pathway in prostate cancer. These findings have the implications in development and treatment of prostate cancer. The detection of DDR deficiency strengthens the importance of clinical data on DDR as biomarker and molecular therapeutic target [49].

8. Future direction

Androgen deprivation therapy (ADT) is the first treatment given for prostate cancer (PCA). However, patient response to ADT is varying with 20–30% developing castration-resistant prostate cancer (CRPC). GL-V9 is a drug candidate where anti-PCA effect involves AKT-hexokinase II (HKII). This interferes with AKT signaling feedback activation under AR inhibition conditions and increases the anti-PCA efficacy [50, 51]. The characterization of biological changes in cancer requires gene set enrichment analysis (GSEA) for tumor control in molecular signaling pathways during adenosine deaminase (ADA) OE [52]. PCA's ability to activate mTOR signaling R (mTORC1 and PI3K/AKT/mTOR) drive pathway in tumor growth requires further investigations. The enrichment of downstream processes as activated by mTOR, like the ribosome biosynthesis, DNA repair, lipogenesis, purine synthesis, and the tricarboxylic acid (TCA) cycle in high ADA tumors, is known as the inosine upregulation [53, 54]. ADA importance is confirmed in addition to the positive enrichment of mTOR signaling via purine receptors if the inosine activity is assumed. ADA enzyme levels spike as the tumor progresses [55]. Chronic activation and ADA upregulation over time may induce altered microenvironmental dynamics to cell-adhesive metabolites and changes in extracellular matrix (ECM), demonstrating a potential therapeutic potential for ADA [56].

Systemic therapies comprising of tyrosine kinase inhibitors (TKIs) or chemotherapy are used for hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), however, antitumor responses by ICIs have also been recently identified. This can be an alternate immune strategy for enhancing antitumor response towards first-line treatment with ICIs. Moreover, the monoclonal combination therapy is emerging [57]. ICIs are also the key in treating NSCLC. Infections are preventable and further associated with clinical characteristics such as cytotoxic chemotherapy (CC) and immune-related adverse-events (irAEs) [58]. Radiotherapy is the preferred treatment for HCC, while nifuroxazide has the tumor growth inhibitory effects. This attenuates radiation-induced upregulation of PD-L1 expression and increases PD-L1 degradation via ubiquitination-proteasome pathway. PD-L1 degradation must be increased by the radiotherapy, which in turn increases T-lymphocytes activation and slows the proportion of Treg cells in spleen [59]. These new pathways or genes can improve the potential cancer treatments. Immunologic cell counts and checkpoint-based genes such as nicotinic acid (NIACIN), a specific anaplastic lymphoma kinase (TAE)-684 also explored for treating clear cell renal cell carcinoma (ccRCC). In exploring and modeling the predictive genes for ccRCC patients, tribbles pseudokinase 3 (TRIB3), glutathione-specific gamma-glutamylcyclotransferase 1 (CHAC1), nicotinamide N-methyltransferase (NNMT), EGFR and solute carrier family 4 member 4 (SLCA4) are the group of genes involved in newly discovered nomogram prediction of high-grade RCC [60]. It is thus vital to look beyond the existing therapies in finding new biomarkers for conducive therapeutic developments.

9. Conclusions

Targeted therapies based on mutant genomes, microbiomes, and microbes are the effective combinatorial strategies in treating malignancies and aggressive cancers. New human physiology related strategies in anti-cancer therapy can be presented such as mutant genome-based HER2/Neu, VEGF/VEGFR, MAPK (RAS/RAF/MEK/ERK) pathway, PI3K/AKT/mTOR pathway, PD-1/PD-L1, high TMB and ICI therapy. In-depth studies by applying these strategies through clinical and animal experiments are crucial. Furthermore, it is important to explore the strategic prevention and treatment considering the prognosis through randomized controlled trials or cohort studies.

ABBREVIATIONS

DDR, DNA damage repair; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/ERK kinase; ERK, extracellular-signal-regulated kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B (PKB); mTOR, mammalian target of rapamycin; TMB, tumor mutational burden; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; PD-1, programmed death-1; MSI, microsatellite instability; HER2/neu, human epidermal growth factor receptor-2; PIGF, placental growth factor; VEGFA, vascular endothelial growth factor A; sVEGFR, soluble VEGFR; TNF-α, tumor necrosis factor-α; IL, interleukin; ELISA, enzyme-linked immunosorbent assay; MAPK, RAS/RAF/MEK/ERK; NSCLC, non-small cell lung cancer; GIST, gastrointestinal stromal tumor; High-TMB, high tumor mutational burden; DNA, deoxyribonucleic acid; RCC, renal cell carcinoma; RNA-seq, RNA sequencing; COB, cobalt; MOTIF, modulator of TMB-associated immune infiltration; TILs, tumor infiltrating lymphocytes; ctDNA, circulating tumor DNA; DR, direct reversal; BER, base excision repair; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end-joining; HRR, homologous recombination repair; DNA-PKcs,

DNA-dependent protein kinase catalytic subunit; AR, androgen receptor; ADT, androgen deprivation therapy; PCA, prostate cancer; GSEA, gene set enrichment analysis; ADA, adenosine deaminase; TCA, tricarboxylic acid; ECM, extracellular matrix; TKIs, tyrosine kinase inhibitors; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; CC, cytotoxic chemotherapy; irAEs, immune-related adverse-events; ccRCC, cell carcinoma; Bcl-2, B-cell lymphoma 2; $CD8^+$, cluster of differentiation 8 positive; IHC, Immunohistochemistry; MSI/dMMR, microsatellite instability/deficient mismatch repair; NIACIN, nicotinic acid; TRIB3, tribbles pseudokinase 3; CHAC1, glutathione-specific gamma-glutamylcyclotransferase 1; NNMT, nicotinamide N-methyltransferase; SLC4A4, solute carrier family 4 member 4.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

YP and KHK—Conceptualization, validation, writing–review. YP—methodology, software, formal analysis, investigation, resources, data curation, writing–original draft preparation, editing, visualization. KHK—supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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