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Protein-Based Anticancer Therapy: Applications, Challenges and Future Directions

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ABSTRACT

Protein-based therapies are currently considered as promising strategy for treating cancer, offering targeted interventions that specifically address the underlying molecular mechanisms driving tumor growth and progression. Monoclonal antibodies, enzyme-based therapies, and immunotoxins are examples of protein-based therapeutics that have shown great potential in improving treatment outcomes. Basically, monoclonal antibodies, such as trastuzumab and pembrolizumab, selectively target cancer-specific antigens, inhibiting the growth of tumors and enhancing the ability of immune system to combat cancer. On the other hand, enzyme-based therapies utilize the unique enzymatic activities present in cancer cells to activate prodrugs or enhance the efficacy of anti-cancer agents within the tumor microenvironment whereas immunotoxins combine the targeting capabilities of antibodies with the cytotoxic effects of toxic proteins, enabling selective destruction of cancer cells. Biomarkers and personalized medicine approaches, based on specific protein signatures, aid in early detection, prognosis, and treatment of health disorders. However, challenges, such as resistance to targeted therapies and effective drug delivery, need to be addressed. Notwithstanding, protein-based therapies hold great promise in improving cancer treatment outcomes, paving the way for more effective and tailored interventions that ultimately benefit cancer patients. This review discusses the multifaceted roles of proteins in cancer therapy, highlighting their diverse functions and therapeutic implications as well as their challenges and future prospects.

Key Words: Cancer, Therapy, Biomarker, Monoclonal Antibody, Protein

INTRODUCTION

Cancer remains a significant global health challenge (Ghufran *et al.,* 2023), necessitating ongoing research into effective treatment strategies. Recently, interest in harnessing the potential of proteins for cancer therapy has increased (Cheng *et al.,* 2019, Huang *et al.,* 2021, Zhu *et al.,* 2022). Proteins are essential for many different cellular functions and initiations of cancer cells frequently reflect their dysregulation. Recently, remarkable progress in cancer therapy has been driven by improved evidences on the molecular mechanisms underlying the onset and spread

of cancer. Thus, targeting specific proteins implicated in cancer growth and spread has been identified as a potential approach towards developing novel, safe and effectively tailored therapeutic interventions.

The use of proteins in cancer therapy has garnered significant attention in recent research because they play crucial roles in the complex landscape of cancer biology, serving as critical regulators of cellular processes that dictate tumor initiation, progression, and response to therapy (Fouad and Aanei, 2017). Hence, understanding the intricate interplay between these molecular entities and their aberrant behavior in cancer cells has revolutionized the development of targeted therapies, offering new avenues for precision medicine approaches.

Significantly, the hallmark of cancer is characterized by dysregulated cellular signaling pathways, driven by aberrant expression or activation of key proteins (Fouad and Aanei, 2017). These proteins encompass a wide array of molecules, including growth factors, receptors, enzymes and transcription factors, which orchestrate intricate signaling networks governing cell proliferation, survival, angiogenesis, and metastasis (Shibata, 2021). Additionally, proteins play indispensable roles in cancer biology by catalyzing crucial biochemical reactions essential for maintaining proliferative signaling, avoiding growth inhibitors, and enabling immortality by replication (Baig *et al.,* 2019). Among these proteins, enzymes such as proteases, kinases, and metabolic enzymes emerge as prominent players, modulating various cellular processes implicated in tumorigenesis. For instance, matrix metalloproteinases (MMPs) facilitate tumor invasion and metastasis by degrading extracellular matrix components, while metabolic enzymes such as lactate dehydrogenase (LDH) fuel the energetic demands of rapidly proliferating cancerous cells, via the Warburg effect as glycolysis proceeds in the presence of oxygen (Cassim *et al.,* 2020). Hence, proteolytic enzymes have been evidenced to have potential in cancer therapy.

However, co-medication using hydrolytic enzymes alongside radiation therapy has shown evidence of reducing acute side effects, showing the role of hydrolytic enzymes in cancer treatment (Gremmler *et al.,* 2021). Moreover, bacterial proteins and peptides have garnered attention for their potential in cancer therapy. Peptides targeting specific proteins involved in cancer cell proliferation and migration are undergoing clinical trials, offering promising avenues for treatment (Karpiński and Adamczak, 2018, Wang et al., 2022). Thus, the potential of therapeutic peptides in cancer therapy represents an evolving area of research with promising implications for future treatments.

Biomarkers, specific proteins, or protein signatures associated with particular cancer types, can facilitate early detection, disease progression assessment, and treatment response prediction. Consequently, the identification and validation of biomarkers have paved the way for personalized medicine, tailoring treatment decisions based on individual biomarker profiles. This approach enables more precise and effective therapeutic interventions, maximizing successful outcomes while minimizing unnecessary treatments and associated side effects (Kwon *et al.,* 2021).

Similarly, the advent of targeted therapies has revolutionized cancer treatment paradigms, offering precision-based interventions that selectively inhibit or modulate the activity of specific proteins implicated in tumor growth and survival (Ke and Shen, 2017, Baig *et al.,* 2019). Therefore, monoclonal antibodies, inhibitors of small molecule and inhibitors at immune checkpoints are key modalities of targeted therapy, designed to disrupt distinct molecular targets and signaling pathways (Sasikumar and Ramachandra, 2022). Additionally, as immunotherapy has been used to stimulate the immune system in an effort to eradicate cancer cells; focus has shifted to proteins at immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), which initiate anti-tumor effects that further lead to long-lasting clinical responses in a variety of malignancies (Sasikumar and Ramachandra, 2022). However, the efficacy of targeted therapies and immunotherapies is often limited by intrinsic and acquired resistance mechanisms, emphasizing the need for combinatorial approaches and personalized treatment strategies tailored to individual patients' molecular profiles (Ribas and Wolchok, 2018).

Targeted Therapy Approach

A cornerstone strategy in cancer therapy is targeted therapy which achieves anticancer effects through various mechanisms which includes selective inhibition of cell proliferation, metastasis, and angiogenesis, induction of apoptosis, and reversal of multidrug resistance (Ke and Shen, 2017, Baig *et al.,* 2019). Thus, by pinpointing specific proteins involved in cancer development, targeted therapies offer the potential for more precise and effective treatments while minimizing damage to healthy tissues. These therapies capitalize on the molecular heterogeneity of cancer cells, seeking to disrupt signaling pathways underlying oncogenesis. Consequently, various modalities of targeted therapy have been developed, including monoclonal antibodies, inhibitors of small molecule and inhibitors at immune checkpoints (Baig *et al.,* 2019; Sasikumar and Ramachandra, 2022).

Monoclonal antibodies (mAbs) are engineered proteins binding to specific cell surface receptors or antigens overexpressed on cancer cells, inhibiting downstream signaling pathways or inducing immune-mediated cytotoxicity. For instance, trastuzumab targets the human epidermal growth factor receptor 2 (HER2) in HER2-positive breast cancer, inhibiting receptor activation and downstream signaling (Riecke and Witzel, 2020). Rituximab, in a similar manner, targets CD20 on B-cell lymphomas, resulting in apoptosis and antibody-dependent cellular cytotoxicity (Seyfizadeh *et al.,* 2016).
On the other hand, small molecule inhibitors are synthetic compounds disrupting the activity of intracellular signaling proteins and/or enzymes crucial for cancer growth and survival. These inhibitors compete with endogenous substrates for binding to the target protein's active site, thereby blocking its enzymatic activity. Imatinib, for example, acts as an inhibitor of the BCR-ABL tyrosine kinase within chronic myeloid leukemia (CML) as discussed by Zámečníkova in 2010. Tyrosine kinases serve as crucial facilitators within the signaling cascade, exerting significant influence over various biological processes such as growth, differentiation, metabolism, and apoptosis in reaction to both external and internal stimuli. The disruption of protein kinase function has been identified as a pivotal factor in the development of human cancers as highlighted by Iqbal and Iqbal in 2014. Again, Vemurafenib effectively suppresses the activity of the BRAF kinase within BRAF-mutated melanoma (Kim and Cohen, 2016). This pharmaceutical compound is specifically designed to target the BRAF kinase, disrupting the intracellular signaling pathway known as the mitogen-activated protein kinase (MAPK) cascade that plays a critical role in regulating the proliferation and survival of melanoma cells. Trastuzumab, a monoclonal antibody, is directed towards the HER2 receptor in cases of breast cancer. Its mechanism of action involves binding to the HER2 proteins, thereby preventing the stimulation of cancer cell growth. Moreover, it enhances the immune system response against breast cancer cells by interacting with the extracellular region of the receptor, inhibiting HER2 homodimerization, and consequently blocking HER2-mediated signaling pathways. These targeted therapies have demonstrated significant clinical benefits in specific patient subsets, revolutionizing cancer treatment in certain cases. However, as targeted therapies have transformed cancer treatment and enhanced patient outcomes, challenges persist, including the emergence of undruggable targeted protein, resistance mechanisms, off-target effects, and the necessity for patient stratification based on molecular profiling. Some of these challenges are being surmounted such as the case of Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) a frequently mutated oncogene (Bailey *et al.,*2016; Prior *et al.,* 2020) occurring in various tumor types but not easily circumvented by administering drugs because there are no classic site for the administered drugs to bind (Fan *et al.,* 2018).

Surprising developments have recently been made in KRAS directly targeted medications, particularly in KRAS (G12C) inhibitors. KRAS proteins transition between active GTP-bound states (on) and inactive GDP-bound states (off) as part of their role as a molecular switch (Kim et al., 2020b; Hang et al., 2021). The KRAS G12C mutation alters this switching mechanism, causing the protein to remain in the active GTP-bound state, leading to uncontrolled cell proliferation and tumor formation. Inhibitors targeting KRAS (G12C) function by irreversibly binding to the distinctive cysteine residue of KRAS G12C, trapping it in the inactive GDP-bound conformation and consequently disrupting downstream signaling pathways (Kim et al., 2020b). In clinical trials, medications like MRTX849 (adagrasib) and AMG510 (sotorasib) have shown promising outcomes. In 2021, AMG510 was generated as the first medication to target KRAS (G12C) for therapeutic usage (Hang *et al.,* 2021; Zhu *et al.,* 2021; Zhu *et al.,* 2022). However, combinatorial approaches involving multiple targeted agents or combination with conventional therapies are under investigation as measure to overcome resistance and augment therapeutic efficacy.

Enzyme-Based Anticancer Therapies

Enzymes, being very efficient biological catalysts, have garnered attention for their potential applications in cancer therapy. Although enzymes are not traditionally associated with direct cytotoxicity, but they are explored for activating prodrugs or enhancing anti-cancer drug activity within tumors, thereby showing promise towards augmenting treatment efficacy (Zhang, *et al*., 2017;Thuenemann *et al.,* 2021). An illustrative example is enzyme-based prodrug therapy (Fig. 1), where non-toxic prodrugs are activated in a selective manner by enzymes in cancer cells or the tumor microenvironment, releasing cytotoxic agents specifically within the tumor while minimizing systemic toxicity, thereby killing the cancer cells without damaging normal tissues. Enzymes like carboxypeptidases, beta-glucosidases, and beta-lactamases are investigated for their prodrug activation potential (Walther *et al.,* 2017; Thuenemann *et al.,* 2021).

Moreover, the adoption of enzyme inhibitors in mitigating against cancer cells constitute a crucial class of targeted therapeutics, designed to selectively block specific enzymes critical for tumor growth and survival (Ouertani *et al.,* 2019; Zámečníkova, 2010). By disrupting key enzymatic pathways in oncogenesis, these inhibitors offer a promising strategy to impede cancer progression while minimizing harm to normal cells. Notably, tyrosine kinase

inhibitors (TKIs) represent a prominent group of enzyme inhibitors targeting the aberrant activation of tyrosine kinases implicated in various malignancies. Tyrosine kinases regulate intracellular signaling cascades governing cell proliferation, survival, and angiogenesis, rendering them attractive therapeutic targets. For example, imatinib mesylate inhibits the BCR-ABL tyrosine kinase in chronic myeloid leukemia (CML), suppressing leukemic cell proliferation and inducing apoptosis (Zámečníkova, 2010; Walther *et al.,* 2017). Similarly, inhibitors like gefitinib and erlotinib target the epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC), inhibiting downstream signaling pathways and tumor growth (Li *et al.,* 2015).

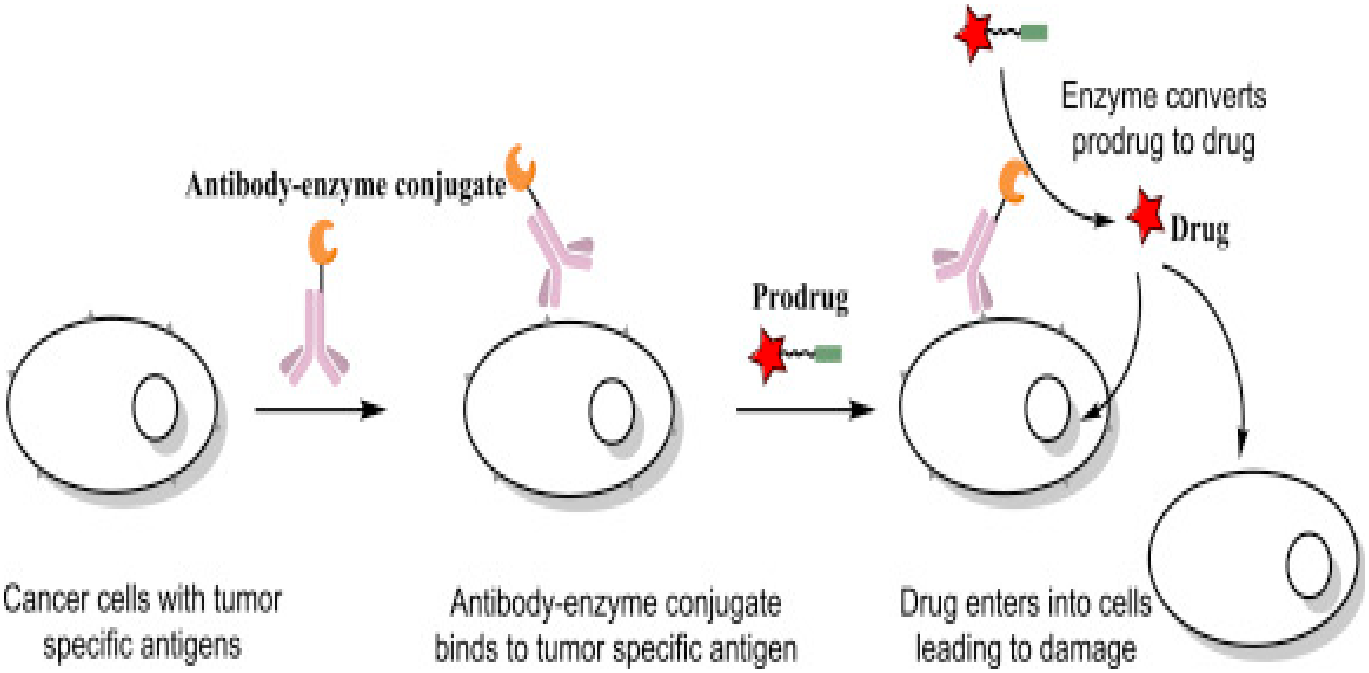

Fig 1: Antibody-directed enzyme prodrug therapy (ADRPT). (Zhang *et al.,* 2017).

Beyond TKIs, other enzyme inhibitor classes, including protease inhibitors and histone deacetylase (HDAC) inhibitors, show therapeutic promise in cancer treatment. Proteases facilitate tumor invasion, angiogenesis, and metastasis by degrading extracellular matrix proteins and promoting tumor cell migration. Consequently, protease inhibitors, like bortezomib targeting the proteasome in multiple myeloma, are effective therapeutic agents in hematological malignancies (Ito, 2020).

HDAC inhibitors modulate gene expression by chromatin structure alteration, inducing growth arrest and apoptosis in cancer cells. Drugs such as vorinostat and romidepsin are approved for cutaneous T-cell lymphoma treatment (Alpdogan *et al.,* 2019). Despite their therapeutic potential, enzyme inhibitors encounter challenges in clinical practice, including drug resistance, off-target effects, and dose-limiting toxicities. Moreover, cancer cell heterogeneity and adaptive responses pose obstacles to long-term efficacy. Therefore, combinatorial approaches, rational drug design, and personalized treatment strategies are pursued to overcome resistance mechanisms and enhance therapeutic outcomes.

Immunotherapy and Protein Targets

Immunotherapy has sufficiently evolved as a revolutionary method of treating cancer, by training the immune system to identify and destroy tumor cells. A crucial aspect of immunotherapy's success lies in identifying protein targets that modulate immune responses within the tumor microenvironment (Sasikumar and Ramachandra, 2022). In retrospect, immunotoxins, a form of immunotherapeutic approach utilizing proteins for cancer therapy, consist of a targeting component, such as an antibody or ligand, fused to a toxic protein or peptide. This targeting component directs the immunotoxin to cancer cells expressing specific surface markers, while the toxic protein induces cell death upon internalization. A typical example involves the usage of ricin, a plant-derived toxin, conjugated to antibodies targeting cancer-specific antigens. These immunotoxins selectively bind to cancer cells, leading to internalization and subsequent inhibition of protein synthesis, ultimately resulting in cell death. Immunotoxins offer the advantage of targeted delivery, enabling the destruction of cancer cells while sparing healthy tissues (Kim *et al.,* 2020a).

Furthermore, immune checkpoint proteins, on the other hand, act as crucial regulators of T cell activation

and function, to maintain self-tolerance and prevent autoimmunity. However, cancer cells exploit immune checkpoints to survive immune surveillance and promote tumor immune evasion. Moreover, by expressing ligands that engage inhibitory T cells receptors such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), tumor cells effectively suppress antitumor immune responses and promote immune tolerance (Seidel *et al.,* 2018, Filippone et al., 2022).

In addition, to counteract immune evasion mechanisms, immune checkpoint inhibitors (ICIs) have been developed for blocking the interaction between inhibitory receptors and their ligands, thereby unleashing antitumor immune responses. Monoclonal antibodies targeting PD-1 (such as pembrolizumab and nivolumab) or those targeting CTLA-4 (such as ipilimumab) have demonstrated remarkable efficacy in various malignancies, leading to durable clinical responses and improved survival outcomes (Hughes *et al.,* 2021).

However, the success of immunotherapy relies on identifying relevant biomarkers to stratify individuals or sufferers that would likely respond to cancer treatment. Tumor expression of PD-L1, the ligand for PD-1, has emerged as suitable biomarker for responding to PD-1/PD-L1 obstruction, with higher expression levels correlating with improved clinical outcomes in certain cancer types (Fig. 2). Additionally, tumor mutational burden (TMB) and microsatellite instability (MSI) have been linked with increased response rates to ICIs, underscoring the importance of tumor immune profiling in patient selection (Le *et al.,* 2015; Rizvi *et al.,* 2015). Immunotherapy presents challenges, including intrinsic and acquired resistance, adverse side effects related to the immune system and identifying optimal combination strategies. Combinatorial approaches, like dual checkpoint blockade or combination with other modalities such as chemotherapy, targeted therapy or radiation therapy are being explored to enhance therapeutic efficacy and overcome resistance mechanisms (Havel *et al.,* 2019).

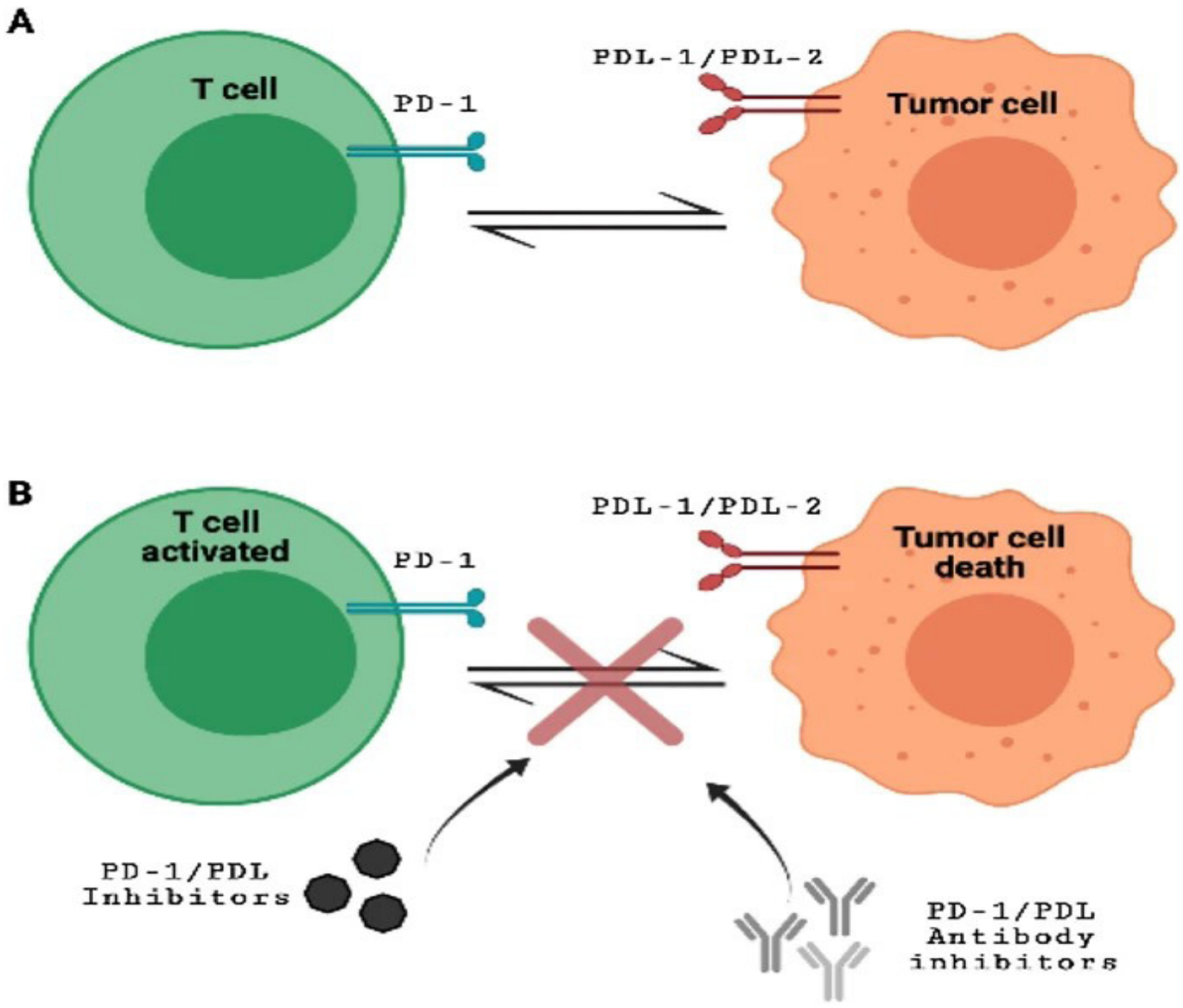

Fig. 2: PD1/PD-L1 immune checkpoint in tumorigenesis (Filliipone *et al.,* 2022)

Biomarkers and Clinical Adoption: Utilizing Protein Signatures

Proteins play a critical role in cancer diagnosis, prognosis, and selection for clinical trials. Proteins have emerged as significant biological molecules with potential as cancer biomarkers. Whether intact or fragments of proteins, these biomarkers hold promise for early cancer detection, therapy prediction, and guidance. The identification and validation of these potential biomarkers as clinical diagnostics offer a substantial opportunity to enhance cancer detection, diagnosis, and treatment efficacy (Kwon *et al.,* 2021).

Furthermore, there is a resurgence of interest in the aspect of amino acid depletion as initiated by enzymes involved in metabolic treatment for cancer. Significantly, amino acid-degrading enzymes have been used in clinical trials to show the effectiveness and safety of enzyme therapy. Thus, in preclinical research, the control of autophagy in conjunction with enzymes that break down amino acids is being investigated as a possible therapeutic strategy that could open up new treatment options for cancer (Wang *et al.,* 2021). Although the use of proteolytic enzyme therapy in complementary oncology has been investigated, the available data does not provide clear proof of the therapeutic effects of enzymes in supportive or antineoplastic treatment. Therefore, the current evidences are insufficient to conclude that enzymes have a beneficial impact on the effectiveness of treatment or the tolerability of different antitumor treatments (Gremmler *et al.,* 2021). Moreover, enzymes as targets for cancer therapy have been extensively explored, particularly regarding their role in angiogenesis surrounding cancer tissue and their vital role in cancer cell proliferation. Targeting these enzymes for cancer treatment can complement existing therapies, potentially enhancing survival rates. Several drugs are undergoing trials for this form of therapy, signifying ongoing efforts to explore the potential of enzymes in cancer treatment (Baig *et al.,* 2019).

In the domain of nanomedicines as concerned with the need for an enhanced cancer therapy, the co-delivery of proteins and drugs has been investigated to achieve improved therapeutic efficacy (Iqbal et al., 2020). Hence, the synergistic effect of protein-based therapy and chemotherapy has demonstrated enhanced therapeutic effects in vivo, indicating the potential of protein-based nanomedicines for improved cancer therapy (Ding et al., 2022; Wang *et al.,* 2022; Fan et al., 2024).

Future Directions

With the introduction of cancer immunotherapy, it is anticipated that the forthcoming trajectory of oncological treatment will prioritize interventions aimed at eradicating cancer, in contrast to the previous focus on therapies designed primarily to extend patient survival. In conjunction with Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) technology and precision medicine, advancements in imaging and detection methodologies are likely to evolve, thereby facilitating expedited diagnosis and treatment of cancer. Numerous experts believe that artificial intelligence (AI)-driven profiling may serve as a valuable tool in determining the most appropriate therapeutic strategy for individual patients.

However, low therapeutic indices and ineffectiveness of drugs have impeded the practical deployment of novel anti-neoplastic medications. Hence, efforts are required to increase the efficiency of both old and new anti-cancer drugs by modifying their pharmacokinetic properties and metabolizing enzymes.

Future research efforts should concentrate on identifying more novel cancer-related proteins suitable for therapeutic intervention. Advances in proteomics and genomics technologies hold promise for identifying new therapeutic targets and biomarkers, facilitating the production/ generation of more effective and personalized cancer treatments.

CONCLUSION

In conclusion, proteins offer exciting avenues for cancer therapy. Targeted therapies, enzyme-based approaches, immunotoxins, and personalized medicine strategies illustrate the potential of these biological molecules in enhancing outcomes from cancer treatment. Thus, research and innovation should continue in the field of protein as it forms profound basis for developing more effective and tailored therapeutic interventions, ultimately benefiting cancer patients' lives.

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