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Targeting CD47-Mediated Immune Evasion and VEGF-Driven Angiogenesis in p53-Mutant Cancers: A Conceptual Framework for Nanoparticle-Based Immunotherapy

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Abstract

TP53 mutations abrogate the control function in cell division, driving oncogenesis and tumor progression. The gene of *TP53*, known as the "Guardian of the genome and maintains genomic stability by regulating the cell cycle, apoptosis, and DNA repair at key checkpoints. Increasing evidence also suggests that *TP53* mutations alter the tumor microenvironment, promoting vascular endothelial growth factor (VEGF)-driven angiogenesis and impairing both innate and adaptive immune responses in cancer cells. These observations provide a rationale for considering angiogenesis, CD47, and immune evasion as therapeutic targets in p53-mutated tumors. In this review, we propose a conceptual nanoparticle-based strategy designed to address both processes with particular emphasis on the CD47–SIRPα axis and VEGF signaling. A ligand-coated nanoparticle can deliver nanoparticles into cancer cells through a ligand-receptor binding site and minimize off target. Another cell component is the surface protein CD47—a prominent "don't eat me" signal—to evade macrophage-mediated phagocytosis. By integrating molecular biology, molecular docking, and nanotechnology, this integrated framework delineates a new era of multi-targeted immunotherapy to overcome therapeutic resistance in p53-mutated malignancies.

Keywords: *TP53* gene mutation; CD47–SIRPα; angiogenesis; tumor microenvironment; nanoparticle-based immunotherapy

1. Introduction

Tumor suppressor gene (*TP53*), is the most commonly mutated gene in human cancers. In addition to losing its tumor-suppressive activity, mutant p53 (mutp53) frequently gains new oncogenic properties of its own, a phenomenon known as "gain-of-function." A growing body of evidence links mutp53 to advanced malignancy and unfavorable clinical outcomes, which makes it an attractive target for new anticancer therapies (1). Functionally, *TP53* is activated by a number of stress stimuli and abnormalities in cell division during the G2/M phase, (2,3). The primary function of the *TP53* gene is to maintain genome stability by arresting the cell cycle in response to DNA damage, promoting cell senescence, and inducing apoptosis. Several possible causes of DNA damage include spontaneous mutations and exposure to carcinogenic substances, such as chemical or physical mutagens (4,5).

Notably, growing evidence indicates that mutp53 not only promote tumor development at the cellular level but also alter the tumor immune environment, reducing effective antitumor responses (6). The tumor suppressor (*TP53*) is critical for preventing neoplastic transformation and tumor progression, However, many challenges remain in improving our understanding of p53 activation-associated disorders (7). Heritable differences in p53 protein can contribute to vulnerable evasion by affecting vulnerable cell recovery to excrescences, cytokine storing in the Tumor micro environment (TME), and inflammatory signaling pathways, In some context, p53 mutations increase the neoantigen load, thereby enhancing the response to checkpoint inhibition (8).

The tumor microenvironment enhances angiogenesis, forming blood vessels and facilitating the oxygen and nutrient supply required for tumor progression (9).

Tumors positive for Programmed Death-Ligand 1 (PD-L1) generally show a favorable response to immune checkpoint inhibitors (ICIs); however, high PD-L1 expression in a tumor is a predictor of poor prognosis [10]. Simultaneous inhibition of the MET, EGFR, and VEGF signaling pathways enhances antitumor activity in non-small cell lung cancer (NSCLC) by blocking receptor crosstalk, thereby halting angiogenesis in cancer cells and dismembering nutrient force to them (11,12,13]. Targeting angiogenesis and immune checkpoints has emerged as a cornerstone of modern cancer immunotherapy (12).

Anti-angiogenic agents, particularly those targeting the VEGF signaling pathway, have demonstrated the ability to normalize tumor vasculature, reduce hypoxia, and enhance immune cell infiltration when combined with immunotherapeutic strategies (14,15).

Immunotherapy has now firmly established itself as a novel pillar of cancer care, from the metastatic stage to the adjuvant and neoadjuvant settings in numerous cancer types (16).
The interaction between PD-1 and PD-L1 negatively regulates the adaptive immune response, mainly by inhibiting the activity of effector T cells while enhancing the function of immunosuppressive regulatory T cells (17).
One of the most prominent innate immune checkpoints is CD47. This ubiquitously expressed transmembrane protein, CD47, functions as a “do not eat me” signal by interacting with signal regulatory protein alpha (SIRPα) on macrophages. This nowhere expressed transmembrane protein, CD47, functions as a “ do not eat me ” signal by interacting with signal nonsupervisory protein nascence(SIRPα) on macrophage (18). Overexpression of CD47 is observed in a wide range of solid and hematological malignancies and is associated with poor prognostic factors and resistance to therapy (19)
By inhibiting macrophage-mediated phagocytosis, CD47 enables excrescence cells to escape ingrain vulnerable concurrence and dampens downstream antigen presentation, which is needed for effective adaptive vulnerable responses. The CD47 protein, as an immunotherapy target, poses challenges for lung cancer treatment (20). These challenges can be overcome by blocking CD47 or destroying it to preclude commerce with SIRP *TP53* mutations abrogate the control function in cell division, driving oncogenesis and tumor progression. These observations provide a rationale for considering angiogenesis, CD47, and immune evasion as therapeutic targets in p53-mutated tumors.
In this review, we propose a conceptual nanoparticle-based strategy designed to address both processes with particular emphasis on the CD47–SIRPα axis and VEGF signaling. A ligand-coated nanoparticle can deliver nanoparticles into cancer cells through a ligand-receptor binding site. Another component is the surface protein CD47—a prominent "don't eat me" signal—to evade macrophage-mediated phagocytosis. By integrating molecular biology, molecular docking, and nanotechnology, this integrated framework delineates a new era of multi-targeted immunotherapy to overcome therapeutic resistance in p53-mutated malignancies. (21).
A new strategy for treating cancer cells involves the use of ligand-coated nanoparticles, protease enzymes, and anti-VEGF agents. The function of the ligands is to direct the nanoparticles exclusively toward cancer cells, ensuring that ligand-coated nanoparticle do not bind to receptors on normal cells. Currently, cancer cell immunotherapy has a relatively low efficiency, ranging from 20% to 40%. Two factors that must be considered in cancer cell therapy are: 1. angiogenesis, both normal and cancer cells require a supply

of oxygen and nutrients via a network of blood vessels; and 2. the CD47 protein, found on the surface of both normal and cancer cells, which provides a "don't eat me" signal through its interaction with SIRPα on macrophages, thereby preventing phagocytosis.

Immunotherapy strategies targeting cancer cells face several limitations, including reduced efficacy and the risk of damage to normal cells. These limitations underscore the need for therapeutic approaches that are more precise, selective for cancer cells, and synergistic. Nanoparticle-based immunotherapy platforms offer a promising approach to overcoming these challenges by enabling targeted delivery of therapeutic agents directly to cancer cells and the tumor microenvironment (22). Functionalized nanoparticles can be engineered to bind cancer-specific surface receptors, enabling the localized delivery of protease enzymes that degrade CD47 and thereby restore macrophage-mediated phagocytosis (23).

A current limitation of immunotherapy is its impact on normal cells; during cancer treatment, many targets miss the intended cancer cells, while normal cells can be affected. Therefore, nanoparticles coated with a ligand, anti-VEGF antibodies to block blood vessel formation, and Protease enzymes to degrade the CD47 protein, respectively. It is one of the immunotherapy alternatives for the future for cancer patients.
In this review, we synthesize current validation linking p53 mutant to vulnerable evasion and Angiogenesis, and critically evaluate emerging nanoparticle-based immunotherapy strategies targeting CD47 degradation and VEGF signaling. By integrating these interconnected pathways, we propose a synergistic framework for next-generation cancer immunotherapy to elicit durable antitumor immune responses and enhance therapeutic efficacy.

2. Molecular basis of p53 and cancer

The p53 protein, as a transcription factor, activates the p21 gene by binding to the p21/CDKN1A promoter and promoting its transcription, thereby arresting the cell cycle. The CDKN1A gene is transcriptionally activated by p53; these elements constitute the p53-p21-RB signaling pathway (15).
Genome-wide experimental and bioinformatic analyses have revolutionized genetic research by enabling scientists to study entire genomes to identify genes associated with diseases, traits, or other biological processes. For example, the p53 protein binding to the

p21 promoter, thereby enhancing transcription of the p21 gene (15,22). The p21 protein inhibits cyclin-dependent kinase (CDK) complexes, which hyperphosphorylate the retinoblastoma (RB) protein (22). This process results in hypophosphorylation of RB, which promotes the formation of RB-E2F complexes and represses transcription of many cell cycle genes (15,23).

The p53–DREAM pathway controls all checkpoints, from DNA synthesis to cytokinesis, including the G1/S, G2/M, and spindle assembly checkpoints. Defects in the p53–DREAM pathway contribute to a general loss of checkpoint control, leading to the development of cancer cells [22]. The function of the *TP53 gene* (wild type) and mutant *TP53* is depicted in Figure 1, mutation of *TP53* gene cause the emergence of cancer cells and uncontrolled cell proliferation,. As a tumor suppressor, p53 plays a crucial role in preventing the development of tumors. Because p53 is essential for regulating DNA repair and cell division, it has been nicknamed the guardian of the genome [24].

Many type of mutation of *TP53* such as missense, frame shift, silent, and nonsense mutation, therefore, molecular analysis p53 mutant as biomarker (25)

Point mutations in the *TP53* gene are the most common in *TP53* mutants, such as the substitution of one purine base for another (e.g., adenine for guanine, A for G) or a purine for a pyrimidine (e.g., adenine for cytosine, A for C). Mutations in the coding frame (exons) of a gene can alter the amino acid sequence of a protein. These changes can alter the characteristics of the protein, performing in loss of function (21). Figure 1 illustrates the function of wild-type and mutant p53. Wild- type p53 maintains genome stability by controlling cell division, apoptosis, and DNA repair.

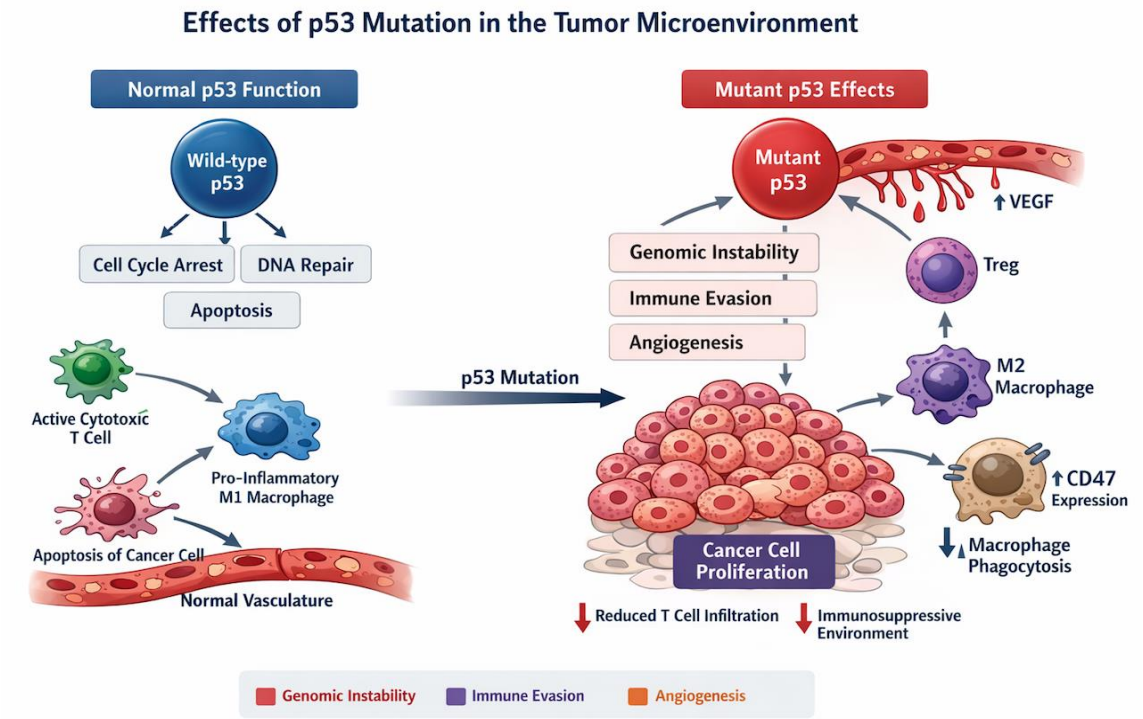

Figure 1. Normal Function of the p53 Gene and mutant. This figure illustrates two distinct pathways: a. Normal p53 Function: p53 activation triggers DNA repair, apoptosis, and cell cycle arrest, thereby promoting genomic stability, and b. Mutated p53 Pathway: p53 mutations lead to disrupted pathways resulting in uncontrolled cell proliferation, Angiogenesis, immune evasion, and resistance to apoptosis.

Gene mutations can occur spontaneously or be triggered by exposure to physical or chemical mutagens, and their molecular basis is closely linked to structural changes in genomic DNA. Mutations in the *TP53* gene can drive cancer aggressiveness by disrupting the mechanisms that regulate cell division [26]. Most of point mutations in the coding frame of the gene create many genetic diseases, such as *sickle-cell anemia*, a disorder due to a single base-pair point mutation in the globin gene, resulting in the substitution of the amino acid from glutamic acid (GAG) to Valine (GTG) in the sixth position of the globin chain [27]. The main types of *TP53* mutations include missense, truncating, in-frame, and splice [28;29]. Observations of the *TP53* mutant have shown that point mutations within the gene's coding region are predominantly present in cancer cells. Mutants of p53 proteins are characterized by a loss of wild-type function and can have a dominant negative effect, but a subset also exhibits a gain-of-function (GOF)[30]. Gain- of-function mutations disrupt p53's excrescence- suppressive conditioning, endowing mutant p53 proteins with new oncogenic parcels [31]. The critical part of p53 as a excrescence

suppressor was further demonstrated in cases with Li- Fraumeni pattern. Li- Fraumeni Syndrome (LFS) cases inherit a shifted *TP53* gene, leading to a dysfunctional p53 protein, which is pivotal for precluding cancer by controlling cell growth, repairing DNA damage, and driving cell death (*apoptosis*). Origin-line TP53 mutations are characterized by a high performance on several cancer types, including bone cancer, sarcomas, brain excrescences, leukemia, and adrenal gland cancers [32,33,34]. The relationship between p53 mutations and CD47 synthesis, tumor angiogenesis, and immune evasion is depicted in **Figure 2**. Nanoparticle-based immunotherapy strategies can overcome several challenges in treating cancer patients. Ligand design is crucial factor, because ligand-receptor binding site have to be strong so that avoid off-target during treatment. Therefore, it is hoped that nanoparticle-based immunotherapy strategies will be able to help the recovery of cancer patients in the future.

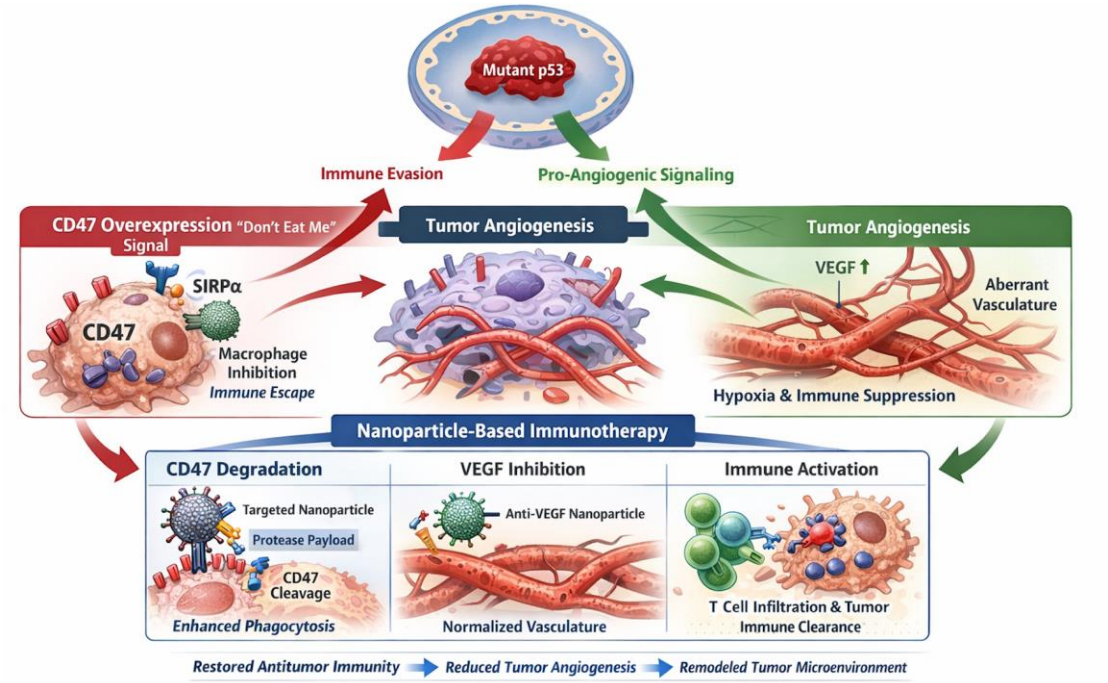

Figure 2. Illustration of tumor-causing p53 mutations and overexpression of the CD47 protein, while the formation of new blood vessel networks (angiogenesis) in cancer cells facilitates metastasis. Nanoparticle-based immunotherapy can be developed to degrade CD47 and inhibit VEGF in cancer cells.

Several evidence showed that increased the *TP53* gene activity underlies the developmental defects in wide range genetic syndrome in mice such as cerebellar hyperplasia, craniofacial defects, hematopoietic defects, and microcephaly, which is characterized by reduced brain size [35]. The role of p53 in the brain may provide therapeutic insights for brain developmental syndromes and cancer [36].

Mutations in the *TP53* tumor suppressor can occur in several ways, and the resulting mutant proteins can have different effects on cancer. Different of the *TP53* mutation types can occur in the genome such as missense, truncating, in-frame, and splice mutations [27, 37]. The p53 mutations in breast cancer are linked to more aggressive growth and cause worse overall survival rates [38].

The most likely cause of *TP53* gene mutations comes from various sources, including physical mutagens such as ultraviolet radiation, which can lead to skin cancer, and carcinogenic substances in food, which can result in somatic mutations in cells of internal organs. Somatic mutations in the *TP53* gene caused by physical or chemical mutagens will not be passed on to the next generation unless the TP53 gene mutation occurs during gamete cell formation, it will be passed on to the next generation. The SNPs of *TP53* mutants can be grouped into three groups based on changes in nucleotide bases, namely: 1. The changes from purine to purine bases (A to G), 2. purine to pyrimidine bases (A to C), 3. pyrimidine to pyrimidine (T to C). Data collection on SNPs in mutant p53 enables the prediction of cancer growth based on *TP53* gene mutations. When the *TP53* gene is mutated, it creates a stable mutant protein whose accumulation is a hallmark of cancer cells. A mutant of p53 is highly associated with advanced malignancies and poor prognosis, which makes it a target for the development of novel cancer therapies [1].

3 Angiogenesis in cancer progression

Angiogenesis, a complex and fascinating process, is the formation of new blood vessels from existing ones. This intricate process is crucial for growth and development in multicellular organisms, as new cell growth requires a nutrient supply through these vessels [38]. Under normal conditions, these signals maintain a balance that ensures blood vessels develop only when and where they are required, such as during growth and healing. However, when this balance is disrupted, it can lead to unusual conditions or diseases [39].

Several chemical signals in the body, including vascular endothelial growth factor and angiogenesis inhibitors are regulated by Angiogenesis. Vascular endothelial growth factor (VEGF), a key player in Angiogenesis, is a signal protein that stimulates the growth of new blood vessels [39,40). Tumor angiogenesis, cardiovascular diseases, and ophthalmic conditions are among the various clinical conditions caused by dysregulated VEGF signaling (39). Angiogenesis inhibitors primarily target molecules in the vascular endothelial growth factor (VEGF) signaling pathway, inhibiting cancer growth and metastasis by preventing the formation of blood vessels that feed cancer (41)

Angiogenesis is crucial for the nutrient supply of wilt-type cells and for the growth, invasion, and metastasis of cancer cells (42,43). Recent advances in molecular and cellular biology have gradually elucidated several biomolecules, including growth factors, chemokines, and adhesion factors, involved in tumor angiogenesis (44).

Blood vessels formation starting before birth and continue to develop throughout our lives. Our bodies rely on tiny blood vessels called capillaries to obtain nutrients. They support cell growth and metabolism by supplying organs and tissues with blood nutrients and oxygen [45]. Angiogenesis or the formation of new blood vessels is triggered by chemical signals sent by cells in hypoxic environments. Its similar to an SOS for assistance. Endothelial cells reorganize in response to signals from other regions enabling the formation of new capillaries. Growth development differentiation the formation of tissues and organs maintenance and physiological regulation all depend on intercellular communication. Cells can interact with one another directly or through ligand-receptor interactions to communicate over great distances [46 ; 47]. Angiogenesis the process that creates blood vessels is primarily influenced by two factors: 1. The emergence of endothelial cell sprouts or new growths from the blood vessel is known as sprouting angiogenesis. A key component in the development of new blood vessels is vascular endothelial growth factor (VEGF). When these sprouts mature they become blood vessels that can supply blood to internal tissue regions that have no other blood supply 2. The microcirculations structure can be significantly altered by the dynamic intravascular process known as intussusceptive angiogenesis. The extension of the intussusceptive pillar seems to be a mechanism for duplicating existing vessels changing the branch angle of bifurcating vessels and pruning unnecessary or ineffective vessels [48]. Angiogenesis works in both healthy cells and cancer depicted on Figure 3. Angiogenesis is used by cancer cells to promote the growth and metastasis of tumors. Pro-angiogenic factors like

VEGF are secreted by tumor cells to promote the development of new blood vessels and guarantee the supply of oxygen and nutrients required for their quick growth. But this process also offers a chance for cancer treatments that are specifically targeted. These treatments can effectively starve the tumor cells preventing their growth and metastasis by destabilizing the angiogenic process. To further improve the tumors ability to elude immune surveillance this disordered vasculature also restricts the infiltration of immune cells including cytotoxic T-cells [49;50]. Additionally in the tumor microenvironment cancer cells use complex mechanisms to inhibit T-cell activity. The expression of immune checkpoint molecules like PD-1 receptors and their ligands PD-L1 (B7-H1) and PD-L2 (B7-DC) is one important tactic. T-cell activation and effector functions are inhibited by PD-1s interaction with its ligands. Tyrosine phosphatase SHP2 is drawn in by PD-1 signaling dephosphorylating important effector proteins and reducing T-cell responses [51;16]. The development of a metabolically aberrant tumor microenvironment the creation of physical barriers that prevent T-cell entry into tumors and the synthesis of molecules that prevent T-cell activation and cytotoxic function are examples of immunosuppressive mechanisms [52].

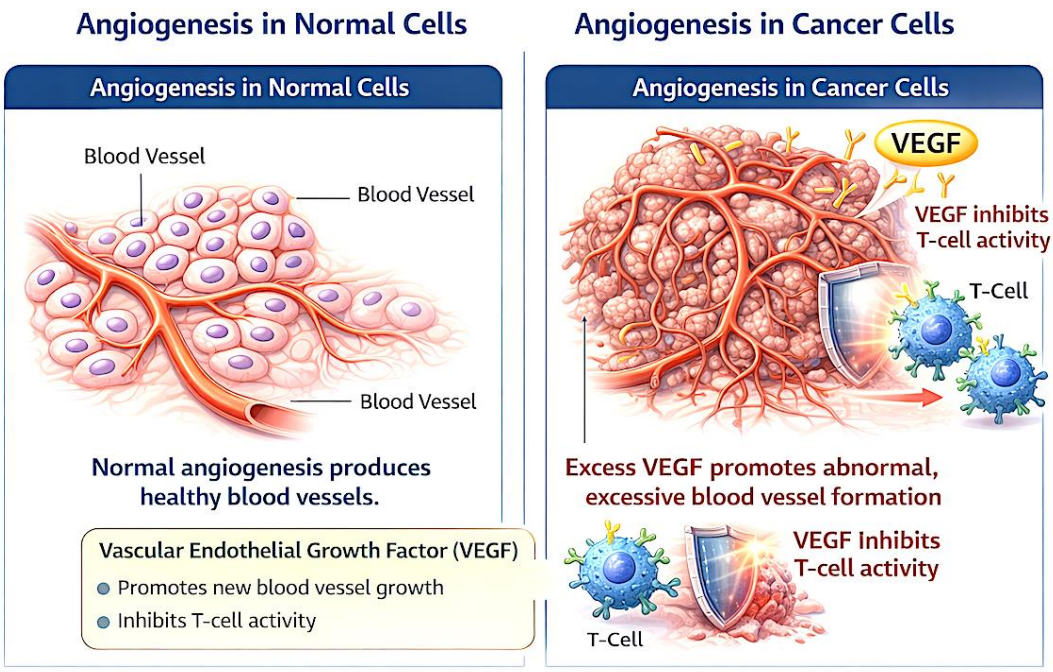

Figure 3. Angiogenesis in wild-type cells (normal cells) and Mutants (cancer cells), which T-cells do not recognize as enemies. Using nanoparticles coated with anti-VEGF and a ligand can block tumor vascularization, allowing T-cells to identify and attack cancer cells effectively.

Understanding these interconnected processes not only highlights their complexity but also the potential for therapeutic strategies that target tumor angiogenesis and immune evasion. The prospect of combining anti-angiogenic agents with immune checkpoint inhibitors could synergistically improve therapeutic efficacy and enhance patient outcomes, offering a ray of hope in the fight against cancer. Specific ligands can bind to cancer cell surface proteins to treat cancer cells via immunotherapy.

4. CD47 degradation and the analysis of cell surface proteins.

CD47 is cell surface protein found in normal cells and cancer cells, these protein function is giving “don’t eat me” signal to macrophages through CD47-SIRPα interaction. The primary function of CD47 is to protect cells from phagocytosis by macrophages.

Using protease enzymes to degrade CD47 is a novel cancer treatment that prevents macrophages from receiving the 'do not eat me' signal. When CD47-SIRPα interacts with the macrophage receptor, cancer cells use the "don't eat me" signal as a defense mechanism. This signal is interfered with by degrading CD47 or blocking the interaction of CD47-SIRPα, which enables macrophages to identify and combat cancer cells (Figure 4).

The lysosome protein RAGA interacts with CD47 and promotes its lysosome localization and degradation. Disruption of RAGA inhibits CD47 degradation, leading to CD47 accumulation, a high ratio of plasma membrane to intracellular CD47 expression, and reduced clearance of cancer cells via phagocytosis [53]. This tactic preserves healthy cells and boosts immune responses by limiting protease activity to cancer cells. The immune evasion of cancer cells is largely dependent on this interaction. By delivering a "do not eat me" signal upon binding to the Signal-regulatory protein alpha (SIRPα) receptor on myeloid cells, it plays a crucial role in maintaining this equilibrium [54]. The elimination of mouse cancer cells is made possible by recent research that demonstrates that blocking the CD47-SIRPα binding sites increases macrophage activity [55]. CD47-SIRPα blockade interaction in

combination with an immune checkpoint inhibitor may have a synergistic effect on antitumor activity, according to preclinical research [56;57]. Cell surfaces harbor the protein CD47, which is essential for self-recognition [49].

Interacting CD47-SIRPα on macrophage inhibits phagocytosis induced by the CD47' "do not eat me" signal. Antibody-dependent cellular phagocytosis (ADCP) by monocytes and macrophages is a key factor in the effectiveness of many therapeutic monoclonal antibodies (mAbs), including anti-CD20 rituximab (RTX), which targets CD20+ B-cell non-Hodgkin lymphomas (NHL) [58;59]. In mouse xenograft models of human cancer, it was discovered that an engineered recombinant SIRPα protein, which has a higher affinity for CD47 than the WT protein and significantly inhibits the endogenous CD47-SIRPα interaction, increased the efficacy of therapeutic mAbs such as rituximab, trastuzumab, and alemtuzumab (an Ab to CD52) [60]. *In vitro* phagocytosis and in vivo immune responses were improved by the engineered SIRP receptor, which demonstrated a 5000-fold increase in affinity for CD47 and synergy with all tested tumor-specific antibodies [60]. Protease enzymes are a novel way to inhibit CD47 on cancer cells, boosting the immune response. This tactic uses ligands and nanoparticles coated with protease enzymes that selectively bind to cancer cell receptors while avoiding binding to wild-type cells. Labeling the ligand's C or N atoms enables in vitro evaluation of the ligand's interaction with cancer cell receptors. In vitro ligand-receptor interactions in cancer cells can be examined with a gamma counter or Positron Emission Tomography (PET). Research can use radioactive labels on the N-ligand atoms to evaluate how well ligands bind to the surface of cancer cells.

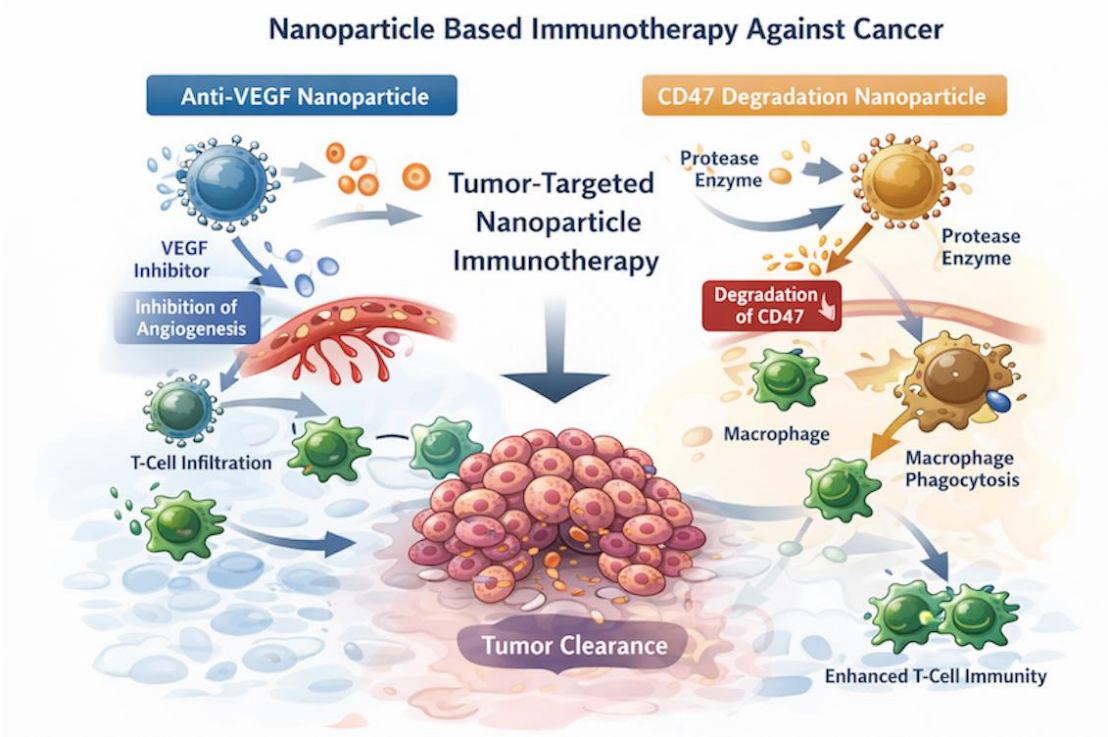

Figure 4. Nano coated with protease enzymes and Ligand; The ligand will direct the nanoparticles to the cancer cells, then bind to the ligand-receptor site, then release the protease enzyme to degrade the CD47 protein, so that there is no signal "do not eat me." from CD47 to the macrophage.

5. Advanced Immunotherapy using Nanoparticles

Recent advances in immunotherapy engineering have enabled innovative approaches to target and eradicate cancer cells more efficiently. The use of nanoparticles coated with protease enzymes and specific ligands designed to bind to cancer cell surface proteins represents a promising strategy. These engineered nanoparticles serve as a vital tool for drug optimization and offer various benefits in cancer immunotherapy [61].

Nanoparticles have the capability to effectively transport medications or protein fragments to tumor tissues via passive or active targeting processes, thus enhancing treatment outcomes while minimizing harm to healthy tissues[62]. Although silica nanoparticles can effectively deliver miR-34a into both normal and cancer epithelial cells grown in culture without significant toxicity, their use in clinical practice is still severely limited by their cytotoxicity and limited uptake [63; 64]. It is possible and safe to use indocyanine green (ICG) in combination with carbon nanoparticles (CNs) to detect sentinel lymph nodes (SLNs) in patients with papillary thyroid microcarcinoma (PTMC) [65]. Their findings suggest that this combination imaging method eliminates more SLNs

and confirms metastatic lymph nodes more successfully than carbon nanoparticles alone. Protein-and ligand-coated nanoparticles show promise for use in cancer treatments in the future. The application of Nanocarriers (NCs) provides a promising strategy to solve the problems faced by traditional chemotherapy drugs, like the imprecise delivery, poor bioavailability, high dose requirement, and the tendency to develop multidrug resistance [66]. We suggest employing immunotherapy to target cancer cells with nanoparticles coated with particular ligands and protease enzymes on this occasion. Immunotherapy can be used to treat cancer by attaching specific ligands to proteins on cancer cells' surfaces. By instructing the protease enzyme to break down the CD47 protein, this ligand stops the CD47-SIRPα interaction and enables macrophages to eliminate cancer cells. Using nanoparticles coated with ligands that target specific cancer cell receptors and protease enzymes offers several benefits. By selecting ligands on the surface of nanoparticles to bind receptors overexpressed on cancer cells, this method offers the advantage of specifically targeting cancer cells. This technique improves tumor tissue retention by allowing nanoparticles to discriminate between targeted and healthy cells. Cancer cells are targeted by nanoparticles coated with ligands and protease enzymes. Targeting ligands that attach to cancer cell receptors can also be added to nanoparticles to enhance antitumor immune responses and minimize off-target effects. 1. e. By engineering nanoparticles to display antigens linked to tumors, antitumor immune responses can be triggered. The toxicity of nanoparticles may be reduced by recent developments in materials science, particularly in nanoparticle engineering. A hybrid material that blends the physical characteristics of the nanoparticle with the biological activities of the peptides, a peptide-nanoparticle conjugate is produced by coating a nanoparticle with ligands using a short polypeptide [67]. Because ligands can direct nanoparticles into cancer cells, combinations of protease enzymes and ligands specifically designed for targeted cancer cell receptors offer a multimodal approach to cancer immunotherapy. Moreover, reduce unintended effects. This technique boosts the immune system to fight tumors and improves drug delivery. As seen in Figure 4, nanoparticles are coated with ligands and protease enzymes. The ligands can guide the nanoparticles toward cancer cells, where proteases can cleave CD47. These developments have greatly advanced the development of more individualized and efficient cancer treatments. Protein nanoparticles are an example of an organic nanoparticle that might be a good choice for lowering toxicity during cancer treatment. A disulfide-containing linker (Luc-linker@HFn) conjugates the luciferin probe-based bioluminescent nanoparticle to its surface, and it

undergoes glutathione-induced cyclization in the cytoplasm of tumor cells [68]. Protein nanoparticles have been developed as ideal drug delivery vehicles for cancer treatment, aiming to reduce drug toxicity and enhance therapeutic efficacy, protein nanoparticles can be combined with inorganic nanoparticles or contrast agents to form multifunctional theranostic platforms (69). Engineered nanoparticles that provide a comprehensive approach to cancer immunotherapy are produced by combining protease enzymes with ligands that target particular cancer cell receptors. Nanotechnology has transformed cancer research, with nanoparticles emerging as powerful platforms for therapy and diagnosis due to their tunable physicochemical properties and biocompatibility. Current insights into the strategies for developing actively targeted nanomedicines across various cancer types are also provided, thus addressing relevant challenges associated with drug delivery barriers.

By specifically identifying and targeting cancer cells, these nanoparticles reduce off-target effects (70). In this instance, they enhance the delivery of medicinal medications and boost the immune system to fight off malignancies or tumors. These developments mark a breakthrough in the search for more individualized and efficient cancer treatments. These developments greatly contribute to the development of more individualized and efficient cancer therapies. Protein nanoparticles are an example of an organic nanoparticle that might be a good choice for lowering toxicity during cancer treatment. Recent research indicates that a disulfide-containing linker (Luc-linker@HFn) conjugates the luciferin probe-based bioluminescent nanoparticle on its surface before undergoing glutathione-induced cyclization in the cytoplasm of tumor cells [68]. To reduce drug toxicity and increase therapeutic efficacy, protein nanoparticles have been developed as ideal drug-delivery vehicles for cancer treatment. There are several problems with protein nanoparticles such as some proteins are not that stable, and their structures may change during synthesis of the nanoparticles [69]. These nanoparticles can minimize off-target effects by specifically identifying and targeting cancer cells, and future directions in personalized cancer nanomedicine approaches are delivered, emphasising the imperative for continued optimization of nanocarriers in precision cancer medicine.

(70, 71). Nanotechnology has transformed cancer research, with nanoparticles emerging as powerful platforms for therapy and diagnosis due to their tunable physicochemical properties and biocompatibility. Nanoparticles enable targeted drug delivery, improved pharmacokinetics, and reduced systemic toxicity compared with conventional

therapies/Here, they enhance the delivery of medicinal drugs and boost the immune system to fight tumors or cancerous cells. These developments mark a breakthrough in the search for more individualized and efficient cancer treatments (72).

6. Conclusion

This paper proposes three strategies to advance cancer cell immunotherapy for future patient outcomes. Three potential success factors for advanced immunotherapy strategies include: **first**, in-depth studies of ligand-receptor interactions in cancer cells with strong affinity of ligand-receptor binding sites. The **second** approach involves nanoparticles coated with protease enzymes and ligands specific for cancer cell surface receptors, offering a targeted approach to degrade CD47 in cancer cells. Degradation of CD47 in cancer cells prevents its interaction with SIRPα, allowing macrophages to recognize and phagocytose them. Finally, **the third** approach, inhibiting VEGF-mediated angiogenesis using anti-VEGF-coated nanoparticles, can block tumor vascularization, allowing T-cells to identify and attack cancer cells effectively. These strategies present a multifaceted approach to cancer immunotherapy, combining precision targeting, immune activation, and tumor growth inhibition. An off-target ligand binding site to cancer cells can be observed in an *in vitro* experiment using a radiolabeled ligand, which was then injected into both cancer cells and normal cells in a separate study. The affinity of the ligand for cancer cell receptors can be detected by Positron Emission Tomography (PET). Furthermore, research and development will be critical in translating these strategies into affordable, personalized treatments for cancer patients worldwide.

Abbreviations

Ab	Antibody
ADCP	Antibody-Dependent Cellular Phagocytosis
CDK	Cyclin-Dependent Kinase
CD47	Cluster of Differentiation 47
CDKN1A	Cyclin-Dependent Kinase Inhibitor 1A
CNs	Carbon Nanoparticles
DNA	Deoxyribonucleic Acid

EGFR	Epidermal Growth Factor Receptor
E2F	E2 Transcription Factor
G2/M	Gap 2/Mitosis
GOF	Gain-of-Function
HFn	Heavy-chain ferritin
ICG	Indocyanine Green
ICIs	Immune Checkpoint Inhibitors
LFS	Li-Fraumeni Syndrome
mAbs	Monoclonal Antibodies
MET	Mesenchymal–Epithelial Transition Factor
miR-34a	MicroRNA-34a
mutp53	Mutant p53
NCs	Nanocarriers
NHL	Non-Hodgkin Lymphoma
NSCLC	Non-Small Cell Lung Cancer
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PET	Positron Emission Tomography
p53	Tumor Protein p53
p21	Cyclin-Dependent Kinase Inhibitor 1A Protein
PTMC	Papillary Thyroid Microcarcinoma
RAGA	Ras-related GTP-binding protein A
RB	Retinoblastoma Protein
RTX	Rituximab

SHP2	Src Homology 2 Domain-Containing Protein Tyrosine Phosphatase 2
SIRPα	Signal Regulatory Protein Alpha
SLNs	Sentinel Lymph Nodes
SNPs	Single-Nucleotide Polymorphisms
T-cell	T Lymphocyte
TME	Tumor Microenvironment
TP53	Tumor Protein p53 Gene
VEGF	Vascular Endothelial Growth Factor
WT	Wild Type

Author Contribution:

Ishak: Conceptualization, Methodology, Investigation, and Writing – Original Draft, Visualization. The author agrees to the published version of the manuscript.

Conflicts of interest

The author declares: no competing interest in this study.

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