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Principle Therapeutic Targets in Anticancer Treatment

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ABSTRACT

The typical cell regulatory mechanisms that control cell survival, proliferation, and differentiation are lost in cancer, which is a complex disease. Targeted therapy has replaced traditional chemotherapeutics in the management of many cancers as a result of molecular and genetic advances in the field of oncology research. Using medicines intended to interfere with particular molecules that have a particularly specific or greater expression profile in cancer cells and are essential for cancer development and progression is the fundamental idea underlying targeted therapy. Conventional methods for destroying cancer cells failed to work. In certain cases of cancer, targeted chemotherapy proved helpful, but its efficacy has frequently been constrained by drug resistance and adverse effects on healthy tissues and cells. Numerous promising therapeutic targets have been discovered in the recent years for the successful treatment of cancer. Several of these promising anticancer targets are discussed in the current review article, including kinases, farnesyl transferase, aromatase, tumour ability to induce angiogenesis, tumour ability to resist apoptosis, tubulin, vascular targeting agents, cancer stem cells, monoclonal antibodies, and epigenetic targets.

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1. INTRODUCTION

Uncontrolled cell growth is the primary cause of cancer, a disease that is a leading cause of death globally. There are about 60 different human physical organs affected by its 200+ various types. (1)

A significant challenge in the development of anti-cancer therapies is creating a medication that selectively and specifically targets cancer cells. Most tumours are hard to find when they first appear, and later cancer-related deaths can be attributed to tumour spread. (2)

Anticancer medicines try to stop cancer from spreading and growing. (3)

Some of the treatments used to treat cancer include surgery, chemotherapy, and radiation therapy; they can be used separately or in combination. Modern anticancer drugs use molecular-targeted therapy, such as focusing on proteins with abnormal expression inside cancer cells, instead of the traditional chemotherapeutics' direct DNA-targeting approach. When compared to traditional anticancer drugs, these molecularly targeted therapies selectively kill cancer cells while causing less damage to healthy cells. Targeted drugs block particular cell signalling pathways that are involved in the cancer cells' aggressive nature. Chemotherapy has gradually improved as a result of the discovery of new anticancer drugs. (2)

Although certain tumours have responded well to targeted chemotherapy, there are some serious downsides, including the emergence of drug resistance and harm to healthy tissues and cells. Drug transporters are overexpressed in many cancer cells, which lowers the levels of drugs inside the cells. (2)

The development of anticancer medications has a very low success rate and effectiveness when compared to the investment. Cancer is a complicated disease, and the majority of anticancer drug development has been concentrated on one promising target. The academic world has made significant efforts to permanently and fully remove cancer. But because of the Despite the disease's complicated genesis, little progress has been made the majority of drug failures humans can be brought on by an ignorance about the genesis of the illness and an exaggeration of the overexpressed aim. The failure of various cancers is related to cancer stem cells. Chemotherapeutics need to be researched more.(2)

Conventional chemotherapy has been the go-to cancer treatment since it was first used more than 60 years ago. Chemotherapeutic drugs can also kill healthy cells like the intestinal epithelium even if they are intended to kill quickly dividing cells like cancer cells. Targeted cancer therapies are a new generation of cancer therapeutics that aim to only treat cancer cells. (4)

Like conventional chemotherapy, targeted cancer therapies use drugs to inhibit the spread of the disease. On the other hand, targeted cancer treatments work through different pathways than conventional chemotherapy. As the name suggests, targeted medicines specifically target certain cancer-related proteins. By concentrating on specific molecular changes that are particular to a given malignancy, targeted cancer therapies may be more therapeutically beneficial for a variety of cancer types, including lung, colorectal, breast, lymphoma, and leukaemia. Despite the fact that the US Food and Drug Administration (FDA) has approved more than 15 targeted cancer medications since 2000, the majority of these drugs are still undergoing pre-clinical and clinical testing before being licenced for use either alone or in conjunction with other regimens. (4)

2. Potential Cancer Target:

• Targeting the inhibition of signal transduction

Cell signal transduction is the process through which cells respond to external stimuli. When tumour cells expand and metastasize, the growth factor and its receptors operate inappropriately, which causes unchecked tumour cell multiplication. When anticancer medications are taken in combination, a potential NDD may be the selective suppression of autocrine and paracrine cell signal transduction, affecting the system of auto-control growth regulation. (5)

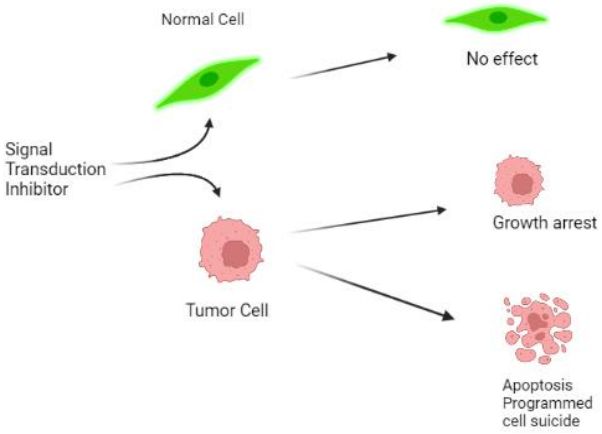

Fig .1 Signal Transduction Inhibitor.(6)

By targeting tyrosine kinase and farnesyl transferase, inhibition of signal transduction take place as follows,

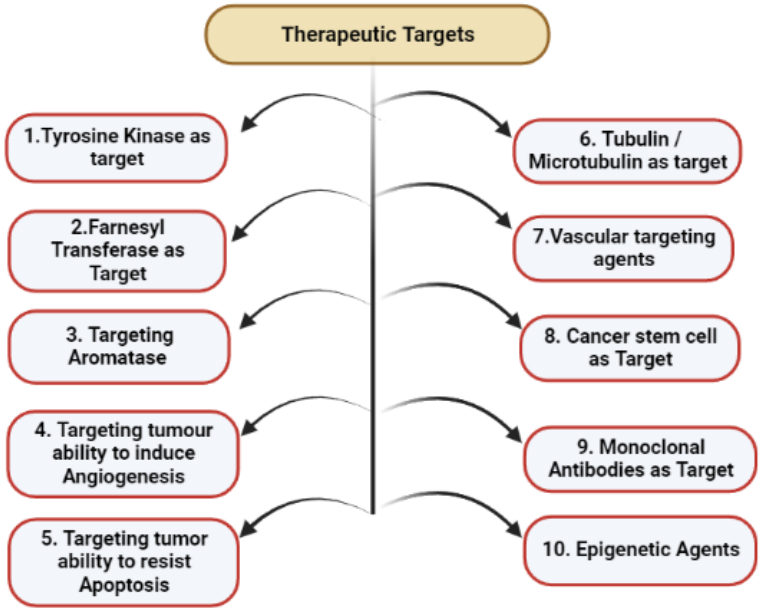

Fig .2 Targets.

2.1. Tyrosine Kinase (TK) as Target:

Tyrosine kinases have become a novel and intriguing therapeutic target for cancer. the significance of tyrosine kinases in cancer and the creation of specific tyrosine kinase inhibitors for cancer treatment, with a focus on small chemical inhibitors. (7)

The TK family of mono-transmembrane -helix proteins include membrane receptor tyrosine kinases as well as cytoplasm non-receptor tyrosine kinases. The membrane receptor tyrosine kinases linked to cancer include the vascular endothelial growth factor receptor (VEGFR) and the epidermal cell growth factor receptor (EGFR), while non-receptor tyrosine kinases include, among others, Src kinase and Bcr- abl kinase. Following ligand binding, the receptors dimerize or couple with the cytoplasm kinase, TK is activated, and the C terminal tyrosine residues are phosphorylated by the tyrosine kinase domains, a process known as autophosphorylation. This is followed by a phosphorylating activating process known as a kinases cascade, which leads to signal amplification. (5)

Throughout the process, a variety of proteins are phosphorylated, which triggers biological processes such cell division, adhesion, proliferation, morphogenesis, angiogenesis, metastasis, and anti-apoptosis. The ATP-binding region of EGFR is connected to TK activity, affecting the production of tumorigenic signals. TK participates in EGFR function. A novel method of treating cancer will be made possible by the suppression of TK, which will suppress EGFR-related cell activity. (5)

PTKs have been targeted in a number of ways, which summarises the categorization of these inhibitors based on how they work. Tyrosine kinases are multidomain proteins found in receptors. The catalytic domain (Mg-ATP complex binding site) has become the most promising drug design target in recent years. (7)

The first medication to be brought into clinical oncology was imatinib, which was then followed by medications like dasatinib , gefitinib, erlotinib, sorafenib, and sunitinib.(8)

2.2. Farnesyl transferase as a Target:

The genes necessary for optimal mammalian cell function are kept in the nucleus of a cell. Unauthorized gene/protooncogene activation is one of the main mechanisms causing improper signal transduction, proliferation, and malignant changes. Among the many genes investigated in cancer research, activated Ras (rat sarcoma) is the oncogene most frequently discovered in human tumours. Ras proteins, which are involved in cell signalling, cell proliferation, and cell death, are expressed as a result of Ras gene activation. (9)

Signalling for cell growth and differentiation is carried out by the low-molecular weight GDP/GTP-binding guanine triphosphatase known as Ras protein, which is generated by the Ras gene. Ras typically performs its function during signal transduction in a GTP-binding

state. Ras, on the other hand, is unable to cling to the membrane because of its weak hydrophobicity. It must be farnesylated by enzymes, which increases its hydrophobicity and enables it to adhere to the inner membrane of the cell. Once Ras protein had served its purpose, it was broken down into the GDP-binding form. Ras mutations, including constitutive Ras mutations, contribute to the development, invasion, and spread of cancer. The activation has been reported. Cancer develops as a result of excessive cell differentiation and proliferation brought on by unchecked cell growth signals. (5)

RAS activating oncogenic mutations are common in cancer, present in 30% of solid adult tumours. Originally created as a therapeutic method to stop cell signalling in RAS-transformed cells, farnesyl protein transferase inhibitors obstruct an important step in the post-translational processing of the RAS protein. (10)

2.3. Targeting Aromatase:(Hormonal targeting)

60% to 70% of breast tumours are oestrogen receptor (ER) and/or progesterone receptor (PGR) positive(11), which indicates that the majority of breast tumours are hormone-dependent. Estrogenic pathways have been proposed for their role in the creation and proliferation of these tumours because they contain higher quantities of oestrogens. Oestrogen levels in breast cancer tissues are around 20-fold higher than those in plasma circulation. Hormonal targeted therapy that concentrates on estrogenic signalling systems has consequently evolved into the gold standard of care for breast cancer. (9)

The cytochrome P450 family of enzymes, including the human aromatase, is produced by the CYP19A1 gene on chromosome 15. It facilitates the rate-limiting and final step in the synthesis of oestrogens, the aromatization of androgens to oestrogens.

It has been discovered that compared to non-cancerous cells, breast cancer tissues express aromatase and produce higher oestrogen. This is one of the main causes of aromatase's enormous level of interest as a breast cancer treatment. (12)

It is composed of two essential proteins: NADPH-cytochrome P450 reductase, which transfers reducing equivalents to cytochrome P450arom, and cytochrome P450arom, a haemoprotein that converts C19 (androgens) to C18 (oestrogens). Androstenedione, the selected substrate, undergoes three successive oxidations before being aromatized. Steroid and non-steroidal inhibitors make up the two kinds of aromatase inhibitors (Ai). Steroidal inhibitors function by covalently binding to an enzyme and making it inactive. They are often

referred to as enzyme inactivators or Type I inhibitors. Inhibitors that are both competitive and irreversible are present. (9)

Around the same time that specific aromatase inhibitors were being created, it was revealed that the anti-epileptic drug aminoglutethimide might reduce the production of adrenal steroid hormones by inhibiting numerous cytochrome P450 enzymes. (12)

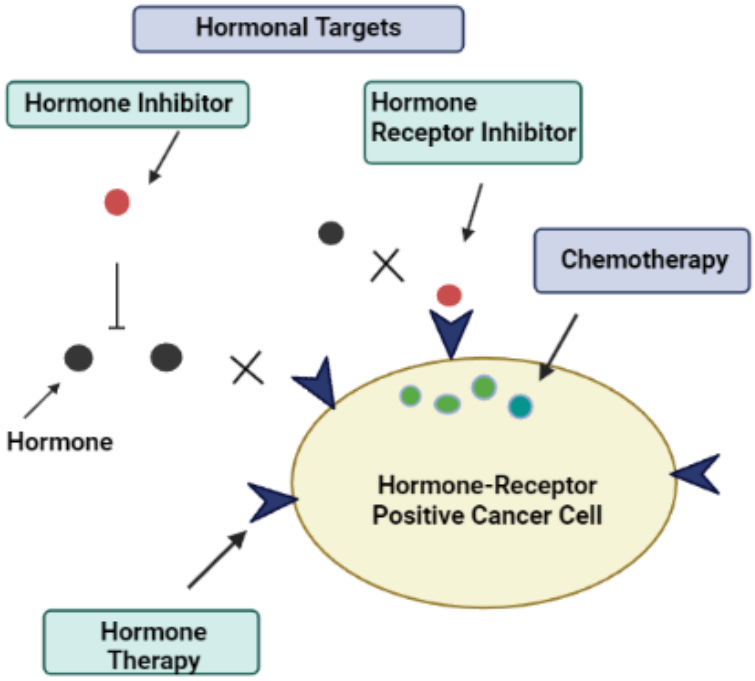

Fig .3 Hormonal Targets.(13)

2.4. Targeting Tumour ability to induce Angiogenesis:

For many solid tumours, particularly their metastases, tumour angiogenesis has been suggested as a potential therapeutic target. The idea was exciting because freshly formed blood capillaries can enter most solid tumours and metastases. (14)

The process of angiogenesis, which is initiated by tumour cells, involves the slow development of tumour cells devoid of blood vessels and the subsequent release of particular angiogenic growth factors. (5)

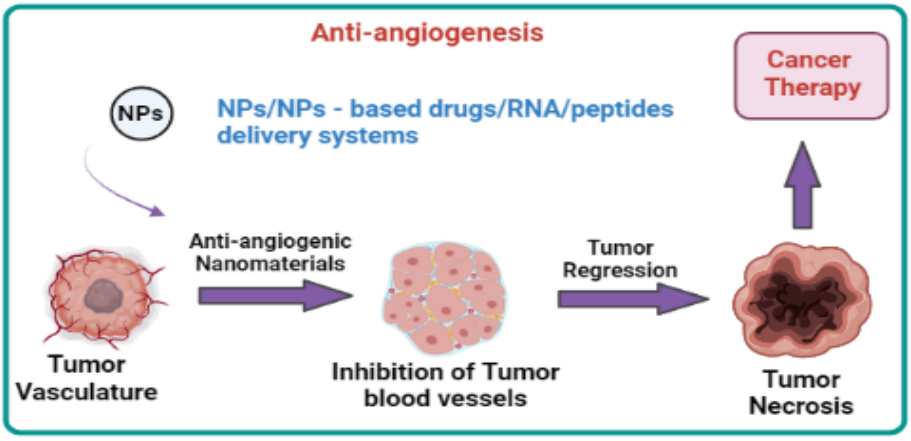

Fig .4 Anti-angiogenesis(15)

Essentially, the tumour itself initiates angiogenesis in tumours. Once the tumour reaches a certain size, it starts to become hypoxic and secrete angiogenic growth factor molecules. These growth factors cause the creation of new blood vessels that penetrate the tumour and support its faster growth by attaching to receptors on nearby blood vessel endothelial cells. The most significant angiogenic growth factor secreted by tumour cells is vascular endothelial growth factor (VEGF)(16). VEGF was recognised early on as a possible therapeutic target due to the fact that it primarily impacts endothelial cells.(14)

In addition to VEGF antibodies that block VEGF from inhibiting the angiogenic signalling chain, further methods to block VEGF signal transduction have been discovered: First, antibodies that target VEGF receptors, then endothelial VEGF receptor tyrosine kinase inhibitors. Third, fusion proteins that contain the binding domain of the VEGF-high-affinity receptor.(5)

Aflibercept, bevacizumab, ranibizumab, and pegaptanib are a few examples of medications that inhibit VEGF activity and hence restrict the growth of new blood vessels. A monoclonal antibody called bevacizumab (Avastin, Roche) acts as an angiogenesis inhibitor by preventing VEGF from doing its job-A.(3)

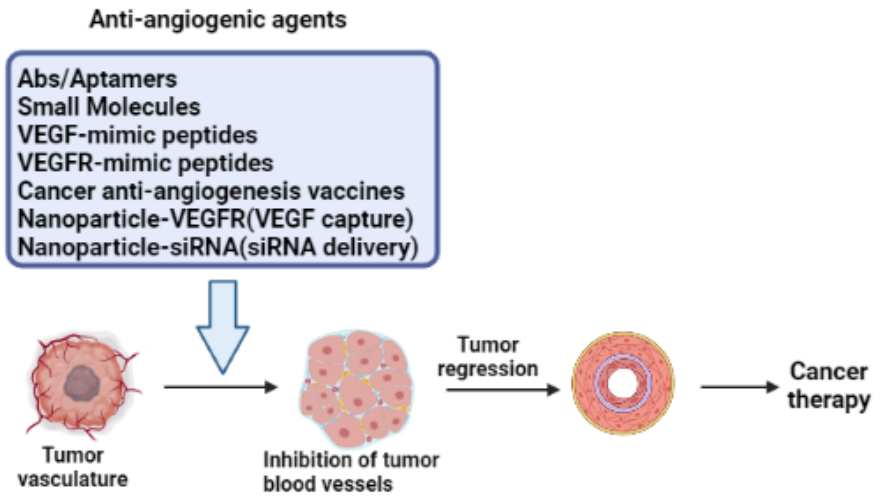

Fig .5 Anti angiogenic agents.

2.5. Targeting Tumor Ability to resist programmed cell death (Apoptosis):

Apoptosis is the cell's natural mechanism for causing programmed cell death. Given that it is involved in both development and homeostasis, it is particularly crucial for long-lived mammals.(17)It is a meticulously controlled technique that aims to get rid of any surplus or unwanted cells. Numerous conditions, including as DNA damage or excessive growth, can start the apoptotic pathway. Apoptosis is triggered by both intracellular and extracellular signals. Two separate mechanisms, intrinsic and extrinsic routes, which are associated with signal type, cause apoptosis. These pathways also go by the labels mitochondrial and death receptor.(18)

Oncogenesis is stopped at several stages, including transformation and metastasis, by apoptosis. Therefore, apoptosis must be suppressed to initiate and advance cancer. Since cell death is a major effector function of many anti-cancer medications, it is crucial in the treatment of cancer. (19)

• Apoptosis in Cancer

Cancer is characterised by uncontrolled proliferation, angiogenesis, and apoptosis evasion regardless of the cause or kind. Cancer prevention is one of apoptosis main goals. The intrinsic pathway is frequently inhibited in cancer, but there are other strategies to stop apoptosis. Loss of apoptotic control causes cancer cells to live longer, which gives mutations

more time to accumulate and have negative effects on differentiation, angiogenesis, tumour invasiveness, and cell proliferation.

• Apoptosis and Cancer Therapy

One approach to treating cancer is to take control of, or perhaps end, the unchecked proliferation of cancer cells. Utilizing the cell's built-in mechanism for dying is a very successful tactic. Additionally, the most successful non-surgical treatment is apoptosis-targeting. Targeting apoptosis evasion, a defining characteristic of cancer that is independent of the cause or type of cancer, is advantageous for treating a variety of cancers. Numerous anticancer drugs focus on various phases of the intrinsic and extrinsic pathways. Two common therapeutic targeted strategies are the stimulation of proapoptotic molecules and the inhibition of antiapoptotic molecules.

Some of the targets that have been researched include alkyl phospholipid analogues (APLS) that act as apoptotic signals, BCL-2 inhibitors, XIAP inhibitors, and death-receptor ligands. Any location along the routes can receive treatment; however, there is no proof as to which target is the most advantageous. More apoptosis-inducing anticancer drugs will be created, and this will lead to a better understanding of the targets. (18)

In leukemic cells from patients with chronic lymphatic leukaemia (CLL) and acute myeloid leukaemia (AML), B-cell lymphoma-2 (Bcl-2) protein expression was increased, inhibiting apoptosis. (20)The anti-apoptotic Bcl-2 protein is inhibited by the new medication venetoclax, causing programmed cell death. (3)

2.6. Tubulin / Micro tubulin as Target:

Cancer cells multiply and grow much more quickly than healthy cells do. Since microtubules are one of the essential elements needed for cell division and proliferation, microtubule-targeting is significant.(21) Development of anti-cancer drugs is being studied. Microtubules, which are common cytoskeletal elements, are produced when and tubulin heterodimer combine. Cell shape development and maintenance, cell division, recombinant cell generation, cell signalling, and cellular motility are all affected by these. In a dynamic equilibrium, tubulin heterodimers and microtubules coexist.(2)

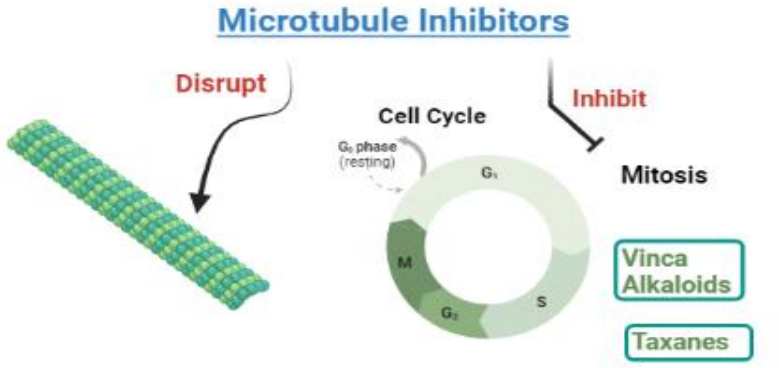

Fig .6 Microtubule inhibitors

• MECHANISMS OF ANTITUMOUR ACTION OF TBAS

While the microtubule polymerization cycle is occurring, the tubulin-subunit should be GTP-bound. Following attachment to the microtubule, the subunit's GTP is reversibly hydrolysed to GDP, and the majority of the -tubulin in the microtubule transforms to GDP-bound form. With GTP-bound -tubulin, the positive end of the microtubule is sealed. For the subsequent tubulin addition cycle, the GTP of capped -tubulin is hydrolysed to GDP, and the exposed GDP -tubulin triggers conformational changes that quickly depolymerize the microtubule with the release of the GDP-tubulin unit.(22) The main components of microtubule dynamics are stochastic periods of expansion and shrinkage brought on by the polymerization and depolymerization of tubulin dimers. (2)

MTS are significant therapeutic targets for the treatment of cancer because to their crucial role in cell proliferation. As a result, drugs that inhibit MT activity, such as TBAS, limit the growth of cancer cells by preventing the normal formation of the mitotic spindle, which is necessary for proper chromosome compression and segregation. Finally, this results in mitotic arrest during the metaphase/anaphase transition, which is followed by cell death brought on by apoptosis. Depending on how they affect the MT network, TBAS are frequently categorised as either MT stabilizing or MT-destabilizing agents. TBAS bind to the b-tubulin subunit of a/b tubulin, either on the tubulin heterodimer (MT-destabilizing agents) or on the MT wall (MT-stabilizing agents), causing MT dynamics to be disturbed and cell death to occur. (23)

Any change in the dynamic instability of microtubules stops cell division and may result in apoptosis.(2)

The vinca and colchicine domains on microtubules and monomeric,-tubulin, respectively, are inhibitors of microtubule polymerization. The proper positioning and movement of chromosomes during cell division depend on microtubule dynamics. An inhibitor alters a cell's microtubule dynamics, impeding mitosis and ultimately leading to cell death. As a result, altering microtubule dynamics is a key area of research for anti-cancer therapies. (2)

2.7. Vascular Targeting Agents:

The supply of oxygen and nutrients to human tumours is dependent on the surrounding vasculature. As a result, anticancer therapy focuses on the tumour vasculature.(24)

Targeting the tumour vasculature is a successful method for treating cancer due to its accessibility to blood-borne medications. Rapid cell division in tumours calls for a constant flow of nutrients and oxygen. Therefore, the development of blood vascular networks is essential for the growth, development, and spread of tumours. Vascular disruption agents (VDAs) have the power to obstruct the blood supply to tumours. Contrary to antiangiogenic medicines, which prevent the development of new capillaries, VDAS target the established cancer vasculature. Tumour vessels are abnormal and different from healthy tissue vessels in that they have an incomplete basement membrane, are poorly organized, twisted, and leaky. They also contain endothelial cells that are actively developing. These variations create a therapeutic window that VDAS could take advantage of to target the tumour vasculature in a targeted manner. The majority of VDAS in development are microtubule binding agents, which disrupt the endothelium cy- to skeleton, causing increased vascular permeability and fast channel closure.(2)

Cancer therapies known as vascular targeting agents (VTAS) cause tumour blood vessels to shut down swiftly and selectively. VTAS block the pre-existing blood vessels in tumours, leading to ischemia and severe haemorrhagic necrosis in tumour cells, unlike antiangiogenic drugs that stop the growth of new blood vessels. Tumour selectivity is a result of differences between the pathophysiology of tumours and normal tissue vasculature (examples include greater proliferation and fragility, as well as up-regulated proteins). Hypoxia can result in radiation and drug resistance, which are resistant to conventional antiproliferative cancer

therapy, and VTAS can destroy tumour cells in locations far from blood arteries where medication penetration is minimal.

Small molecules and ligand-based VTAS are the two types of VTAs that are grouped together because they both result in widespread necrosis by causing acute vascular shutdown in tumours. Among the tiny molecules are the micro tubulin destabilizing drugs combretastatin A-4 di sodium phosphate, ZD6126, AVE8062, and Oxi 4503, as well as the flavonoid DMXAA .In ligand-based VTAS, tumours are treated with medications that block blood vessels by binding specifically to antibodies, peptides, or growth factors that bind to tumours rather than to normal vasculature.(25) As a result of the endothelium being destroyed in solid tumours, capillary sprouts and blood vessel blockage occur as a result of the tumour cells dying from a lack of oxygen and nutrients.(26)

2.8. Cancer Stem Cell as a Target:

A cancer stem cell (CSC) is a type of tumour-dwelling cell that may perpetually divide, self-renew, and develop. The CSC can self-replicate and divide asymmetrically to maintain their proliferative capacity. For a brief period, CSCS can produce daughter cells that multiply incredibly swiftly. In the tumour mass, these cells can grow and generate a sizable number of non-CSC cells. The development of tumours and the upkeep of a highly proliferating cell population in tumours are both accomplished by CSCs. Leukemic stem cells (LSCs) in acute myeloid leukaemia in humans (AML) were the first CSCS to be identified.(2)

For the development of effective anti-cancer medications, the CSC population must be addressed. CSCs are crucial for the growth and spread of tumours because they have the capacity to multiply for a very long time. To effectively halt the spread of the disease, the CSC population must be eliminated. Targeting the CSCS population is challenging, though.(2)

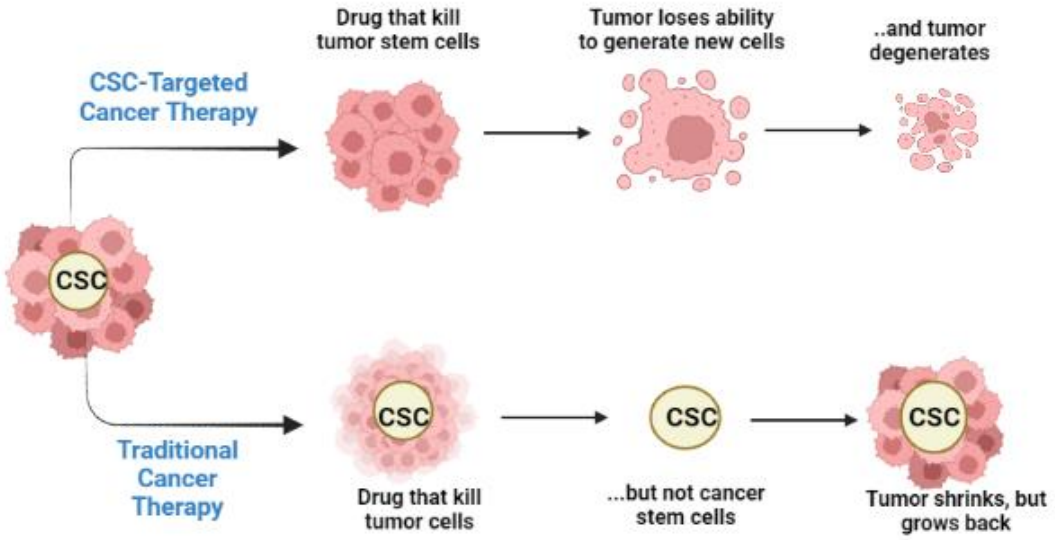

Fig .7 Targeting Cancer Stem Cell

• CSC AND THEIR MICROENVIRONMENTS THERAPEUTIC STRATEGIES

CSC Targeting Techniques

A promising treatment approach for halting the progression of human cancer and reducing the risk of recurrence is CSC targeting. Some of the therapeutic strategies discussed involve targeting certain markers, blocking ABC transporters, altering miRNA expression, disrupting core regulatory signalling pathways required for the cell type, and promoting CSC differentiation and death. Signalling systems that have been suggested as potential CSC biology targets. Among the important pathways identified are Wnt, Notch/Delta-like ligand (DLL), CXC chemokine receptor 1 2/CXCL8/FAK, and Sonic hedgehog (Shh)/Patched (Ptch)/Smoothened (Smo).(27)

The CSC Environment

The tumour environment includes immune cells, multipotent stromal cells, and CAFS as a target. endothelium, perivascular cells, and the cytokines and growth hormones they release This environment also contains extracellular vesicles and extracellular matrix (ECM) components inside a dominant hypoxic zone. The production and maintenance of CSCs, immune system protection for the tumour, and activation of EMT, which improves tumour progression, invasion, and recolonization as secondary tumours, are all attributed to the tumour stroma. As a result of their interactions with TME niche components, CSCS can also

become drug resistant. In order to treat CSCs and prevent medication resistance, targeting the TME may be a valuable indirect treatment strategy. (27)

2.9 Monoclonal Antibodies as a Targets:

Immunoglobulins, another name for antibodies, are Y-shaped proteins that help the body recognise and get rid of invading antigens like viruses and bacteria. In reaction to the presence of an antigen, the immune system generates them. Antibodies are heterodimers made up of two light and two heavy chains. Each light chain is linked to the long chain by a disulfide bond, whereas heavy chains are linked by many disulfide bridges. In the late 1800s, monoclonal antibodies (mAb) were initially applied to the treatment and diagnosis of cancer. It has now been demonstrated to be one of the best treatments for solid tumors.(2)

In healthy individuals, antibodies identify and label foreign harmful particles that are present in the body as the first step in the elimination of these alien infections or abnormal cells. The body's immune system then attacks and eliminates the targets that the antibodies have labelled. The amino acid sequence in the variable region determines how specific an antibody is to a particular antigen. In addition to direct antibody action, which involves blocking receptors, inducing apoptosis, or delivering a cytotoxic agent to the target receptor, antibodies can also cause immune-mediated cancer cell death, which includes controlling T cell activity and antibody-dependent cellular cytotoxicity (ADCC), as well as specific antibody effects on tumour vasculature. (28)The main mechanism of mAb-mediated immunotherapies is ADCC. (2)

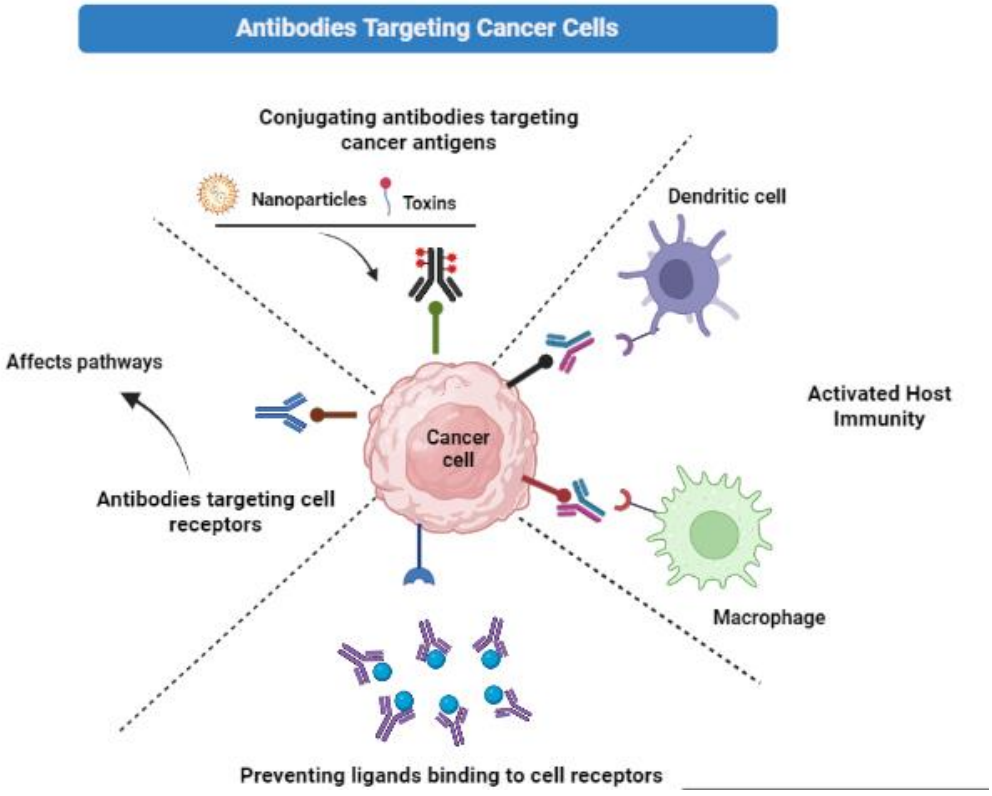

Fig .8 Antibodies Targeting Cancer Cell.

2.10 Epigenetic Agents:

Contrary to genetic processes, epigenetic alterations can be undone. Due to this inherent plasticity, learning how abnormal epigenetic mechanisms result in malignant transformation may offer fresh perspectives on how these systems might be targeted as part of a cancer treatment. Among the hematologic malignancies for which DNA hypomethylating agents and histone deacetylase inhibitors have received approval are T cell lymphoma [vorinostat (approved in 2006), romidepsin (2009)], multiple myeloma (MM) [panobinostat (2015)], and myelodysplastic syndrome (MDS] [azacitidine (2004) or decitabine (2006)].(29)

Normal cells have a moderate proportion of spontaneous mutations, but cancer cells have extensive DNA and chromosomal changes. The development of invasive and metastatic malignancies is accelerated by increased genetic instability, which also selects more cancerous tumour cells. With a few rare exceptions, the essential elements and genes involved in genome replication and maintenance have not changed over the course of evolution.(3)

• Drug Development HDACs (Histone Deacetylases) as a Target

Recent research has shown that the regulation of gene expression in eukaryotes is significantly impacted by changes in chromosomal structure and histone protein. These changes include methylation, ethylation, phosphorylation, and ubiquitination, with chromosome ethylation enzymes being closely associated with cancer. (30) The degree of ethylation of chromosomes is regulated by histone acetyltransferases (HATS) and histone deacetylases (HDACS), which also affect transcription, cell cycle, gene differentiation, DNA replication, and carcinogenesis. (5)

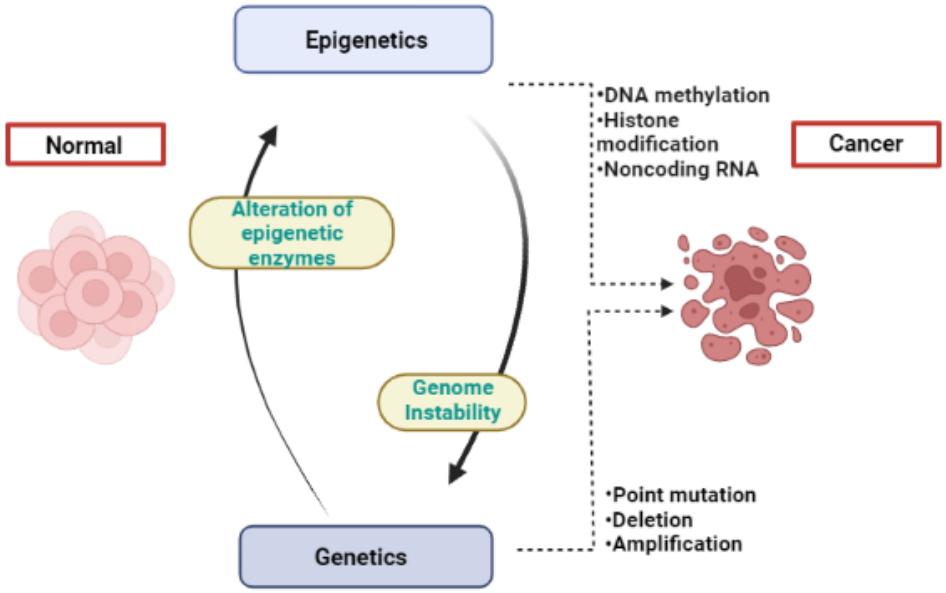

Fig .9 Epigenetic Targets.(31)

CONCLUSION:

Since cancer is a complex disease, a single target strategy has thus far failed to completely eradicate it. Cancer cells create a variety of intricate defence mechanisms to counteract the cytotoxicity caused by the medicine. Selected cancer cell lines responded well to the multi-targeting anti-cancer drugs, which partially alleviated the MDR problem. Because they can hide from your immune system, cancer cells can survive. In order to make it simpler for the immune system to locate and eliminate cancer cells, some targeted medicines can identify cancer cells. Other targeted medicines give your immune system a boost so that it can fight cancer more effectively. A promising approach for the management and total elimination of many malignancies may be targeted therapy.

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