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Responsive Drug Delivery Based on Tumor Microenvironment

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Abstract: The limitations of chemotherapy in toxicity and patient compliance made the targeted and stimuli responsive drug delivery as the focal point in oncological research. This article reviews the responsive drug delivery systems that leverages the pathological characteristics or conditions of tumor microenvironment [TME] such as hypoxia, acidic pH, overexpressed enzymes, high levels of reactive oxygen species [ROS] and glutathione [GSH], to specifically release the drug and increase the accumulation of the drug at tumor site and reduce the unnecessary damage to healthy cells, thus decreasing the side effects. These physiological abnormalities act as triggers to release drug at required site. These drug delivery systems incorporate pH sensitive/responsive moieties, enzyme cleavable links, redox sensitive components allowing for precise control over when and where drugs are released, thereby minimizing damage to healthy tissue and increasing therapeutic efficacy. These intelligent systems have the potential to address issues with conventional treatment, such as off-target effects, systemic toxicity, low bioavailability, and drug resistance. As research evolves these technologies are likely to play a key role in future of cancer treatment. This review also presents brief idea of the TME and its salient characteristics, explains how TME-responsive moieties enable drug release, and briefly summarizes the basic ideas of targeted and stimuli-responsive delivery.

Keywords*: Tumor Microenvironment, Chemotherapy, Stimuli Responsive Drug Delivery, Targeted Drug Delivery, Ph Sensitive/Responsive Moieties, Enzyme Cleavable Links, Redox Sensitive Components.*

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I. INTRODUCTION

At present, the cancer became the main causes of death throughout world. A sequence of consecutive gene mutations that cause aberrant cell proliferations are typically the cause of cancer [1]. The timeline shows revolutionary treatment over the decades that improved patients' quality of life. Beginning with Wilhelm Conrad Rontgen's discovery of X-rays in the late 1800s, which allowed radiation to be used alongside surgery for cancer treatment, and tracing back to the mid-19th century when general anesthesia was first introduced to facilitate the more expansive surgical procedures [2]. Removing the tumors surgically followed by radiotherapy and/or chemotherapy, is one of most widely advised conventional cancer treatment approach. Though conventional chemotherapy showed reduced mortality and morbidity, it is also accompanied by certain limitations. Surgery is suitable at initial stages of disease. Radiation and chemotherapy tend to damage healthy cells particularly those with are rapidly dividing, this leads to numerous adverse effects. Another significant drawback of traditional cancer treatment is drug resistance [3].

Even with the progress in cancer research, there are still cancers that are hard to cure. Targeted drug delivery improves survival by targeting anticancer drugs to specific locations, maximizing efficacy, and reducing toxicity to healthy tissues. In contrast to conventional formulations, it employs functionalized carriers to enhance drug concentration at the target and minimize damage to healthy cells, thus making chemotherapy safer and more effective [4]. Tumor targeting is classified into 2 types: passive and active targeting. Passive targeting has an increased permeability and retention effect (EPR) attributed to fast onset of hyper-permeable complex tumor vasculature with dysfunctional lymphatic drainage of pathological tissue (tumor), which permits nanoparticles to reach the tumor environment. The active targeting strategy in contrast, is based on compositional decoration of drug

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carriers' surface with tumor-specific ligands including aptamers, antibodies and also for receptors overexpressed by the tumor cell [5,6]. The expectation from this strategy is enhanced localization of anti-cancer drugs at the tumors and prevent their distribution to unnecessary sites, which in turn enhances the effectiveness. But EPR effects demand that the diameter of the nanocarriers should be greater than 100 nm, whereas tumor penetration prefers the size to be about 30 nm, thereby implying that nanocarriers with preferred EPR effects cannot have beneficial tumor penetration. Despite more than 10% targeting efficiency, monotherapies of nanomedicine fail to provide long-lasting therapeutic effects, since remission usually follows relapse because of pro-tumorigenic microenvironments or re-activation of cancer stem cells [6,7].

Researchers are targeting nanoscale drug delivery systems for the treatment of cancer, in which, stimuli-responsive lipid-based systems, nanocarriers, and prodrugs have received the most interest based on their increased selectivity, biocompatibility, tumor sensitivity, and clinical feasibility, in addition to convenient scalability and adaptable formulation choices [5]. Stimuli-responsive drug delivery systems alter nanocarriers through the addition of responsive moieties that modulate size, charge, or ligand exposure. These moieties can cause the nanocarrier to change its size, electrical charge, or expose/hide targeting ligands in response to stimuli. These changes improve drug release, uptake by cells, tissue accumulation, and penetration. They are particularly promising for targeted medication delivery and have more therapeutic effects and less negative effects than conventional nanocarriers [7]. This review shall present a brief overview of tumor microenvironment [TME] responsive drug delivery for tumor targeting mainly focusing on five key elements of tumor microenvironment-overexpressed enzymes, low pH, hypoxia, elevated levels of reactive oxygen species [ROS] and glutathione [GSH], which have shown the potential to act as stimuli in smart drug delivery. Figure 1. illustrates the five key characteristics of the tumor microenvironment (TME) that play a crucial role in the development of stimuli-responsive drug delivery systems.

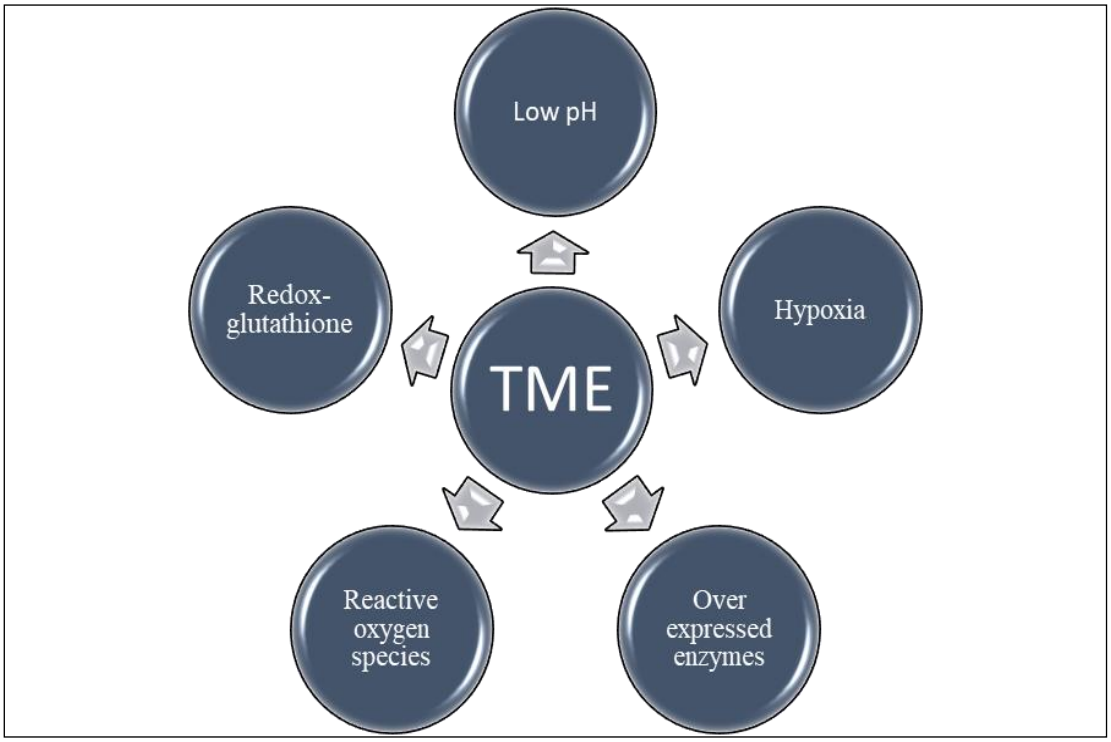

Fig. 1: Key Characteristics of Tumor Microenvironment (TME)

A. Tumor Microenvironment [TME]:

The environment surrounding a developing tumor and its TME is dynamic and ever-evolving. Though its content is diverse among tumors, shared components are immune cells, stromal cells, blood vessels, and the extracellular matrix (ECM). The "TME is critical and not a passive bystander, with an active participation in progression of cancer" [8]. An active role of TME in cancer progression includes engaging with tumor cells, aiding their survival, invasion, and metastasis from the outset of growth. These TME unique characteristics can be used for TME targeted delivery [9]. Few key elements of TME are briefly discussed below.

➢ *Hypoxia:*

One of the unique features is hypoxia, where deep-seated tumor cells suffer from oxygen deprivation due to irregular vascular networks within solid tumors [9]. The rapid growth of cancer cells requires a lot of nutrition and oxygen within the tumor. This leads to problems with blood vessels at the tumor site and the formation of irregular micro vessels, which can damage the microcirculation. Hence there is a drop in partial pressure of oxygen gradually from the exterior to deep interior of tumor. The oxygen partial pressure can be

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reduced to 0–2.5 mm Hg which makes the TME hypoxic [10].

➢ *LOW Ph:*

Numerous studies have revealed that the extracellular space of the tumor tissue has a pH between 6.5 and 6.8, which is weakly acidic, due to the Warburg effect, which is caused by uncontrolled energy metabolism, insufficient perfusion, and lactic acid generation.

The excessive acidity of the tumor extracellular milieu is a common pathogenic characteristic of solid tumor tissues, as opposed to the neutral environment of normal tissues. While the normal physiological pH is between 7.2 and 7.5, but the extracellular TME pH is acidic, ranging from 6.5 to 6.9 [10,11].

- *Warburg Effect: [12]*

In the 1920s, Otto Warburg noted that tumors took up large quantities of glucose and metabolized it to lactate even in the presence of oxygen—a process referred to as aerobic glycolysis or the Warburg effect. Despite oxygen and undamaged mitochondria, this occurs in tumors and other growing cells by increase in glucose uptake and lactate generation which results in lower pH at TME. Though extensively researched, its precise advantage for cell growth and survival is still not understood.

➢ *Over Expressed Enzymes*

Enzymes, made of proteins or RNA, play a crucial role in biological processes by speeding up chemical reactions with high selectivity and efficiency. They function under mild conditions and are essential for metabolism and other life-sustaining activities at the molecular level [10]. Along with pH and hypoxia, the tumor microenvironment also presents with modified expression of some enzymes in tumors, which may be used for TME-specific release of drugs. The majority of enzymes overexpressed in the TME belong to the protease family, like membrane metalloproteinases (MMP), or the lipase family, like phospholipase, hyaluronidase (HAdase), γ-glutamyl transpeptidase, and esterase compared to normal cells and helps for targeted delivery [10,11,13]. For example, compared to normal prostate tissue, prostate cancer cells have significantly higher expression of the prostate-specific membrane antigen (PSMA), also referred to as glutamate carboxy peptidase. Another illustration would be the high expression of cathepsin B in the majority of malignancies, including those of the breast, lung, prostate, etc. [13].

➢ *Reactive Oxygen Species:*

Aerobic respiration is an effective energy-generating process, in all eukaryotes and their evolution. The aerobic respiration produces reactive oxygen species (ROS) such as superoxide, hydrogen peroxide and hydroxyl radicals. These can be harmful to DNA, proteins and lipids. ROS affect the behavior of cancer cells as well as the stromal elements of the tumor to regulate cancer development and survival [14]. ROS also play a key role and crucial for intracellular and extracellular signaling molecules [15]. The primary notion of "oxidative stress" is a surplus high level of reactive oxygen species (ROS) which are produced from intensive metabolism and oxygen consumption at mitochondria. ROS are crucial for cancer in various aspects, including angiogenesis, inflammation, proliferation, migration/ invasion, and immune-escape. This makes it possible for cancer cells to endure the harsh surroundings [16]. Hence tumor cells produce greater amounts of reactive oxygen species (ROS) than regular cells because of oncogenic transformation, which increases aerobic metabolism. Increased ROS production is mainly via the mitochondrial respiratory chain and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathways. Moreover, genetic alterations and alterations in energy metabolism patterns of tumor cells can enable the production of ROS. The concentration of hydrogen peroxide [H_2O_2] has been calculated to in the TME up to 100×10^{-6} m, which is ≈100 times greater than that in normal tissues, making it a key characteristic within the TME of stimuli-sensitive nanomedicine [10,11].

➢ *Glutathione [GSH]:*

High metabolic demands of tumor cells because of their high proliferation rates. Although ROS are unavoidable by-products of oxidative metabolism, their formation and detoxification are regulated by a wide variety of processes. GSH pathway is the antioxidant pathway through the mitochondrial enzyme GPX4 that is responsible for the removal of harmful lipid peroxides and other ROS species [17]. This is leading to high levels of reducing glutathione (GSH) in an effort to sustain redox homeostasis. Normal cells maintain lower concentrations between 1 and 5 mM, while tumor cells exhibit elevated levels of GSH, typically ranging from 5 to 10 mM. [10,18].

II. STRATEGIES DEVELOPED:

A. Hypoxia Responsiveness:

As discussed above, Tumor hypoxia is an area of low oxygen concentration caused by an insufficient supply, one of the most characteristic aspects of the tumor microenvironment. In comparison with healthy tissues, which contain a pO_2 of 40–60 mm Hg, tumor tissues usually contain below 10 mmHg, even as low as 0–2.5 mmHg. These abnormal tissue states provide tumor cells various physical, chemical, and biological properties, like low pH and high redox potential. Understanding these characteristics is useful for scientists to optimize the architecture of novel nanomaterials and result in more efficient diagnosis and treatment Hypoxia-responsive nanocarriers present a promising approach for targeted drug delivery. This can be realized using either hypoxia-activated prodrugs (HAP) or hypoxia-responsive nanocarriers [19,20]. Certain reductases preferentially reduce hypoxia-activated prodrugs (HAPs), commonly referred to as bio-reductive drugs, to produce cytotoxic species that exclusively target hypoxic tumor cells and show minimal toxicity to normal tissues. As of right now, several types of HAPs, including quinones, nitroaromatics, aliphatic N-oxides, and hetero-aromatic N-oxides, have been synthesized. The most prevalent ones include PR-104, EO9 (apaziquone), TH-302 (evofosfamide), SN30000, AQ4N

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(banoxantrone), and tirapasamine [21]. Hypoxia responsive polymeric drug carriers, the polymeric vehicles having at least a hypoxia-induced functional moiety in their structure which at low PaO2 can be switched on and alter the structure of carriers ultimately releasing the cargo [22].

Such drug delivery systems can be made sensitive to the tumor hypoxic milieu by incorporating hypoxia-sensitive agents, such as nitro and azo chemicals, which are bio-reduced in the hypoxic environment of tumor cells, into the design of polymer-drug conjugates or nanoparticles [23]. Due to the Warburg effect, cancer cells undergo aerobic glycolysis metabolism of glucose, and drugs have the capability of enhancing redox cycling or electron donating, thereby supporting the overexpression of certain enzymes like DT diaphorase (DTD), nitro reductase, azo reductase, methionine reductase, etc. in hypoxic cells [19,24]. Nitro reductase a flavin linked enzyme and NADPH are involved in the reduction of nitro groups to their corresponding amines nitroso, hydroxyl amino, amino groups. The required reducing equivalent may be supplied by NADH and NADPH. Azo-reductases and NADPH lower azo compounds to aniline groups [19,23,25]. Various drug delivery systems have been developed by many researchers based on the above mechanism. Mingzhi Zhu et al developed a hypoxia-responsive drug delivery system using an organic solvent volatilization method. The team prepared an amphiphilic polymer, poly(ethylene glycol)-phthalic acid-nitroimidazole (PEG–PA-NI), through the coupling of PEG to nitroimidazole and utilized it for preparing hypoxia-responsive micelles encapsulated with the anticancer drug doxorubicin (DOX). The reduction of nitroimidazole to its water-soluble form, 2-aminoimidazole, by nitroreductase breaks the micelle structure, facilitating drug release [26]. Derivatized nitroimidazole loaded into liposome membranes to produce a hypoxia-responsive liposomal drug delivery system allowed triggered disassembly of the liposomes for drug release. In vivo fluorescence imaging indicated that selective release of the liposomes occurred at the hypoxic tumor location [27]. A hypoxia-responsive hybrid liposomal drug delivery system was constructed by Long M et al which consist of azo-inserted organoxysilane-based lipid analogue as a responsive unit. They stated that Hybrid liposomes are highly stable in structure to prevent premature leakage of drugs under normal physiological conditions and highly sensitive to respond to hypoxia after arriving at the sites of tumors [28].

B. pH Responsiveness

There are pH gradients between many human body's tissues and cellular compartments. In this scenario, tumor tissue is 0.5–1 pH-units more acidic than the pH level of adjacent normal tissue by reasons of metabolic glycolysis and lactic acid generation. At the cell level, there are pH gradients between cellular compartments like lysosomes (pH 4.5–5), endosomes (pH 5.5–6), and the cytosol (pH 7.4) [29] and this distinctive nature has been exploited to develop various strategies for targeted delivery.

The reversible deprotonation and protonation of ionizable groups is responsible for the pH response of polyelectrolytes. The pKa at which the protonated and deprotonated structures are present in equal concentrations, is a critical indicator of the way the polymer ionizes at various pH values. In general, Basic polymers, which take protons at a relatively low pH, and acidic polymers, which release protons at a relatively high pH, are the two categories of ionizable polymers. These contain moieties such as amines, pyridines, morpholines, piperazines or carboxylic acids, sulphonic acids, phosphoric acids, boronic acids, etc. Amines, in particular tertiary amines, which allows the pKa to be readily tailored. The amines were noted to have a slightly lower pKa when the amines are alkylated with a longer hydrophobic chain [30]. The tumor microenvironment being acidic induces protonation of pH-sensitive groups, thus disturbing hydrophilic-hydrophobic balance within the nanoparticle, subsequently leading to structural change and release of drug cargo loaded within. Typically, pH-responsive systems are prepared either from acid-sensitive linkers or ionizable groups [11].

- *pH Sensitive Groups:*

In normal tissues and blood, the polymer Poly(l-histidine) (P(His)) containing pendant imidazole groups is hydrophobic. But in acidic environments, such as tumor tissues and intracellular endocytic vesicles, it is hydrophilic. This pH dependent phase transition leads to destabilization of vehicle or drug delivery system. This pH sensitivity has made imidazole-containing polymers extensively researched as tumor-targeted DDSs [31,32]. The pKa of imidazole group is around 6, and therefore this group is protonated in slightly acidic milieu [33].

Poly(ethylene glycol) methyl ether acrylate-block-poly(L-lysine)-block-poly(L-histidine) triblock co-polypeptides [p(PEGA)30-b-p(Lys)25-b-p(His)n] were synthesized and designed by John JV et al for pH-sensitive administration of drug to tumors. These hybrid vesicles were stable under physiological pH (7.4) but destabilized under acidic tumor pH upon swelling of the poly(L-histidine) block. Their pH responsiveness permitted controlled and extended drug delivery in CT26 cancer cells and dose-dependent cell killing [34]. Poly(β-amino esters) (PBAE), a synthetic, pH-sensitive, hydrolytically degradable polymer, originally synthesized in 1970 by Ferruti. In its normal state, it has limited solubility and remains in the hydrophobic zone. Upon decreasing pH, the amine groups protonate, enhancing solubility and bringing about volume expansion. This induces the "proton sponge effect," which facilitates drug release by enhancing lysosome escape and nanoparticle dissociation, enabling targeted drug release in cancer cells [31,35]. The pH-responsive polymeric micelles were created by Min KH et al employing hydrophilic methyl ether poly(ethylene glycol) (MPEG) and pH-responsive/biodegradable poly(beta-amino ester) (PAE) by copolymerization via a Michael-type step polymerization to create an MEPG-PAE block copolymer. Amphiphilic MPEG-PAE block copolymer spontaneously formed polymeric micelles of nano-sized diameter by self-assembly, exhibiting a sharp pH-dependent micellization/ demicellization transition at the tumoral acidic pH 6.4 [36]. Poly(2-(diisopropylamino)ethyl methacrylate)) (PDPA) is another pH-sensitive polymer whose hydrophobic/hydrophilic phase transition is below pKa 6.5,

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due to the protonation of amino groups and thus it is a very interesting polymer for the delivery of therapeutic molecules to cancerous cells with acidic microenvironment [37].

➢ *pH Sensitive Linkages*

pH-sensitive DDSs have been created by introducing pH-labile chemical linkages into the polymer segments or the polymer/carrier–drug conjugates. These include acetal, hydrazone, cis-acotinyl, orthoester, β-carboxylic acid amide, and glycerol ester groups which are stable under alkaline or neutral conditions but hydrolyzed at acidic pH, thereby allowing the release of the entrapped drugs by breaking the nanocarrier or the conjugated drugs by degradation of the polymer/carrier–drug bond [38]. When hydrazine, ketones, or aldehydes condense, hydrazone is produced. Hydrazone bonds are a type of covalent bond that is also acid responsive, much like imine bonds. Because hydrazone bonds are hydrolytic in nature and readily break in acidic conditions and hence applied in design of acid-sensitive carriers for responsive product [39]. Long YB et al. created new cross-linked responsive micelles (x-micelles) from polyurethane that have pH-sensitive hydrazone groups and photo-responsive coumarin derivatives. According to their findings, x-micelles can dissociate in acidic environments and remain stable in physiological settings [40]. Acetals and ketals possess two alkoxy groups on the same carbon, with the additional central carbon substituent for ketals in contrast to acetals. At acidic environments, protonation of a single oxygen atom activates the nearby carbon, leading to bond cleavage and hydrolysis. Research has shown that polymers with acetals and ketols can decompose into soluble monomers in the acidic tumor microenvironment [41]. Arman Moini Jazani et al. created two acid/reduction-degradable block copolymer nano assemblies with disulfide pendants in micellar cores and acid-cleavable ketal linkages at core/corona interfaces [42].

C. Enzyme Responsiveness

Enzymes are involved in nearly every stage of cancer development, such as angiogenesis, cell proliferation, and metastasis. Many enzymes are greatly upregulated in tumor tissue microenvironment, compared with relatively low expression in normal tissues, presenting the possibility of the development of enzyme-responsive DDSs [43]. Tumor microenvironment shows increased secretion of several enzymes like proteases, peptidases, and lipases, each having a particular chemical characteristic. Significantly, solid tumors overexpress proteases (e.g., matrix metalloproteinase-MMP-1, MMP-2, MMP-9 & Cysteine proteases- Cathepsin B, Cathepsin L), peptidases (e.g., carboxypeptidases, aminopeptidase), and lipases (e.g., phospholipase A2) [44]. The enzymatic activity is tied to a specific tissue or the enzyme occurs in greater abundance at the target location where the nanomaterial can be designed to release drugs through enzymatic breakdown of the carrier. For instance, some polymeric nanoparticles possess biological motifs that are cleavable by enzymes. When the nanoparticles interact with the enzyme, the polymer shell degrades, and the cargo (such as a drug) is released [45].

➢ *Matrix Metalloproteinases [MMPs]*

MMPs are found in virtually all human cancers. They may be expressed by normal fibroblasts in the surrounding stroma, cancer-associated fibroblasts, or by non-fibroblastic cancer cells. This is of paramount importance, because MMPs can shape the tumor microenvironment through the promotion of angiogenesis, tumor expansion, and metastasis. Conversely, MMP expression is correlated with tumor aggressiveness, stage, and prognosis in patients. Almost all members of the MMP family have been identified as being dysregulated in human cancers, with MMP-1,-2,-7,-9,-13, and -14 leading the list. Altogether, these considerations suggest that MMPs are good candidates for therapeutic intervention [46]. MMPs constitute a class of zinc-dependent endopeptidases [47]. Some sensitive peptide sequences cleave with matrix metalloproteinase such as GPLGIAGQ, GPLGV, GPLGVRG, and PVGLIG. They have been described for the construction of MMP-2/9-sensitive conjugate. MMP-2/9 is said to be able to cut short peptides of a certain sequence regardless of their secondary or tertiary structures. Zhang X et al developed stimuli-responsive drug delivery system, by incorporating an MMP-2/9 cleavable oligopeptide GPVGLIGK-NH2 (GK8) as spacer which was cleavable by MMPs [48]. A novel nanoparticle, known as MEMSN, was developed by Zhang J et al for the targeted treatment of tumors. It possesses a targeting peptide sequence (RGD) and an MMP-sensitive surface peptide (PLGVR- Pro-Leu-Gly-Val-Arg). The targeting peptide is covered to protect it from normal cells by a poly(aspartic acid) (PASP) coating. In experiments, MEMSN did not interact with regular cells, but when it got to cancer cells, the coating of PASP was stripped away followed by hydrolyzation of PLGVR at the MMP-rich tumor cells by MMP enzymes, which exposed the targeting property and enabled the nanoparticles to be internalized into cancer cells [49].

➢ *Cathepsins*

Three types of cathepsins have been identified: aspartic cathepsins (cathepsins D and E), serine cathepsins (cathepsins A and G), and cysteine cathepsins (cathepsins B, C, F, H, K, L, O, S, V, W, and X). Among these, cysteine cathepsins are the most predominant in malignant disease evolution. These are lysosomal proteases. Within the cleft, active side chains catalyze the lysing of peptide bonds by serine, cysteine, and threonine proteases covalently. In contrast, metallo- and aspartic proteases hydrolyze peptide bonds by noncovalently binding highly active water molecules [50]. Mesoporous silica-coated quantum dots nanoparticles (QDs@mSiO2) and an enzyme-activatable cell penetrating peptide (CPP) were combined by Li J. et al. After loading antitumor drug, doxorubicin (DOX) and subsequent exposure to proteases in tumor cell environment, the enzymatic cleavage of peptide sequence activates oligo cationic TAT residues on the QDs@mSiO2 surface and guide the DOX delivery into cellular nucleus. These experiments verified that the responsive enzyme DOX-loaded CPP-QDs@mSiO2 nanoparticles are capable of selectively releasing DOX in tumor cells with overexpressed cathepsin B enzyme. In contrast, minimum nuclear-targeted drug accumulation and decreased cytotoxicity are seen in enzyme-free cells [51].

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➢ *Phospholipases*

Phospholipases (PLAs) are a widespread group of enzymes having the common property of hydrolyzing phospholipids, Phospholipases A2 are members of a PLA superfamily of enzymes, which are broadly distributed among living organisms. Lyso-phosphatidyl-choline (LPC), a key lyso-phospholipid product produced by PLA2 activity, facilitates the spread of cancer. PLA2s break down acyl-ester bonds at the phospholipid components' sn-2 location in the cell membrane [52]. Prodrug-activating enzymes in tumors should meet two conditions: (a) much greater expression and activity within tumor tissue than in normal tissues and (b) a substrate specificity that is amenable to the design of prodrugs. One group of enzymes that meet these requirements is the phospholipase A2 (PLA2) family, namely secretory PLA2 type IIA (sPLA2). Numerous human malignancies, including those of the breast, stomach, pancreas, prostate, small intestine, and colon, have been shown to overexpress sPLA2. Jensen SS et al described the design and synthesis of a new class of liposomes derived from lipid prodrug chemotherapeutics that harness the elevated sPLA2 activity of the tumor microenvironment to release anticancer ether lipids (AEL) [53].

D. ROS Responsiveness

Reactive oxygen species (ROS) are free radicals and highly reactive ions whose induction would be potentially mutagenic to the cellular DNA that is associated with progression of many cancer cells. Due to their biological relevance, the use of ROS-responsive units like superoxide, hydroxyl radical, hypochlorite ion, hydrogen peroxide, singlet oxygen etc. The ROS in polymeric nanoplatform for controllable drug release is emerging. [54]. Several types of ROS-sensitive prodrugs or carriers, like those bearing thioether, selenide/telluride, diselenide, thioketal, arylboronic ester, aminoacrylate, oligoproline, peroxalate ester, have been examined regarding smart drug delivery system [DDS] application. The main drug release mechanisms associated with ROS are ROS-activated carrier solubility modification, ROS-induced carrier cleavage, or ROS-activated prodrug linker cleavage [55]. **Table 1** summarizes commonly used ROS-sensitive materials and their mechanisms of action.

Table-1: Some ROS Responsive Materials with their Drug Release Mechanism [54,55,56,57]:

ROS-Responsive materials	**Mechanism of Drug Release**
Selenium-based responsive polymers	In a ROS environment, Se groups are oxidized to hydrophilic selenosulfone, causing micelles or nanoparticles to depolymerize and release the drug. Diselenide bond breakage in ROS environment.
Sulfur-based responsive polymers [thioether, thioketal, vinyl di-thioether linkers]	The oxidation of thioethers to sulfoxides increases their hydrophilicity and induces drug release through solubility switching. Keto thiols undergoes bond cleavage in regions rich in ROS to release ketones, thiols, and releases drugs.
Tellurium-based responsive polymers	Oxidation of Te-containing polymers in H_2O_2 environment may lead to phase transition from hydrophobic to hydrophilic, changes their solubility, leading to drug release.
Aryl boric ester-based responsive polymers	A solubility switch mechanism on the basis of H2O2 oxidation is one of the uses for which the arylboronic acid/ester functions have been developed as ROS-sensitive groups. In conditions containing a high amount of ROS, the arylboronic ester linker is also cleaved.
Oxalate ester-containing polymers	Oxidation of oxalate by H_2O_2 leads to alcohol and CO_2 formation, causing nanoparticles to degrade and release their cargo.

Various drug delivery systems have been developed by various researchers owing to the above mentioned mechanisms. Few of them are discussed below.

A redox-responsive drug delivery system (DDS) was constructed by Žid L et al utilizing doxorubicin (DOX) as a model drug and encapsulated into a porous silica carrier (SBA-15). Disulfide-linked cystamine derivatives were conjugated onto the surface of the carrier. They reported that disulfide bonds were cleaved by redox molecules, such as DTT, present at higher levels in cancer cells, inducing DOX release. They stated that system was found to release DOX in accordance with redox conditions and was detectable through magnetic measurements [58]. Oddone N et al designed a new ROS-responsive prodrug, mPEG-TK-MPH by conjugating melphalan to methoxy polyethylene glycol through a thioketal (TK) linker. In human U251 MG glioma cells and rat C6 cells, the prodrug spontaneously generated nanosized micelles and shown more cytotoxicity and anticancer activity than its non-ROS-sensitive cousin (mPEG-MPH). Notably, it did not show toxicity in normal astrocyte cells (DI TNC1), indicating its selectivity. These results indicate that TK-based prodrug design presents a promising approach to targeted and safer glioblastoma treatment [59]. Xu X et al. efficiently developed a new ROS-sensitive polyprodrug nanoplatform with penetrating ability deep into the tumor for cancer theranostics. These nanoparticles are responsive to intracellular ROS for releasing intact anticancer drugs by the chain-breakage mechanism and efficiently inhibiting the growth of tumor cells. The presence of ROS-cleavable thioketal bonds allows for accurate and efficient release of the drug, improving the therapeutic efficacy [60].

E. Glutathione Responsive:

GSH is a tripeptide, consists of glutamate, cysteine, and glycine. It is mainly found in the cytoplasm of the cells and

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plays a key role in maintaining the balance of physiological redox processes. The levels of GSH in healthy cells are more within the cell than outside the cell. In cancer tissues, the levels of GSH may increase as much as 4 times than healthy cell [44]. This significant difference in GSH levels between cancer and normal cells makes it possible to exploit the reducing milieu as an internal stimulus for drug delivery systems. Glutathione plays a role as a reducing agent and donates a hydrogen atom from its thiol group to a particular chemical component [the responsive material] in the nanocarrier of drug delivery. When redox-sensitive chemical components are incorporated into nanocarriers, they are often linkages that, when a hydrogen atom is accepted, will cause a conformational change that will result in breakage and opening of the gap in the structure of the nanocarrier, causing it to disintegrate and release the anti-tumor agents into the cell [61]. Prodrug nanomedicine based on nanomaterials is regarded as a potential tool for tumor targeting with a high drug loading capability, and by altering the nature of bond polymer or polymers, desired properties could be obtained. For example, stimuli-responsive cleavable bonds between the polymer and drug could be employed for target delivery of the drug to the specific microenvironment [62]. The disulfide bond under the risk of rapid cleavage by GSH is the most common and effective mechanism in this context. Redox-responsive DDS based on disulfide bonds have also been employed in a variety of other nanocarriers such as zwitterionic dextran nanoparticles, single-walled carbon nanotubes, chitosan-based nanoparticles, PEGylated micelles and mesoporous silica nanoparticles [63]. Under conditions of high amounts of reduced GSH in cancer cells, the disulfide cross-links can be readily degraded into sulfhydryl groups which leads to the breakdown of carriers and thereby to the release of cargoes. This may be achieved by the incorporation of disulfide links into polymer-based carriers to modify polymeric chains with disulfide containing linkers, which in turn may be attached to drugs, facilitating their delivery to targeted locations [64].

Li Y et al. used cysteine-bearing telo-dendrimers to create a reversible disulfide cross-linked micelle formulation for targeted drug administration. They reported that drug was more slowly released from cross-linked micelles compared to non-cross-linked micelles, but accelerated in a reducing environment and in mice bearing ovarian cancer, the cross-linked micelle formulation of a drug was reported to be effective than both the non-cross-linked formulation and Taxol at equal doses [65]. Besides disulfide bonds, Diselenide bonds also show equivalent reduction sensitivity and redox-responsiveness as those of disulfide bonds. Also succinimide-thioether linkage is reducible to give exogenous glutathione-cleaved product to enable fast intracellular release. Succinamide-thioether linkage shows higher stability and slow release of drug cargo compared to disulphide bonds [66]. Cancer cells produce more ROS and GSH than normal cells, thus forming a specific redox environment. Diselenide bonds, which can be responsive to oxidation and reduction, are also commonly incorporated in redox-sensitive drug delivery systems. ROS in this setting can oxidize diselenide bonds into selenate, while GSH can reduce them into selenol. Once the diselenide bonds break the drug release is facilitated within cancer cells [67]. Chaoping Fu et al. showed the synthesis of indocyanine green (ICG)-loaded diselenide-presenting polymeric nanoparticles by the supercritical fluid (SCF)-aided rapid and convenient synthesis method for ROS/GSH-responsive drug delivery platform towards enhanced anticancer therapy [68].

III. CONCLUSION

Cancer remains a significant obstacle in the field of medicine despite years of research. Eliminating the harmful side effects of traditional chemotherapy remains a significant challenge. An ideal solution to this issue is offered by intelligent drug delivery systems. Scientists have created targeted drug delivery strategies that are very promising and offer new hope by identifying and utilising the unique characteristics of the tumour microenvironment (TME). Unlike conventional therapies that have limited tumour specificity and systemic toxicity, these smart systems respond selectively to internal tumour stimuli such as low pH, hypoxia, high enzymatic activity, or elevated levels of ROS and GSH. These stimuli serve as triggering agents or responsive switches. TME-sensitive linkers are used in carriers as part of strategies. These moieties stay stable in circulation, but upon exposure to specific TME stimuli, they undergo structural or chemical changes that initiate drug release exclusively at the tumour site. Transforming tumour weaknesses into therapeutic strengths is the fundamental idea.

This targeted approach allows for controlled drug release, enhances drug accumulation at the tumour site, and reduces adverse effects on healthy tissues. Early experimental results typically show great promise, especially in improving therapeutic indices and overcoming drug resistance, even though the concept is still developing. Precision oncology and personalised medicine will be advanced by ongoing research into microenvironment-responsive systems. With increasingly sophisticated knowledge of the TME, forthcoming innovations in intelligent drug delivery systems can be expected to deliver still further precision, efficacy, and safety, opening the way to more efficient and patient-centric cancer treatments.

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