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Review on – Enzyme-Responsive Nanoparticles for Antitumor Drug Delivery

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ABSTRACT :
The research into the potential of nanoparticles (NPs) as innovative implements for cancer diagnosis and treatment has advanced significantly during the last few decades. The use of practical and effective nanoparticle-based technologies in clinical change is still a difficulty. Both academic and clinical studies have shown a strong interest in the design, preparation, and evaluation of diverse smart NPs with particular physicochemical reactions in physiological situations associated to tumours. Smart enzyme-responsive nanoparticles in particular have the ability to predictably and selectively interact with certain enzymes expressed in tumour tissues, resulting in tailored administration of anti-tumor medications, decreased systemic toxicity, and increased therapeutic impact. Additionally, NPs interact with internal enzymes with great efficiency and typically in mild settings (low temperature, aqueous medium, neutral or nearly neutral pH). Protein molecules called enzymes serve as catalysts for a variety of biological processes. The drug's dose is mostly determined by the enzymes. As xenobiotic metabolizers, enzymes are crucial. The bioavailability of medications is governed by the activity or mode of action of enzymes. Means enzymes are a major factor in the regulation of the therapeutic effect. Infectious disorders, chemoprevention, and a number of other ailments can all be treated using the premise of enzyme inhibition. By utilising the intriguing physico-chemical properties of several materials in a nanoscale level, nanoparticles are created that can release their cargo when certain enzymes are present. Nanocarriers can be used and modified with enzyme-labile links to offer on-demand enzyme-responsive drug release, reducing the side effects of medicinal drugs. In the current review, we provide an overview of drug delivery systems that can carry medications to the tumour microenvironment and trigger the release of those medications in response to particular enzymes that are highly expressed in particular tumour tissues. With this approach, a flexible platform for intelligent drug release at the site of action is provided.[1,2,3]

I. INTODUCTION:

Cancer is one of the main causes of death worldwide. Although numerous research lead to preparation of novel nanoplatform for cancer treatment, few nanoscale drug delivery systems have been approved for clinical application.

Nanotechnology-based platforms provide great opportunities for monitoring, prevention, diagnosis and treatment of various disease.The cancer microenvironment, or tumor microenvironment include non-cancerous cells such as tumor-associated fibroblasts, immune cells and vasculature cells, which are required to secrete and produce the proteins for the tumor cells growth. Tumorigenesis is a multistep, dynamic and intricate process comprised of three phases: initiation, progression, and metastasis [3].

The targeted delivery of drugs directly into biological cells needs nanoscale design of the pharmaceutic vehicles. Nanoscopic particles are promising drug carriers due to their adjustable size, shape, porosity and surface properties .For inorganic nanosystems, particles can be modified with active-targeting ligands that are sensitive to a certain enzyme. This approach can further broaden the design flexibility and scope of applications by endowing the nanoparticle with enzyme responsive properties when the nanomaterial itself is not responsive to enzyme [6]. Enzymes are proteins which folds into different shapes and enable size reduced molecules to fit within them. Enzymes are biological catalysts acting on a substrate molecule which will be its target site. Enzyme converts these reactants to product molecules and thus needed by every cell to carry out a reaction at a significant rate. Since enzymes are specific and extremely

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selective, these mainly determine the metabolic pathway in which the cell further proceeds. Enzymes are site targeted and interlocks with a lock and key mechanism to the substrate. The extent of enzyme binding to the substrate determines the response of reaction. This specificity of enzymes is exploited by combining with the concept of vesicular drug delivery[11].

II. METHODS:

1.General Mechanism For Enzyme-Responsive Controlled Drug Release From NPs:

Every biological and metabolic process in the human body heavily relies on the actions of enzymes. Drugs are released from nano particles (NPs) in an enzyme-responsive mechanism when a particular enzyme catalyses chemical events that result in the disintegration, dissociation, or morphological changes of the parent NPs. Severe destruction of NPs exposed to enzymes, which typically results in burst release of pharmaceuticals, is not necessary nor preferable in order to produce a regulated release profile of drugs. Controlled modifications to the macro-scale structure of NPs in a tumour microenvironment including particular enzymes typically result in the desired controlled release of medicines [1].

2.Enzymosome:

An innovative, developing targeted vesicular drug delivery technology is enzymes. Enzymosomes primarily use enzymes that are integrated into cell-like structures with a strong lipid backdrop and have a specific catalytic function for a substrate. They produce newly created liposomes with covalently attached enzymes to lipid molecule surfaces. The liposomes were designed to provide the right microenvironment inside of them for the enzymes to become disabled. Liposomes are tiny vesicles having an aqueous environment surrounding a lipid bilayer. Drugs that are hydrophilic may disperse in the internal aqueous compartment, while those that are lipophilic are integrated into the phospholipid-cholesterol lipid bilayer membrane. Lipid-based drug delivery systems are beneficial in particular aspects such as lowering volume of distribution, interrupting drug clearance, and altering the distribution of drug with enhanced capillary permeability towards the infected tissues and reducing toxicity associated with normal tissues, proving to give an effective nanoscale drug delivering for clinical use. According to research, these were specifically effective in the therapeutic management of breast cancer, metastases, etc [10].

3.Bioenzyme-based nanomedicines for phototherapy :

The unique benefits of non-invasiveness, good manipulation, and precise remote control make phototherapy an effective option for cancer treatment. Through the conversion of light energy into heat and harmful ROS by agents, such light-mediated therapeutic techniques as PTT and PDT enable the suppression of tumour growth. Through a number of synergistic processes, phototherapy and bioenzyme-based nanomedicines can work together to increase the therapeutic efficacy. Nanomedicines based on bioenzymes have been utilised to treat tumours because they can successfully stop tumour growth by altering biological processes at the cellular or molecular level. Furthermore, the near-infrared (NIR) photothermal effect mediated by nanomedicine can interact with the enzymes in a variety of ways, such as by controlling enzyme release and regulating enzyme activity, leading to a more potent synergistic effect in the therapy of cancer[12].

4.Enzyme-triggered release in cancer treatment

The suggested approaches for curing tumours with over expressed enzymes all entail extracellular drug release, and they may involve passive tumour buildup that takes advantage of the EPR effect in addition to active targeting. Regarding enzyme over-expression in the extracellular environment of sick tissue compared to healthy tissue, there is a great deal of knowledge about cancer biology. Although the general practicality of such a plan has not yet been demonstrated, there may be other enzymes of interest in intracellular compartments that can be used for drug release. Another possibility is that the amounts of intracellular enzymes in malignant cells and normal cells do not differ enough from one another, although this information is not yet available in the context of medication administration. However, it might be conceivable to develop new, extremely effective methods by combining the targeting of over-expressed receptors that cause cellular internalisation with enzymatically degradable liposomes. Illustration showing blood vessel fenestration in a tumour as a result of the tissue's inflammation and tumour growth. Through gaps between the endothelial cells lining the blood artery, the liposomes extravasate into the extracellular space while moving through

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the bloodstream. Here, the liposomes may come into contact with secreted enzymes such sPLA2 or MMPs, which will subsequently hydrolyze the membrane moieties and cause the release of the medication. Despite this, all effective approaches have relied on secretory enzymes, with medication release taking place in the extracellular compartment of the tumor[25].

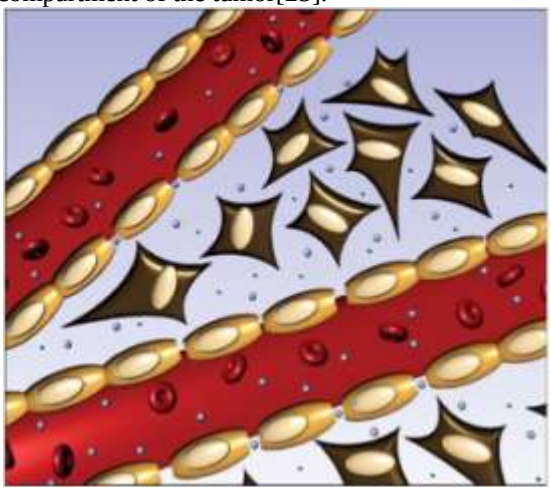


Illustration showing blood vessel fenestration in a tumour as a result of the tissue's inflammation and tumour growth. Through gaps between the endothelial cells lining the blood artery, the liposomes extravasate into the extracellular space while moving through the bloodstream. The liposomes may run into these enzymes here [25].

5.Metabolic Enzyme Considerations in Anti-tumour Activity:

Numerous anticancer medicines are processed by enzymes, and this process is vital. Depending on the drug and its mode of action, the precise enzymes implicated can change. Listed below are a few instances of enzymes frequently used in the metabolism of anticancer medications:

a.Metabolism in Phase I:
Cytochrome P450:
Several cytochrome P450 enzymes in the liver metabolise several anticancer medications, including as tamoxifen, irinotecan, and cyclophosphamide. Drugs are transformed into their active or inactive forms by use of these enzymes. Some of the well-known CYP enzymes involved in medication metabolism are CYP3A4, CYP2D6, and CYP2C19.

Dihydropyrimidine dehydrogenase:
DPD is important in the metabolism of fluoropyrimidine drugs like 5-fluorouracil (5-FU). Deficiencies in DPD activity can lead to increased toxicity of these drugs.

b.Phase II metabolism:

A number of anticancer medications, including SN-38 (the active metabolite of irinotecan), are glucuronidated by UDP-glucoronosyltransferase (UGT) enzymes. The medications become more water-soluble as a result of the conjugation reaction, which speeds up the process of removing them from the body.
Carboxylesterases: These enzymes serve as catalysts for activating some prodrugs, such as capecitabine, which is transformed into 5-FU[28].

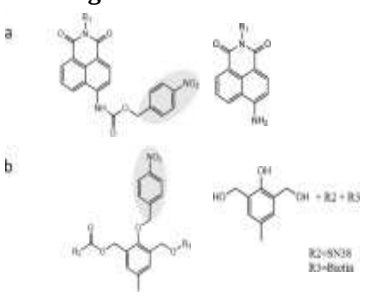
6. Enzymes targeted for special groups:

a. Nitroreductase

Since many years ago, the activity of nitroreductase (NTR) has been well-understood in a variety of systems, including bacteria, yeast, trypanosomes, and hypoxic tumours. They are a type of flavin-related oxidoreductase that is promiscuous and characterised by its capacity to reduce aromatic nitro substituents. Aromatic substrates exhibit relatively high reactivity with NTR as a result of their strong contact, which is mediated by hydrogen bonding, -stacking interaction, the hydrophobic effect, and other mechanisms. The substrate's nitro group is first converted to a nitroso group, then to a hydroxylamine group, and lastly to an amino group. NTR activity in human cells seems to have only been documented in hypoxic tumours up to this point. The fact that hypoxia can also result in a rise in reductive stress and an over expression of reductases, this may be connected to the tumor's hypoxic state. NTR can be utilised for treating and diagnosing cancer owing to these properties [32].
chemical structures involved in the text.

Enzyme Prodrug Product

NTR



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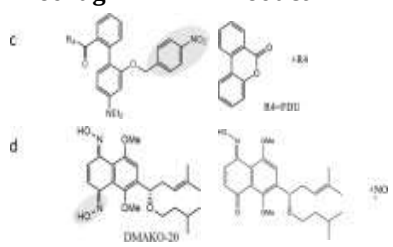
Enzyme Prodrug **Product**



7.Enzyme Responsive DDS:

Smart medication administration has been made possible by the up-regulation of certain enzymes in the tumour microenvironment and within tumour cells. To create enzyme-responsive DDS for tumor-tropism drug delivery, a variety of enzymes including proteases (such as matrix metalloproteinase/MMP and cathepsin B), phospholipases (such as phospholipase A2), and peptidases (such as aminopeptidase) have been explored. The following are some possible actions of the enzyme-responsive DDS: (i) The construction of nanocarriers with structural scaffolds susceptible to specific digestive enzymes or the use of an enzyme-sensitive linker between the nanocarrier and medicines. Many hurdles still need to be addressed in the development of enzyme-responsive DDS for cancer therapy. First of all, although certain enzymes have identical active sites and catalytic processes, they favour the same substrates. Second, not only do different cancer types have varying levels of enzyme expression, but so do tumours of the same kind in different people and in various regions of the tumour.

Nanoparticles With Enzyme-Responsive Core:

The active medications are found inside the core of NPs, where they are confined by chemical covalent conjugation or physical contacts. The release of pharmaceuticals can be initiated by structural alterations such as disintegration, macroscopic deformation, charge switching, covalent bond breaking, and other processes upon the activity of enzymes towards functionality built into the core. It has been shown that the family of over 20 zinc-containing proteinases known as matrix metalloproteinases (MMPs) can catalyse the core breakdown of peptide-based NPs. Among them, MMP-2 and MMP-9 are of particular importance for the development of enzyme responsive anti-tumor drug delivery systems due to their proved correlation with cancer cell invasion and metastasis formation.

Nanoparticles With Enzyme-Responsive Crown:

For applications in drug delivery, surface modification of nanoparticles with hydrophilic moieties is often needed to increase water solubility, prevent drug leakage, avoid reticuloendothelial system (RES) reorganisation, improve interactions with cells, and facilitate cellular uptake. Hyaluronic acid (HA), synthetic polymers cross-linked by peptides, proteins or peptides, and other materials with high hydrophilicity have all been studied. These materials are of tremendous relevance for the production of NPs with enzyme-responsive crowns.This hydrophilic auxiliary of NPs is intended to detach once the NPs have reached the targeted action sites and aid in the release of the active medicines that are contained. Due of the strong relationship between certain diseases and enzymes, particularly tumours, it will be extremely desirable for the development of enzyme-triggered deshielding remedies in this manner.
[33,1].

8.Stimuli-ResponsiveDrug Release:

An active chemical is either encapsulated in the delivery system or covalently linked to it in order to be delivered to the targeted area of the body. In order to release a medicine, it must first undergo endocytosis or fuse with the cell membrane (in the case of lipid delivery systems), and then it must be stimulated. Changes in enzyme levels, pH, and temperature are examples of internal stimuli that are inherent to the bodily part that is being stimulated. External stimuli include magnetic fields, ultrasound, and light [33].

9.Enzyme-Sensitive Release:

In some forms of cancer, the pattern of enzymatic protein expression in the tumour may be changed. Controlling the release of a drug from delivery systems when enzymes are involved involves two major strategies:

An enzyme that is overexpressed in the tumour environment cleaves a linker that is used to attach the medicine to the delivery device.

Embedded enzyme cleavage sites in the scaffolds' envelope cause the envelope to rupture close to or inside the tumour, releasing the medicine that is enclosed within.

To date, a number of enzyme-sensitive materials have been produced. For instance, a metalloproteinase-sensitive octapeptide has been created and employed as a linker. Phospholipase, -

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amylase, glucose oxidase, and cancer-associated proteases are other enzymes that have been employed for drug release [37].

III. CONCLUSION:

The abnormal enzyme activity that accompany biological diseases are caused by the crucial function that enzymes play in catalysing biological events. In order to improve therapeutic efficacy and diagnostic precision in cancer therapy, endogenous enzyme-triggered nanomaterials based on liposomes, polymers, inorganic/organic hybrids, and small molecules have been utilised.

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