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Polyaspartamides as a Drug Delivery Platform

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Abstract: ***Cancerous diseases present a formidable health problem worldwide. While the chemotherapy of cancer, in conjunction with other treatment modalities, has reached a significant level of maturity, efficacious use of such agents is still restricted by numerous pharmacological deficiencies, such as poor water solubility, short serum circulation lifetimes, and low bioavailability resulting from lack of affinity to cancer tissue and inadequate mechanisms of cell entry. More critically still, most drugs suffer from toxic side effects and a risk of drug resistance. The class of Polyaspartamides anticancer drugs, although outstandingly potent, is particularly notorious in that respect. Among the countless methods developed in recent years in an effort to overcome these deficiencies, the technology of polymer-drug conjugation stands out as a particularly advanced treatment modality. The strategy involves the bioreversible binding, conjugating, of a medicinal agent to a water-soluble macromolecular carrier. Following pharmacokinetic pathways distinctly different from those of the common, nonpolymeric drugs, the conjugate so obtained will act as a prodrug providing safe transport of the bioactive agent to and into the affected, that is, cancerous cell for its ultimate cell-killing activity. Polymer-drug conjugation involving polymer-based and other medicinal agents has unquestionably matured to a practical tool to the pharmaceutical scientist, and all indications point to an illustrious career for this nascent drug delivery approach in the fight against cancer.***

Article

I had heard this particular lecture on Polyaspartamides in an occasion and I loved the idea about the innovative drug delivery system which the Proffesor said.

The following is an attempt to put the same innovation in a few words.

Polyaspartamides were first reported in 1950s and were employed as plasma expander in early 1970s. Polyaspartamides continue to attract the attention of researchers due to their excellent biocompatibility and biodegradability. These polymers are readily synthesized in gram quantities, and structural variation of these polymers is straight forward.

Poly(amid amine) (PAMAM) dendrimers are the first complete dendrimers family to be synthesized, characterized and commercialized. Dendrimers can be used as a drug delivery vehicle to address poor bioavailability and low solubility of small molecules, as well as for multidrug delivery of hydrophobic and hydrophilic drugs. Dendrimers are highly branched, core-shell nanostructures with precise architectures and low polydispersity. Dendrimers are synthesized in a generation-by-generation fashion around a core unit, resulting in a high level of control over size, branching points, and surface functionality. Drugs can be incorporated into dendrimer carriers by passive encapsulation, where the drug is physically encapsulated in the interior or by covalent attachment of the drug to the dendrimer by chemically reactive functional groups to generate a drug-dendrimer conjugate. Targeted dendrimer drug carriers can be synthesized by the conjugation of targeting moieties on the periphery of the dendritic carrier. Based on this extensive activity, they are recognized as a unique new class of synthetic nanostructures. Dendrimers allow the precise control of size, shape and placement of functional groups that is desirable for many life science applications.

Polymeric micro and Nanoparticles are effective carriers that allow for controlled and targeted drug delivery of small molecules, DNA and proteins in order to improve the bioavailability and bioactivity of a drug. Polyester-based nanoparticles, formed by emulsion or nanoprecipitation techniques can be designed to have a range of degradation times (see example technique). Particle degradation and drug release kinetics are controlled by the physiochemical properties of the polymer (e.g., molecular weight, hydrophobicity, and polydispersity).Moreover Stimuli-responsive polymers have been widely employed to enable targeted delivery and controlled release in response to changes in their environment. Stimuli-responsive polymers undergo rapid changes in their microstructure from a hydrophilic to hydrophobic state, triggered by external stimuli, including heat, pH, and ionic strength. Drug delivery systems (micelles, micro gels, and hydro gels) composed of responsive polymers release the drug during the collapse and expansion of the network in the aqueous environment. The most extensively investigated temperature/pH sensitive systems are based on poly (N-isopropylacrylamide). Site-specific or localized delivery of drugs or bioactive factors can be achieved using polymeric hydro gels. Polymer hydro gels can be designed with a wide range of polymers and cross linking schemes to make materials that have controlled and sustained drug release. For example, PEG-based hydro gels, formed from by chemical cross linking multifunctional PEGs, have been used to deliver small molecules and growth factors. Natural polymers (Chitosan), biodegradable polymers (PLGA) and stimuli-responsive polymers such as PNIPAM have also been fabricated into hydro gels for localized and controlled drug, protein, or gene delivery.

On this note We realized that Polyaspartamides can easily cross the cell membranes and translocate entrapped peptides intracellularly, while maintaining cyto-compatibility. We further explored that the antibacterial Polyaspartamides can selectively kill mycobacterium smegmatis over E.coli or mammalian cells. The cause of this selectivity and the mode of action of the synthesized amphiphilic Polyaspartamides to solubilise curcumin through physical entrapment. This results in suspensions in aqueous medium that are stable for months. By exploiting the ready intracellular translocation of Polyaspartamides, we deliver curcumin into mammalian cells (both cancerous and normal cells). Upon intracellular

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delivery, curcumin causes selective killing of breast cancer cells over normal human embryonic kidney cells.

References

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