Biomedical Polymers

Drug delivery and molecular imaging

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During the last two decades significant advances have been made in the development of biocompatible polymers as the platform for drug delivery and molecular imaging. The idea of using synthetic and natural biocompatible polymers as a platform to improve pharmacokinetics and delivery efficacy of small molecular therapeutic drugs is not new. Biomedical polymers have been widely used as carriers for drugs for example, polymer-drug conjugates, polymeric micelles, polymer protein conjugates and polyplexes have been designed for the delivery of chemotherapeutics, proteins and gene therapeutics. The conjugation of drugs to polymers can increase solubility and stability of the drugs while reducing their systemic toxicity. The coupling of drugs to water soluble biomedical polymers has the principal effect of limiting cellular uptake by pinocytosis, and therefore altering drug pharmacokinetics at the whole organism and cellular level. The polymer drug conjugates can passively accumulate within solid tumour tissues due to the hyperpermeability of tumour blood vessels and poor lymphatic drainage of tumour tissues, a phenomenon termed as "Enhanced Permeability and Retention (EPR) effect". Also, polymers can be designed to be multi-functional and can be modified by using targeting-moieties to enhance drug targeting to specific tumour sites.

With the incorporation of imaging agents into biomedical polymers, polymeric drug delivery can also be applied in the design of novel contrast agents or probes for molecular imaging. Unlike traditional diagnostic imaging, molecular imaging has a potential to help imaging various targets or pathways. Imaging modalities that have been applied in human subjects for in vivo evaluation include Ultrasound, Optical Imaging, Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). The incorporation of imaging agents into biocompatible polymers alters their pharmacokinetics, prolongs the retention of the agents in the tissue of interest, improves their specificity, and has a potential to help improve the accuracy of clinical diagnosis. Applications for different imaging modalities include MRI, SPECT, PET, Ultrasound and Optical Imaging.

In fact, the applications of biomedical polymers for drug delivery and molecular imaging are not mutually exclusive. The concept of drug delivery can be combined with molecular imaging to design more effective and specific imaging agents; after labelling the polymeric drug delivery systems with appropriate imaging probes, non-invasive visualisation of the delivery system reveals the complicated mechanisms of in vivo drug delivery and its correlation to pharmacodynamics. The combination of drug delivery and molecular imaging on the same polymer platform will result in more effective image-guided therapies. The earlier a disease can be diagnosed and a therapeutic drug can be delivered, the better the chance that the disease can be cured quickly. This is the rationale for the combination of polymer platform in drug delivery and molecular imaging.

The study of biomedical polymers in drug delivery and molecular imaging is becoming more and more comprehensive. Already, numerous studies have been undertaken on the application of biomedical polymers in optical imaging and MRI, including development of bioactivatable polymeric fluorescence probes, novel biodegradable macromolecular MRI contrast agents, non-invasive visualisation of in vivo drug delivery of polymeric conjugates with contrast-enhanced MRI, bifunctional polymeric conjugates for image-guided interventional procedures and so on. Molecular imaging with macromolecular imaging probes is effective to non-invasively and accurately assess therapeutic efficacy of new therapeutics in both pre-clinical and clinical drug development.

For example, MRI is an imaging modality that measures the difference in the longitudinal or transverse relaxation rates (1/T1 or 1/T2) of water protons in different tissues. Unlike other imaging modalities, MRI provides very high spatial resolution and is very adept at morphological imaging and functional
With MRI, treatment efficacy can be evaluated over extended periods of time, inter-individual variability is reduced, and therefore statistical significance may be obtained with much smaller groups. Hence, non-invasive visualisation of polymer-drug conjugates’ delivery on in vivo has been applied after labelling the conjugates with imaging probes. Although the MR signal intensity is not linearly correlated to the Gd(III) concentration in the tissues, it provides qualitative or semi-quantitative information about the structural effect of polymeric conjugates on in vivo drug delivery. MR images revealed a size-dependent, dynamic and heterogeneous distribution of the conjugates in organs and tumour tissues and the number of animals used in the study is greatly reduced. Currently, traditional biopsy-based pharmacokinetics studies are still needed for validating the imaging approaches. The two readouts from biopsy and MRI are complementary. Combining sensitive molecular imaging approaches such as PET or optical imaging with MR imaging allows the accurate and assimilated study of the pharmacokinetics/pharmacodynamics of a polymeric drug delivery system.

Polymers have also been used for image guidance and treatment assessment during interventional procedures. Both imaging agents and anti-cancer drugs can be loaded onto the same polymer platform to prepare bifunctional agents for image-guided therapy. The combination of contrast enhanced MRI with photodynamic therapy would provide accurate localisation of interstitial lesions, guiding specific light irradiation to the tumour tissue in photodynamic therapy. This has been demonstrated by using a bifunctional polymer conjugate containing an MRI contrast agent Gd-DTPA and a photosensitizer meso[6]-mesochlorin e6 (Mce6), poly-(L-glutamic acid)-(Gd-DTPA)-(Mce6) conjugate.

Biomedical polymers are able to favourably modify the pharmacokinetics of therapeutics and imaging probes and improve their efficacy in therapy or disease characterisation. Biomedical polymers based nanomedicine has a significant advantage over that based inorganic nanomaterials in terms of versatility and safety. Application of biomedical polymers in drug delivery, molecular imaging and nanomedicine will generate new and more efficacious therapeutics and imaging probes to improve human health, which will also create tremendous opportunities to pharmaceutical and biotechnology industry. Currently, several polymer drug conjugates and polymeric imaging agents are in clinical trials in the U.S. and Europe, and one is already being used in Japan.

In summary, the application of biomedical polymers benefits from their large sizes and unique pharmacokinetic properties. It has the potential to have an important impact on the way in which drugs are delivered. The impact will be the establishment of powerful diagnostic and therapeutic tools for pharmaceutical industry in the development of effective drug delivery systems and imaging probes, and non-invasive approaches for preclinical and clinical drug development.

References:

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