Chemistry of Contrast Media

Particles and Polymers

Basic Considerations on the Use of Particles and Polymers in Molecular Imaging

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Learning Objectives:

- To review the *in vivo* behavior of macromolecular imaging agents
- To understand how to optimize the pharmacokinetics of Nano-sized imaging agents
- To evaluate the unique toxicities anticipated for of macromolecular imaging agents

From the biological and chemical perspective, macro-molecules, polymers, and particles that are used in imaging agents, can be categorized as non-biodegradable or biodegradable. Non-biodegradable materials generally have covalently-bound, single macromolecular structures that do not have bio-cleavable bonds such as ester- disulfide or amide-bonds that may be degraded by specific enzymes in the body. In contrast, biodegradable materials are single molecules with bio-cleavable bonds including bio-degradable polymers or self-assembled particles which *compose* of charge or biphasic (hydrophobic-hydrophilic) molecules such as liposomes and viral capsids or metal crystals including iron oxide Nano-particles. Imaging agents made by non-biodegradable materials can be designed in a straightforward fashion because injected agents are not metabolized and are excreted unchanged from the body. In contrast, imaging agents based on biodegradable materials will form metabolites which may have different rates of excretion compared with the parent compound. These factors add complexity to the design of biodegradable imaging agents. On the other hand, metabolites may enable more rapid overall excretion than non-biodegradable agents.

To effectively target cells in the body, macromolecular imaging agents must be able to evade the reticuloendotherial system (RES). If not, such agents will be rapidly trapped by the liver and the spleen and will not be available for the target. Moreover, rapid sequestration in the liver and spleen increases the likelihood of immunogenicity. In order to evade the RES, agents should be hydrophilic and close to neutral charge. Therefore, to ensure this behavior the surfaces of “stealth” agents are generally coated with hydroxyl group-rich moieties such as polyethylene glycol (PEG). In general, excretion rates and routes are determined by the size of agents or their breakdown products. If agents or their breakdown products are small enough (<6nm in diameter), those agents will be filtered through the glomerulus and rapidly excreted into the urine (unless there is binding to the proximal tubules). In some cases, agents composed of softer, more flexible molecules, can be larger than 6nm but still be reliably excreted by the kidneys. In contrast, larger agents will circulate longer in the blood and will be trapped and excreted through the liver to the bile resulting in slow clearance. Agents with rapid clearance are generally preferable due to their higher safety profile than those with slow clearance. However, toxicity is also dependent on the nature of the degradation products. Additional complexity is added when the agents or their degradation products interact with plasma proteins such as albumin and macroglobulins where there are added concerns regarding clearance and immunogenicity. Ultimately, the value of a macromolecular imaging agent will be determined by its ability to leak into a tumor, be retained that called enhanced permeability and retention (EPR) effect, yet be cleared by the background organs as quickly as possible. This represents the supreme challenge of designing and testing larger molecular weight imaging agents.