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Editorial

Toxicological Concerns of Modified Biomaterials in Drug Delivery

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The nanotoxicology of the biomaterials and their derivatives is an important consideration before their clinical application as drug delivery nanocarriers. The biopolymers are considered to be non-toxic, biodegradable, non-immunogenic, non-mutagenic, no carcinogenic, and biocompatible in nature. However, there is no assurance that their derivatives and nanoscale formulations will also exhibit the same properties to that of the native biomaterials. They may cause various interactions with fluids, cells, and tissues, starting at the portal of entry and then via a range of possible pathways towards target organs. At the site of final retention in the target organ(s), the nanoparticles may trigger mediators, which then may activate inflammatory or immunological responses. Thus, the design of the biopolymer-based nanoparticles with the specific sizes is one of the most important criteria for drug delivery application. It is worthy to mention that the modified natural polymers such as polysaccharides are currently being investigated as potential therapeutic agents. Further, the nanoconjugation of active drug substances with the bio-polysaccharide is also under investigation as possible drug carriers. The plenty of functional groups in the polysaccharide structures allow functional modification of the native polymers and design of different types of nanocarriers. The hydrophilic biopolymer carriers can also prevent opsonization and circulate in blood for a longer duration, thus improving the drug targeting efficiency. In most of the cases, the toxicity or biological activities are overlooked during their evaluation. Some functional materials also exhibit biological activities, in particular sulfated derivatives, and the activity may be combined with the drugs of similar category to have synergistic therapeutic effects, thereby enabling the reduction of drug doses. All these can be illustrated with some valuable literature reports.

For instance, the sulfated derivative of curdlan has been found to completely inhibit HIV-1 virus replication *in vitro*. In phase-I clinical trials, the derivative is well tolerated up to 200 mg/70 kg, however unexpectedly produced CD4 lymphocytes in HIV-infected patients at higher doses, which may have therapeutic implications. It is also well tolerated with few reportable side effects for the patients treated with antivirals for 21 days with IV infusions of 50-200mg/70kg BW. Systematic decrease in platelets and increase in p24 antigen as is seen with dextran sulfate is not observed for this derivative. Treatment with this derivative seems promising against cytomegalovirus (CMV) in HIV infected patients, even with once daily dosing of this short half-life drug (2h). Multiple daily dosing or the continuous infusion, it may lead to improved efficacy against both HIV and CMV, especially in combination with reverse transcriptase inhibitors.

While the clinical applications of dextran are growing, its safety concerns in a particular application need to be addressed. High Molecular Weight (MW) dextran induces generation of anti-dextrin antibody, leading to anaphylactoid reaction in some patients.

The dextran's (> 40 kDa) are more toxic than heparin and the toxicity is dependent on molecular weight. The effects of various MW compounds upon the plasma proteins and the formed elements of the blood may determine toxicity. At low oral dose, the large MW, dextran sulfates form insoluble complexes with fibrinogen. At higher dosages, agglutinates of the formed elements of the blood are demonstrable as conglutination thrombi or emboli in blood vessels. The small MW dextran sulfates (~7.5kDa) show qualitatively similar anticoagulant action to that of heparin and comparable low toxicity, and therefore appear likely to be equally safe for therapeutic use as anticoagulants. Nonetheless, it has been demonstrated that continuous intravenous dextran sulfate infusion is toxic, producing profound but reversible thrombocytopenia in human subjects and extensive but reversible alopecia. Because of its toxicity and lack of beneficial effect, dextran sulfate is unlikely to have a practical role in the treatment of symptomatic HIV infection. It is not unusual to observe apparently contradicting activities of the same polysaccharide. A subtle difference in MW, degree of branching, or the type of monomers can result in a significant differences in their biological effects. Moreover, the biological effects and fates of excess polysaccharides and degradation products are not entirely clear.

Some nanomaterials have inherent affinity to specific cells/organs and hence, they can be employed for targeted nano-drug delivery applications, if toxicity profiles are found favorable.