Formulated nanogels: a strategy for selective intracellular drug delivery

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Abstract

Over the past years, the application of nanotechnology to the administration of therapeutic molecules has been a crucial investment in the treatment of a wide range of human diseases [1-2]. The importance of controlled intracellular delivery of drugs is two-fold: i) to augment the delivery efficiency of the active principles, avoiding under- and over-dosing, and ii) to precisely reach the biological target, limiting undesirable off-target effects. Among the different classes of nanovectors, nanogels are promising tools to perform controlled and sustained drug release. In particular, the formulation of nanocarriers able to load and release both hydrophilic and hydrophobic active principles could lead to a unique and versatile system.

We propose the design of nanogels performing tunable intracellular release of hydrophobic and hydrophilic molecules in different biological applications: in details, our fields of interest are the liver disease [3], cancer and the damaged central nervous systems, with a specific focus on the activation of microglia pro-inflammatory phenotype that promotes the neurodegeneration [4].

The hydrophobic payload is evaluated to counteract the nonalcoholic fatty liver disease (NAFLD), such as the hepatic steatosis: hydroxytyrosol (HT), chosen as antioxidant and anti-inflammatory molecule, was encapsulated within the nanogel networks and intracellularly released, avoiding metabolic alterations and the loss of the therapeutic cargo in the extracellular environment. The biological effect of nanovector-mediated HT delivery is superior to the traditional free drug administration, demonstrating that formulated nanogels may represent a more effective strategy for protecting liver cells from the development of hepatic steatosis.

Otherwise, the hydrophilic drug release is proposed using two functionalization routes: the former based on the formation of chemical bonds between the drug and the nanogel through a thiol-sensitive linker [5], and the latter based on the generation of ionic interactions between the drug and the polymeric network [6]. In the first case, the selectivity of drug delivery is due to the disulphide bond that can be disrupted intracellularly by glutathione or cysteines present in the cytosol; in the second case, the drug release is tuned by the electrostatic interactions between the nanogel and the drug in the biological environment.

However, the *in vivo* application of these biomaterials is strictly linked to their capability to selectively interact with specific inflamed, damaged or malignant cells, avoiding the immune response and the consequent undesired macrophage uptake. For this reason, nanogel functionalization with different coating layers, based on specific chemical moieties, could promote the selective interaction with target cells and modulate the cell uptake. A first evaluation has been conducted through the rational decoration with PEG (PEGylation) and amine groups, which has demonstrated the opportunity to tune the nanogel internalization in microglia culture. This result can be considered as the first stage to design smart nanogels coated with sensitive groups, such as peptide sequences or responsive chemical moieties, for damaged cell signaling detection and targeted therapies.

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