Abstract

During last three decades, a great effort was invested to the development of polymer conjugates of low molecular drugs with the aim to improve the specific targeting of drugs to diseased tissues, cells and organs. The main reason for this effort was the fact that high molecular weight copolymers have a favourite distribution profile in tissues and organisms. A linker between a polymer backbone and drug has very important role: it is possible to synthesize a biodegradable linker, which can be enzymatically hydrolyzed. Conversely, there is a possibility to synthesize an inert linker, resistant to the hydrolysis. Proper choice of the suitable precursor-polymer is also essential, hence it has to accomplish all of the stringent demands for biocompatibility. Macromolecular polymer-drug conjugates tend to accumulate in solid tumors because of the so called enhanced permeability and retention (EPR) effect.

There is a whole range of possible applications of high molecular polymer-drug conjugates. In the introduction part of this thesis, I summarize potential use of drugs based on poly(*N*-(2-hydroxypropyl)methacrylamide) (HPMA) copolymers. Moreover, I introduce some therapeutically important proteins used in experimental drug discovery.

In our laboratory, we have developed a concept of HPMA copolymers containing a targeting group (specific inhibitor), an affinity anchor (biotin), and a reporter group (fluorescent label). As a target for the analysis of these conjugates we chose several therapeutic targets, namely glutamate carboxypeptidase II (prostate carcinoma cell membrane marker), HIV-1 protease, and pepsin. Due to their specific properties, we denominated our HPMA copolymer conjugates “iBodies”, a conjunction of an “inhibitor” and “antibodies”.

The enzyme inhibition assays and binding constant determination by surface plasmon resonance revealed that attachment of inhibitor molecules to the copolymer macromolecule preserves binding properties of the inhibitors. iBodies were then used for efficient isolation of all above mentioned proteins from cell lysates. Finally, iBodies were successfully used along with anti-GCPII antibodies in confocal microscopy and flow cytometry. The results prove that iBodies can serve as a fully synthetic substitution of antibodies.

Key words: HPMA conjugates, glutamate carboxypeptidase II, HIV-1 protease, antibody mimetics, protein targeting

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