POLY(2-OXAZOLINE)s AS POLYMER THERAPEUTICS

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Introduction and Discussion

The term "polymer therapeutics" is used for a multifold of therapeutically active compounds and formulations that involve the use of polymers being an active compound by itself or a combination of a given polymer with an active drug as a conjugate or a formulation.[1] The recent success of polymer therapeutics i.e. in cancer therapy is because of specific delivery possibilities of polymers and polymer-drug conjugates such as the EPR effect,[2] in combination with the significantly reduced toxicity of polymer-conjugated drugs and the significantly enhanced bioavalability of linked or formulated active compounds as most potent drugs are insoluble in aqueous media.[3] Taking advantage of the vast synthetic and preparative possibilities of polymer science to tune the solubility, size, architecture and functionality of polymers and polymer aggregates, polymer therapeutics are no longer only subject of pre-clinical research. Among the countless choices of hydrophilic polymers suitable for the design of polymer therapetics, poly(ethylene glycol) (PEG) is the most prominent example. Especially formulations using *Pluronics* [4,5,6] and the therapeutic (and commercial) success of PEG-drug and PEG-protein conjugation known as "PEGylation" [7] paved the way for upcoming polymer therapeutics. One major and persistent drawback is, however, the dispersity of mass and functionality of polymers. As the molar mass and molecular size plays a significant rule in i.e. the biodistribution and pharmocokinetics of polymers, highly defined polymer systems are required.

Currently, poly(2-oxazoline)s (POx) are discussed as a potential candidate and possible (better?) alternative to PEG for the design of next-generation polymer therapeutics.[8,9,10] Such as PEG, POx is prepared by living ionic polymerization and products are highly defined in terms of molar mass dispersity and architecture. Moreover, in contrast to PEG, POx offers the possibility to fine tune the (water)solubility [11,12,13,14,15,16] by the polymer pendant group and also allows additional pendant group functionalization [17,18,19,20,21,22] for the ligation of drugs and/or drug-targeting moieties such as peptides.[23] The water solubility of poly(2-methyl- or 2-ethyl-2-oxazoline) (PMeOx, PEtOx) is similar to PEG, however, as PMeOx shows no amphiphilicity, PEtOx displays a similar amphiphilic character as PEG.[24] It is still unknown if "POxylation" would have similar effects as PEGylation in terms of elongated blood circulation times of conjugated proteins, reduction of toxicity of conjugated drugs, biodistribution, pharmacokinetics, excretion, endocytosis etc. as both polymers are structurally quite different. However, early [25,26,27,28] and current [29,30,31,32,33] results are more than promising.

In this contribution, selected examples of the properties and use of POx as potential polymer therapeutics will be presented. This will include the use of amphiphilic POx copolymers as high-capacity delivery systems for hydrophobic drugs, especially paclitaxel as a potent anti-cancer drug,[34] POx for the formulation of fullerenes as antioxidants for the treatment of brain-related diseases associated with increased levels of superoxide,[32] POx copolymer-enzyme conjugates as a new platform for enhanced cellular delivery [31] and POx-stabilized virus-like particles (POx-VLPs) as a new drug-delivery platform.[35] In this context the relevant properties of various POx homo- and copolymers such as biodistribution and excretion (mice),[30] cytotoxicity and cell uptake as a function of the structure and amphiphilic contrast of POx [33] will be discussed.

Conclusions.

Poly(2-oxazoline)s are a versatile polymer platform for the specific design and use as polymer therapeutics because of their chemical and structural variability and biocompatibility. However, it is still to be shown how POx-based therapeutics behave in complex biological systems including the human body.

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