Enzyme sensitive liposomes in chemotherapy and potentiation of immunotherapy

Cancer is one of the leading causes of death in the world, and improved treatment approaches are urgently needed. One of the major treatment regimes used in the clinic today is chemotherapy. However, chemotherapeutic drugs are often hampered by poor circulation and low specificity, leading to low efficacy and induction of severe adverse effects. Interestingly, the pharmacokinetics and biodistribution of drugs can be substantially altered by encapsulation in liposomal drug delivery vehicles. The first chapter of this thesis gives a brief introduction to cancer followed by a discussion of the applicability of liposomes as drug delivery vehicles in cancer therapy.

The second chapter describes the development of a liposome system with an inbuilt release mechanism triggered by secretory phospholipase A2 (sPLA2). This enzyme is expressed at elevated levels in many human cancers, and as such represents a potential cancer specific trigger mechanism. The presented study validates the concept of sPLA2 induced release. However, in vivo evaluation reveals severe toxicity, potentially related to off-target activation of the trigger mechanism.

In the third chapter, a matrix metalloproteinase (MMP) sensitive liposome system is evaluated. Here cationic liposomes are engineered with an MMP cleavable PEG construct, aimed at shedding the PEG layer upon encounter with cancer expressed MMP enzymes, leading to exposure of the cationic charge and enhanced uptake in cancer cells. It is demonstrated that although exposure of cationic charge leads to enhanced uptake, it does not necessarily lead to enhanced bioavailability of the drug, underlining the importance of a release mechanism.

The fourth chapter explores the impact of the immune system on the efficacy of liposomal oxaliplatin. The chapter starts with an introduction to the cancer-immunity cycle and to how treatment approaches can aid this interplay. Subsequently it demonstrates that the presence of a functional immune system is important in the efficacy of liposomal oxaliplatin, and that this efficacy can be substantially enhanced by combination with the immune modulatory agent R848.

In the fifth and last chapter it is concluded that the potential of liposomes in cancer drug delivery is highly dependent on extensive knowledge of the interplay between the intrinsic parameters of the liposome, the phenotype of the cancer and the potential effects on off-target tissues. Furthermore, it is underlined that effective cancer therapy requires approaches that target several different aspects of the cancer, and that in the case of liposomal oxaliplatin this can be partially achieved by combination with an effective immune modulatory agent. Finally it is speculated that further improvement of the presented treatment strategy might be obtained by targeting additional aspects of the cancer-immunity interplay not already addressed.

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