Targeting of cationic Liposomes to the Synovial Endothelium of Rheumatoid joints - a new promising drug delivery system

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Introduction: The healthy endothelium consists of quiescent endothelial cells that, under appropriate stimulation, can undergo profound changes leading to an activated phenotype. Activated endothelial cells of the synovial vasculature play a major role in the inflammatory process occurring in rheumatoid arthritis (RA) and enhanced angiogenesis contributes to the formation and maintenance of the pannus in RA. Thus, the endothelium can be used as a gateway for drug delivery and therapy. Cationic liposomes have been shown to target angiogenic endothelial cells in tumors and chronic inflammation in mice. They may also serve as potent vehicles for drug delivery to the synovial vasculature of rheumatoid joints.

To test whether cationic liposomes can serve as vehicles for drug delivery in RA we investigated the targeting of fluorescently labelled cationic liposomes (LipoRed) to the activated synovial vasculature of knees from arthritic mice.

Materials and Methods: Targeting of LipoRed to the synovial vasculature was analysed by intravital microscopy (IVM) in mice with antigen induced arthritis (AIA). Synovial tissue was investigated at day 8 after AIA induction. Time resolved binding of liposomes was quantified at functional vessels of the microvasculature. Targeting of cationic liposomes to TNF-alpha stimulated skin vessels was studied by IVM in a hamster skinfold chamber.

Results: In a time dependent manner, intravenously applied LipoRed enriched more then threefold in the synovial vasculature of AIA mice when compared with healthy mice. In AIA animals maximum binding measured as relative fluorescence ($F_{max}$=142 RFU) was already achieved 5 min after LipoRed application ($t_{max}$) and dropped to the half maximum after 100 min ($t_{max}/2$) compared with healthy mice with a $F_{max}$=48 RFU, $t_{max}$=15 min and $t_{max}/2$= 60 min [Image_1]. After local TNF-alpha application in a skinfold chamber, the binding profile of LipoRed observed in subcutaneous vessels of hamsters was very similar to the one found in the synovium of AIA mice. LipoRed application 1 h after the TNF-alpha stimulus resulted in a fast, threefold enrichment of liposomes at the blood vessels, when compared with non treated animals.

Discussion: Based on our in vivo data, cationic liposomes seem to be very well suited to deliver compounds to rheumatoid joints for diagnosis and/or therapy. Furthermore, our results from animal experiments suggest that cationic liposomes could be a promising treatment option for RA.