HOW LIPOSOME TRAFFICKING IN NON-APC INFLAMMATORY IMMUNE CELLS IN BLOOD CIRCULATION DRIVE THE ACCUMULATION OF LIPOSOMES IN INFLAMMATORY REGIONS: UNRAVELLING AN ESSENTIAL MECHANISM OVERLOOKED BY THE EPR EFFECT

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The ability of liposomes, the most common type of nanocarriers, to effectively reach inflammatory lesions is believed to rely on their competence to passively accumulate through endothelial gaps in diseased blood vessels, the so-called EPR effect. Despite the promising results that are obtained in this context, there is still a lack of consist data evaluating the impact of the liposomes physicochemical properties on their capacity to passively target distinct (inflammatory) immune cell subsets and contribution to liposome accumulation. In this work we compared the biodistribution and immune cell targeting capacity of 4 i.v. injected types of cholesterol-based liposomes with a comparable size (± 180 nm) but different physicochemical properties as model liposomes in healthy and inflammatory conditions (arthritis model). While positively charged liposomes are not or only slightly reaching inflamed regions, neutral charged liposomes (with or without PEGylation) show a significant higher accumulation in the inflamed region. The accumulation is correlated to liposome uptake in inflammatory monocytes that maturated into monocyte derived monocytes in the inflammatory lesion and largely driven by the CCR2-CCL2 chemotactic gradient. Additionally, long circulating liposomes in the blood circulation function as a 'depot' and facilitate the continuous targeting of newly attracted monocytes in the blood. This liposome-trafficking mechanism was corroborated using an in situ autologous transfer of (liposome positive) immune cells in a CIA model. Altogether, chemotactic immune cell transport towards inflammation region is an important factor contributing to therapeutic outcomes that have been solely attributed to EPR effect in literature.