Extracellular vesicles-Liposomes Hybrid thermoresponsive nanovesicles for selective tumor targeting

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Immune cells are clinically relevant in solid tumor behaviour, considering their consistent presence in the tumor mass and their active role. In this context, M1 macrophages act as tumor suppressors during early stages through the release of pro-inflammatory cytokines as well as cytotoxic mediators. Recently the M1-derived extracellular vesicles (EVs) gained the interest of scientific community because they reflect the surface architecture and bioactive cargos of parent cells, thus allowing both a tropism towards tumor microenvironment and the capability to induce the in situ macrophage reprogramming from M2 to M1. In these attempts, this work aims to combine thermoresponsive liposomes with M1-derived EVs in order to realize hybrid nanosystems capable of reaching tumor site easily and releasing massively the cargos after application of external hyperthermia. In brief, EVs were isolated from M0 and M1 murine macrophages, then physicochemical characterized in terms of particle size, polydispersity index, stability parameters and FACS analysis. The hybrid thermoresponsive nanosystems were obtained through the freeze–thaw process, validated by FACS analysis and their thermoresponsiveness behaviour was investigated through fluorescent probe release, by comparing its rate at 37°C and 42°C. The results obtained confirmed through a massive and higher payload's release during the first 1 h of incubation at 42°C than 37°C. *In vivo* tumor targeting analysis revealed a higher accumulation of hybrid nanosystem made up of M1-EVs and liposomes than liposomes. These results strongly suggest the potential use of synthetized hybrid nanosystem for the development of an effective targeted and stimuli-responsive personalized anticancer therapy.