Extracellular vesicle/prodrug-mediated specific treatment of HER2+ve breast cancer xenografts in mice

AC Matin
Stanford University, USA

This talk is concerned with therapeutic uses of EVs (exosomes) and deals with gene-delivered enzyme prodrug therapy (GDEPT), which promises to confine drug generation to the tumor at a high concentration and mitigating off-target effects. A new prodrug [6-chloro-9-nitro-5-oxo-5Hbenzo-(a)-phenoxazine (CNOB)] and the Escherichia coli enzyme HChrR6 that we discovered, and improved, and our recent success in specifically targeting it to implanted orthotopic HER2+ve breast cancer (BC) tumors in mice will be discussed; HChrR6 converts the harmless CNOB to the highly cytotoxic drug, 9-p amino-6-chloro-5H-benzo[a]phenoxazine-5-one (MCHB). As mRNA is superior to DNA for gene delivery and EVs less subject to immune rejection, mRNA encoding the HChrR6 enzyme-loaded EVs that displayed an anti-HER2 scFv antibody (on a chimeric protein termed EVHB) were used. These “EXO-DEPT” EVs—but not the non-directed, non-mRNA containing EVs-impacted CNOB activating capability specifically on the HER2+ve BT474 cells in vitro and caused the complete arrest of implanted orthotopic BT474 tumors in immunocompromised mice. This is the first time that foreign functional mRNA was successfully delivered using EVs4. As the anti-HER2 scFv in EVHB can be replaced by other targeting moieties, this approach can be employed to treat any disease overexpressing a specific marker. In vivo ablation of the tumor is a potent method for stimulating robust HER2-specific adaptive T- and B-cell responses. Results will be presented of ongoing work in collaboration with Dr Kim Lyerly (Duke University) on the reinforcing effect of this response on the efficacy of the EXODEPT/CNOB regimen. A BC mouse model driven by an oncogenic form of human HER2 (HER2Δ16) is being used. It relies on mammary-specific expression of HER2Δ16, leading to aggressive breast tumor development within weeks of induction, with strong central tolerance to the HER2Δ16 epitope. Measurements underway involve HER2-specific systemic T-cell responses (T-cell ELISPOT assays from harvested splenocytes; assessment of cytokine flow), tumor regression and mouse survival.

amatin@stanford.edu