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Intratumoral heterogeneity and identification of tumor initiating cells (tic) for cancer vaccination

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Cancer vaccination strategies require vaccination against cancer antigens that are expressed on tumor cells. However, with the recognition that most cancer consists of heterogeneous tumor cells that expresses different markers and antigens during cancer progression it has become imperative to identify the tumor cells that are responsible for cancer initiation and progression and target these cells for effective vaccination against cancer. These cells are also known as Tumor Initiating Cells (TIC) or Cancer Stem Cells (CSC) and our laboratory is involved in identifying these cells and developing immunotherapy strategy against them for cancer vaccination.

Our studies with advance stage lung cancer bio-specimens from Malignant Pleural Effusion (MPE) patients have indicated that tumor cell heterogeneity exists in terms of cell surface markers expression (CD44, CD166, cMET, MDR1, uPAR) and molecular markers associated with TIC/CSC (BMI-1, hTERT, EZH2, OCT-4). These primary tumor cells express the CD44 surface marker on most of the tumor cells (75-95%). However, the intensity of CD44 surface marker expression varies and cells can be identified and sorted as high CD44 ($CD44_{hi}$) and low CD44 ($CD44_{lo}$) expressing cells. The $CD44_{hi}$ cells are more efficient in forming soft agar colonies (1.5-2.5 times), are more tumorigenic in NOD/SCID ($IL\text{-}2_{null}$) mice and express high level of specific TIC/CSC molecular markers than $CD44_{lo}$ cells. The $CD44_{hi}$ cells have significantly lower miR-34a than $CD44_{lo}$ cells and introduction of miR-34a resulted in 80-95% reduction of soft agar colonies. The cells were also evaluated for adenoviral entry receptors (CAR, avb3, avb5) for consideration of targeted gene-therapy. Remarkably, over 80% of the CD44 cells co-express CAR and av5, but not av3. These cells undergo apoptosis by UV radiation and can also be efficiently loaded on human dendritic cells (DC) for efficient delivery to the immune system.

Biography

Saroj Basak is involved with vaccination research and translational cancer therapy at UCLA. His research works involve development of immunotherapy and gene therapy strategies against cancer using viral vectors (adenovirus, helper-dependent adenovirus, lentivirus) and dendritic cells mediated immunotherapy. He has numerous publications and has received several grants for improvement of vaccination strategies for cancer. He is an expert in pre clinical studies; animal model development using primary cancer cells, dendritic cells mediated vaccination and therapy. Currently his laboratory is involved with identifying and characterizing cancer initiating cells and development of targeted therapy and vaccination strategies against these cells. His laboratory is also involved in evaluating the effect of biologics and natural products in overcoming drug resistance in cancer.

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