Possibility of tuning the differentiation state of tumor associated macrophages towards tumor controlling phenotypes

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Abstract

Although various immune cells could infiltrate the cellular and tissue environment surrounding a tumor, the tumor microenvironment nevertheless presents immunosuppressive conditions unfavorable for immune cells to conduct large scale attack on cancer cells. For example, T-cells that make it to the tumor microenvironment are typically non-functional in containing tumor growth. On the other hand, macrophages could infiltrate the tumor microenvironment and is an important cell type modulated by and which also modulates the tumor. Specifically, two variants of macrophages with different phenotypes are known to exhibit close interactions with tumors. Known as M1 and M2 macrophages, they present dichotomously different signals to the tumor. Specifically, M1 macrophages control tumor growth while M2 macrophages promote tumor growth. Thus, from a treatment perspective, it would be desirable to tune the phenotypes and cell differentiation program of macrophages towards the M1 subset. To do that, differential gene expression of macrophages in the M1 and M2 lineages must be understood. Such a goal could be achieved with the profiling of tumor associated macrophages from tumor biopsy samples for gene expression patterns characteristic of the two dominant macrophage lineages. Single cell RNA-sequencing conducted after flow cytometry sorting of M1 and M2 macrophages would highlight gene expression patterns associated with each lineage, and the cellular differentiation programs that prompted entry into particular macrophage subtype. Knowledge of gene expression pattern associated with each macrophage lineage is not useful for tuning their differentiation state unless specific transcription factor that trigger the regulon could be identified. To this end, transcription factors that have been upregulated in the differentiation program could be profiled from the transcriptome data, and help inform the design of vectors for targeted overexpression of specific transcription factor for modulating cellular differentiation of macrophage. Given their low immunogenicity, adeno-associated virus (AAV) could serve as vectors for ferrying the gene cassette containing specific transcription factors into macrophages. Delivery methods for the AAV could be via targeted local infusion of vectors to tumors or through the systemic circulation, but the latter approach would result in lower transfection efficiency. Collectively, possibility exists of tuning the differentiation state of macrophage associated with tumors for enabling tumor controlling lineage to be dominant. Such immuno-targeted therapy would harness the body's macrophages for controlling tumor growth and represents a treatment option that may yield fewer side effects compared to conventional chemotherapy. But, identification of genes that control lineage-specific differentiation program and the delivery of gene cassette to macrophages for modulating their differentiation remain key challenges.

Keywords: macrophages, immunotherapy, differentiation state, RNA-sequencing, transcriptome, transcription factor, gene expression pattern, adeno-associated virus, transfection, tumor,

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Conflicts of interest

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