PREAMBLE
Solid tumors are heterogeneous in composition since they contain many different host cell types in addition to the tumor cells. The host cells infiltrating the tumor mass include stromal cells of the tissue where the tumor is growing as well as the migratory immune cells. With tumor progression, these non-tumor host cells gradually acquire a pro-tumoral function and influence the tumor microenvironment for developing signatures of malignancy. Moreover, tumor-educated neighboring non-tumor host cells are polarized in such a way that they paralyze host-protective anti-tumor immune responses and aid in tumor growth, angiogenesis and metastasis. Among the various host cells infiltrating the tumor mass, macrophages and T regulatory cells are specifically important due to their profound influence on solid tumor progression.

Macrophages recruited to the tumor stroma, commonly known as tumor associated macrophages (TAM), play an unusual but very important role in tumor progression. TAM resemble alternatively activated M2 form of macrophages and consequently produce very high amount of immunosuppressive cytokines like IL-10 and TGF-β in resting condition as well as when activated with their classical activator, LPS. TAM are also crucial for initiation of angiogenesis and lymph-angiogenesis at the tumor microenvironment. Moreover, TAM actively take part in the initiation of tumor metastasis by inducing epithelial to mesenchymal transition (EMT) of tumor cells. Furthermore, TAM may induce the differentiation of drug resistance cancer-stem cells within the tumor microenvironment. In addition, TAM restrain effector T cells function at the tumor site by employing direct (contact-mediated) and/or indirect (secreted soluble molecules-mediated) immunosuppressive modalities. TAM may also suppress T cells activity by antagonizing chemokine signaling crucial for homing of effector T cell. Moreover, TAM may produce T regulatory cell attracting chemokines to enrich the T regulatory cell
frequency within the tumor mass for suppression of anti-tumor T cell responses. Therefore, it is now widely accepted that these highly immunosuppressive TAM are crucial for the progression of most of the solid tumors. However, it is yet to be explored how tumor infiltrating macrophages are alternatively polarized to become TAM within the tumor microenvironment.

T regulatory cells are immensely important for the growth and persistence of solid tumors within a host. T regulatory cells are originally destined to protect the host from excessive inflammation by suppressing the immune responses and tumors cleverly utilize this immunosuppressive potential of T regulatory cells for their own favor. Most of the solid tumors enrich T regulatory cell frequency by producing chemokines to attract thymic T regulatory cells and induce their proliferation or they may induce extra-thymic differentiation of T regulatory cells from naïve T cells at the tumor microenvironment to suppress the anti-tumor responses against the growing tumor. These extra-thymically derived T regulatory cells are known to play a crucial role during tumor metastasis. However, the mechanism of extra-thymic differentiation of T regulatory cells from naïve T cells at the tumor microenvironment remains unknown.

Thus, it seems that immunotherapeutic approaches which include modulation of TAM as well as suppression of T regulatory cell function may induce host protective immune responses against most of the solid tumors.

Therefore, this study has depicted the mechanism of alternative polarization of macrophages and differentiation of T regulatory cells at the tumor microenvironment. In addition, this study has shown a way for the generation of an effective anti-tumor response by modulating both of the TAM as well as T regulatory cell function at the tumor microenvironment.