PROGNOSTIC SIGNIFICANCE OF M1/M2 TUMOR-ASSOCIATED MACROPHAGES WITH PIGMENTATION IN UVEAL MELANOMA

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Background Tumor-Associated Macrophages (TAMs) are associated with an unfavorable outcome in uveal melanoma (UM). Literature showed the correlation between UM with monosomy 3 and an inflammatory phenotype including the presence of TAMs. TAMs in UM with monosomy 3 are predominantly pro-angiogenic M2 polarized macrophages which are characterized by CD163. They promote tumor progression and produce cytokines IL 10 in high amounts. Whereas M1 which is characterized by CD68 is generally considered a potent effector cell that kills microorganisms and tumor cells. They produce pro-inflammatory cytokines IL12 in high amounts. Studies showed that there was less melanin secretion in the presence of M1 macrophages but increased in the presence of M2 macrophages. Additionally, high melanin content could lead to high metastatic potential in UM. TRP1 (Tyrosine Related Protein 1) regulates eumelanin synthesis in the Asian population. The oncogenic potential of TAMs in association with pigmentation has not been investigated in UM in the Asian population. Therefore, our study aimed to detect the prognostic significance of TAMs and TYRP1 expression levels in UM patients.

Methods Fluorescence In Situ Hybridization (FISH) to detect monosomy 3 was done on 40 UM tissue samples. Immunohistochemistry (IHC) of CD68, CD163 & TRP1 was performed on all UM tissue samples. mRNA expression level of TRP1 was measured by qRT-PCR in all fresh UM cases. ELISA was performed to quantify the expression of IL-10 and IL-12 in UM patients’ serum samples. Cox proportional hazard model and log-rank test were used to determine the prognostic outcome of these markers.

Results Infiltrating macrophages in UM cases were predominantly of M2 phenotype. The density of CD163 cells was significantly increased in UM with monosomy 3 and high TRP1 expression compared to disomy 3 and loss of TRP1. Expression of CD163 and TRP1 was correlated with high pigmenta- tion and BAP1 loss. Moreover, UM cases showed high IL10 concentration in comparison to the normal choroid. No significant changes in IL-12 concentration were observed. High expression of TRP1 protein showed reduced disease-free survival (p<0.001).

Conclusions Our study showed that high pigmentation might affect the tumor microenvironment in UM by increasing the densities of M2 macrophages leading to tumor progression. This might have a role in the absence of effective antitumor immune responses in UM patients. Our study could provide the development of new therapeutic options that can overcome the immunosuppressive effects.

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REFERENCES

Ethics Approval Ethical approval was obtained from the Institute’s Ethical Committee, All India Institute of Medical Sciences. (approval ID# IECPG-501/17.07.2019)
Consent Written informed consent was obtained from all patients before participation in this study.

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