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Editorial

Molecular insights into tumor microenvironment and targeted therapies

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The years 2020 and 2021 brought with them unprecedented and ever-changing challenges for the scientific and medical community worldwide. COVID-19 has pushed humankind to the limits of our capacity when it comes to innovation, self-discipline, communication, compassion, and care. As we ring in 2022, the Omicron variant is making its' presence felt, with natural selection appearing to prefer this variant over the previously dominant Delta variant.[1] As we continue to watch and learn from this virus that has changed the shape of our lives and our worlds, we also continue to strive for excellence in molecular and clinical oncology as a community. Here, we continue our tradition of reporting interesting and potentially game-changing advances in molecular and immuno-oncology.

METFORMIN-LOADED MANNOSE-MODIFIED MACROPHAGE-DERIVED MICROPARTICLES REPROGRAM THE TUMOR IMMUNE MICROENVIRONMENT AND IMPROVE ANTI-PD-1 THERAPY

Immune checkpoint blockade of programmed death 1 (PD-1)/PD ligand-1 (PD-L1), despite its initial promise, has been unable to elicit durable anti-tumor response in many patients mainly due to the immunosuppressive tumor microenvironment (TME) and the condensed tumor extracellular matrix (ECM) which resists anti-PD-1 antibody penetration. One of the main factors causing the immunosuppressive TME is the accumulation of M2-like tumor-associated macrophages (TAMs) which promote tumor growth, recruit other immunosuppressive cells, and deplete anti-tumor T cells from the tumor. Recently, metformin (Met) has been shown to repolarize M2-like TAMs to M1-like TAMs which are anti-tumor in nature. Considering this and the expression of mannose receptors in M2-like TAMs, researchers engineered Met-loaded, mannose-modified macrophage-derived microparticles (Met@Man-MPs) to deliver Met to M2-like TAMs.[2] They carried out *in vitro* and *in vivo* studies and found that Met@Man-MPs significantly inhibited tumor growth by repolarizing M2-like TAMs to M1-like TAMs, degraded the collagen of the tumor ECM, and recruited $CD8^+$ T cells into the tumor. The degradation of collagen boosted the tumor accumulation of anti-PD-1 antibodies, while the reprogrammed anti-tumor TME inhibited tumor progression. Compared to treatment with either Met@Man-MPs or anti-PD-1 antibodies, the combination of both showed greatly improved inhibition of tumor growth while maintaining least toxicity.

PLASMINOGEN-ACTIVATING INHIBITOR-1 (PAI-1) IMPAIRS TREATMENT RESPONSE TO ANTI-PD-1 THERAPY IN MELANOMA PATIENTS

PAI-1, a serine protease, is often overexpressed in tumors where it seems to have multiple effects such as recruitment of certain TAMs and endocytosis of PD-L1. In this recent study, Ohuchi *et al*., 2021,[3] investigated PAI-1's immunomodulatory effects and if it affects response to PD-1 blockade in melanoma patients. The researchers quantified PAI-1 in tumor tissues and sera of patients, which combined with clinical data, showed that responders to PD-1 blockade had low expression of PAI-1, which corresponded with their other finding that PD-1 expression increased with the decrease of PAI-1 expression. To investigate PAI-1's immunomodulatory effects *in vitro*, $CD163^+$ M2 TAMs were treated with PAI-1 which decreased their production of CXCL10 and CCl22 (which recruit anti-tumor immune cells) and increased the production of CXCL5 (recruits immunosuppressive cells). Further investigation *in vivo* by quantifying $CD8^+$ T cells (anti-tumor) in patient samples showed that $CD8^+$ T cells decreased as PAI-1 expression increased. PAI-1 may, therefore, be considered as a predictive biomarker for PD-1 blockade in melanoma patients. Furthermore, since inhibiting PAI-1 may increase treatment response in non-responders, the authors are starting a Phase II trial for evaluating the combination of nivolumab (anti-PD-1) and TM5614 (PAI-1 inhibitor) in melanoma patients.

PROMISING IMMUNOTHERAPY COMBINATION FOR BRAF+ MELANOMA

Melanoma drug dabrafenib, used for melanoma with specific BRAF mutations, acts by blocking BRAF activity. Another treatment, trametinib, acts on the protein MEK. Both have been in use for a few years independently and in combination for advanced melanoma with certain BRAF mutations.[4] Now, with the availability of immunotherapy drugs (such as PD-1 and cytotoxic T lymphocyte-associated protein-4 blockers), the combination of approved targeted melanoma drugs with immunotherapy was considered. The DREAMSeq clinical trial results were presented recently,[5] which showed that early on, if immunotherapy is administered, patients demonstrate higher survival rates, overall. They evaluated 73 patients who had two treatments – of which 27 had immunotherapy first, then switched to targeted therapy; and 46 who had targeted therapy first and underwent immunotherapy second. The researchers aim to look at biomarkers to determine which regimen is suitable for various individuals based on their unique molecular profile.

A BIOMARKER TEST FOR NEUROFIBROMATOSIS (NF) TYPE 1

NF1 affects as many as one out of 3000 people globally and is due to a mutation in the gene for NF1 protein. It can result in large benign tumors on nerves that are known as plexiform neurofibromas, of which a subset (15%) may turn into malignant peripheral nerve sheath tumors (MPNSTs). It is estimated that four out of five individuals with MPNST do not survive more than 5 years. Developing a biomarker test would be critical to be able to predict whether the benign tumors will become malignant. In a new study,[6] patients with plexiform neurofibromas, untreated MPNST, and healthy controls, n = 23, 14, and 16, respectively, were evaluated. Cell-free DNA from blood samples taken from these patients was compared that certain signatures were noted that set apart the MPNST samples from those taken from the other two groups. The study shows promise for the development of a blood test for screening and preemptive action in individuals with the NF1 mutation.

REFERENCES

1. Joshi S. Omicron in delta dominant India: Implications and outcome. Indian J Med Sci 2021;73:287-8.
2. Wei Z, Zhang X, Yong T, Bie N, Zhan G, Li X, *et al*. Boosting anti-PD-1 therapy with metformin-loaded macrophage-derived microparticles. Nat Commun 2021;12:440.
3. Ohuchi K, Kambayashi Y, Hidaka T, Fujimura T. Plasminogen activating inhibitor-1 might predict the efficacy of anti-PD1 antibody in advanced melanoma patients. Front Oncol 2021;11:798385.
4. Ganguly S, Ghosh J, Mishra D, Biswas G, Dabkara D, Roy S. Early experience with dabrafenib-trametinib combination in patients with BRAF-mutated malignant melanoma a single-center experience. South Asian J Cancer 2021;10:187-9.
5. Atkins MB, Lee SJ, Chmielowski B, Ribas A, Tarhini AA, Truong TG, *et al*. DREAMseq (doublet, randomized evaluation in advanced melanoma sequencing): A phase III trial ECOG-ACRIN EA6134. J Clin Oncol 2021;36 Suppl:356154.
6. Szymanski JJ, Sundby RT, Jones PA, Srihari D, Earland N, Harris PK, *et al*. Cell-free DNA ultra-low-pass whole genome sequencing to distinguish malignant peripheral nerve sheath tumor (MPNST) from its benign precursor lesion: A cross-sectional study. PLoS Med 2021;18:e1003734.

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