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605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

DNA Vaccines Against GPRC5D in Myeloma

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Introduction:
Myeloma is an incurable disease despite improved survival from the ongoing immunotherapy revolution. Virtually all myeloma cases are preceded by MGUS, a condition affecting over one million Americans. Smoldering myeloma is an asymptomatic clonal plasma cell disorder between MGUS and myeloma. Smoldering myeloma is distinguished from MGUS primarily for clinical reasons because the risk of progression to malignancy in the first five years after diagnosis is different: 10% per year in smoldering myeloma vs. 1% per year in MGUS. Yet the risk of progression is not constant, and in a subset of MGUS patients, the risk evolves from a low chance of progression to a high degree of probability of progression to MM. Therefore, patients with smoldering myeloma and MGUS are potential subjects for myeloma prevention. GPRC5D is an emerging novel immunotherapeutic target for myeloma, with several ongoing clinical trials using CAR T cells and antibodies directed against GPRC5D.
Methods:
Nanoplasmid is a next-generation plasmid technology that bypasses the antibiotic selection when amplified in *E. coli* by expressing a 150 bp RNA-OUT antisense RNA and uses the highly productive heat-inducible R6K origins for DNA replication. With a <500 bp backbone, Nanoplasmids achieve significantly higher expression levels than pVAX1, the most widely used plasmid in DNA vaccine development. We used Nanoplasmid to express human GPRC5D and introduced it into mice via electroporation xenografted with mouse cancer cells that express the human GPRC5D gene. We examined the animals and determined whether the prophylactic vaccines prevented myeloma development and progression.
Results:
We found that mice vaccinated with the human GPRC5D Nanoplasmids had both humoral and cellular responses against the GPRC5D protein. The DNA vaccines were active in reducing tumor development from human GPRC5D-expressing tumors.
Conclusions:
GPRC5D-targeting DNA vaccines are a cost-effective prevention agent for MGUS and smoldering myeloma.

Disclosures No relevant conflicts of interest to declare.

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