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POSTER PRESENTATION Open Access

Immunologic hierarchy and promiscuity of melanoma helper peptides

Yinin Hu*, Gina R Petroni, Walter C Olson, Andrea Czarkowski, Mark Smolkin, William W Grosh, Patrice K Rehm, Cheryl F Murphy, Elizabeth J Coleman

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Background

Melanoma vaccines have been designed to expand specific CD8+ T-cells, but melanoma-reactive helper T-cells also can have antitumor activity. We previously observed clinical activity of a vaccine incorporating 6 melanoma helper peptides (6MHP), and found associations between CD4+ T cell response and survival. With the present study, in the spirit of personalized cancer immunotherapy, we define the relative immunogenicity and HLA allele promiscuity of individual helper peptides, and

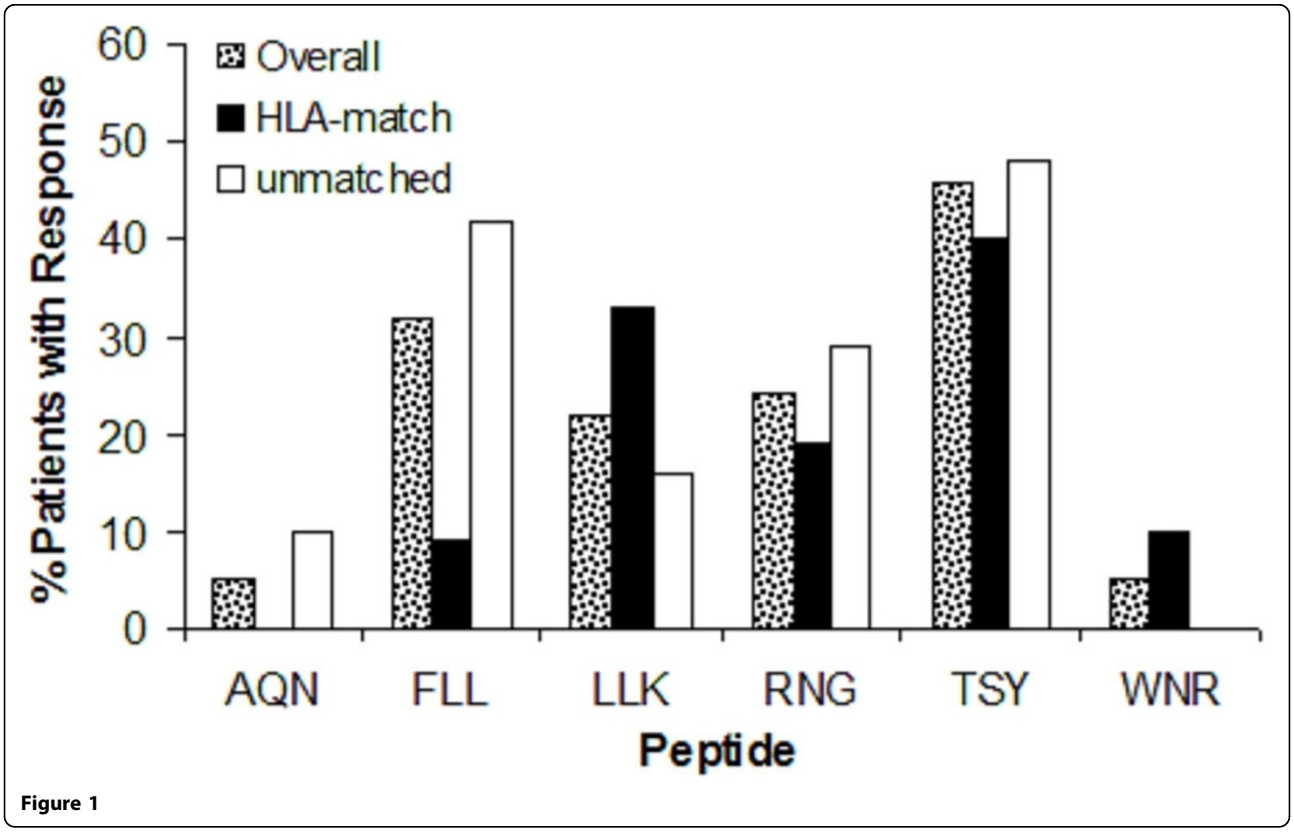

Figure 1

University of Virginia, Charlottesville, VA, USA

identify helper peptide-mediated augmentation of melanoma-specific CD8+ T-cell response.

Methods

Thirty-seven patients with stage IIIB-IV melanoma were vaccinated with 6MHP in incomplete Freund's adjuvant. The vaccines contained 6 peptides: gp10044-59 (first 3 amino acids: WNR), Tyrosinase56-70 (AQN), Tyrosinase386-406 (FLL), Melan-A/MART-151-73 (RNG), MAGE-A3281-295 (TSY), and MAGE-A1, 2,3,6121-134 (LLK). Peripheral blood mononuclear cells (PBMC) and sentinel immunized nodes (SIN) were collected. CD4+ T-cell proliferation was assessed by thymidine uptake after exposure to peptides. CD8+ T-cell response was assessed by direct IFN-γ ELIspot assay against 14 MHC class I-restricted peptides.

Results

Vaccines induced CD4+ T cell responses to the 6MHP pool in 78% (29/37) of patients in SIN and 57% (21/37) in PBMC for an overall response rate of 81% (30/37), with responses to an average of 2 peptides per patient. The two most frequently immunogenic peptides were TSY at 49% (18/37) and FLL at 32% (12/37). HLA restriction was not limited to alleles originally described; for each peptide, the proportion of immune responsive patients whose HLA-DR expression matched those originally described was similar to the proportion of patients with different HLA-DR expression (unmatched, Figure 1). Vaccine-associated CD8+ T-cell response was observed in 45% (5/11) of patients, and three of these patients demonstrated CD4+ T-cell response toward TSY.

Conclusions

The 6MHP vaccine has CD4+ T-cell immunogenicity beyond known HLA-DR restrictions. Patients whose tumors express tyrosinase, MAGE-A3, and several other MAGE proteins may be ideal for vaccination with 6MHP. The 4 most immunogenic peptides warrant further study, perhaps in combination immune therapies.

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