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Identification and validation of HLA-A24 XBP1, CD138, and CS1 peptides and induction of antigens-specific CD8+ T cell immunity using a multipeptide cocktail: Preclinical basis for vaccine therapy in HLA-A24 patients with multiple myeloma and other cancers

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XBP1 (X-box binding protein 1), CD138 (Syndecan-1) and CS1 (SLAMF7) are highly expressed antigens associated with tumor pathogenesis in cancers including multiple myeloma (MM) and various solid tumors. We have previously reported on the use of HLA-A2 peptides specific to these antigens to generate specific cytotoxic T cells (CTL). Vaccinations with these pooled peptides are currently in phase I/II clinical trials in patients with smoldering MM or triple negative breast cancer. The current studies extend this concept to the patients with HLA-A24, the second most dominant MHC-Class I in North America and the most common in Asia to broaden the patient population eligible for this cancer vaccine. Immunogenic HLA-A24 peptides derived from the antigens were evaluated. The identified XBP1 unspliced $(UN)_{185\text{-}193}$ (I S P W I L A V L), XBP1 spliced $(SP)_{223\text{-}231}$ (V Y P E G P S S L), $CD138_{265\text{-}273}$ (I F A V C L V G F) and $CS1_{240\text{-}248}$ (L F V L G L F L W) peptides were highly HLA-A24-specific and immunogenic, and induced *ex vivo* antigen-specific CTL with anti-MM activity in an HLA-A24 specific manner. Furthermore, a cocktail containing the four HLA-A24 peptides evoked MM-specific CTL with distinct phenotypic profiles (CD28, CD40L, 41BB, CD38, CD69) and anti-tumor activities, evidenced by perforin/CD107a/IFN-γ/IL-2/TNF-α production induced by HLA-A24+ MM cells. The multipeptide-specific CTL included antigen-specific memory CD8+ T cell subsets expressing T cell activation and immune checkpoints antigens (CTLA, PD1, LAG3, TIM3). Treatment of the multipeptide-CTL with specific inhibitors against mTOR, AKT, HDAC6 or specific immune checkpoints enhanced frequency/activation of antigen-specific central memory CTL and their anti-tumor activity. These results highlight the potential therapeutic application of an HLA-A24 multipeptide vaccine to induce MM-specific CTL with a broad spectrum of anti-tumor activity, which may extend to solid tumors (breast, colon, and pancreatic cancer) expressing these antigens.

Biography

Jooeun Bae has completed his PhD in Biomedical Science from Virginia Polytechnic Institute and State University, Blacksburg, Virginia. He holds a Master's Degree in Major in Immunology and Microbiology from University of Maryland, Baltimore, Maryland followed by a Bachelor's Degree from University of Maryland, Baltimore, Maryland. He attended the American Society for Hematology conference in San Diego, California USA.

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