5）Focal adhesion kinase as an immunotherapeutic target

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[Translational Relevance]

The findings reported herein hold significant translational value for developing immune-based therapies for various tumor types. We report for the first time that focal adhesion kinase (FAK) functions as tumor-associated antigen (TAA) for the induction of anti-tumor helper T-cell responses. Because FAK is widely expressed on various tumor types, it can be considered as a "universal" TAA, allowing any immune therapeutic strategy using this antigen to be widely applicable in the general cancer patient population. Because the 2 peptide epitopes from FAK that are described in this manuscript were shown to be "promiscuously MHC-class II restricted", they could be used clinically in patients expressing various MHC class II alleles. These epitopes could be used in the manufacturing of peptide or DNA therapeutic vaccines, or for the generation of anti-tumor T cell lines to be used for adoptive immunotherapy.

[Background]

Focal adhesion kinase (FAK) is a ubiquitously expressed non-receptor tyrosine kinase involved in cancer progression and metastasis that is found overexpressed in a large number of tumors such as breast, colon, prostate, melanoma, head and neck, lung and ovary. Thus, FAK could be an attractive tumor associated antigen (TAA) for developing immunotherapy against a broad type of malignancies. In this study, we determined whether predicted T cell epitopes from FAK would be able to induce anti-tumor immune cellular responses.

[Methods]

To validate FAK as a TAA recognized by CD4 helper T lymphocytes (HTL), we have combined the use of predictive peptide/MHC class II binding algorithms with in vitro vaccination of CD4 T lymphocytes from healthy individuals and melanoma patients.

[Results]

Two synthetic peptides, FAK143-157 and FAK1000-1014, induced HTL responses (Fig. 1) that directly recognized FAK-expressing tumor cells (Fig.2) and autologous dendritic cells pulsed with FAK-expressing tumor cell lysates in an HLA class II-restricted manner (Fig.3). Moreover, since the FAK peptides were recognized by melanoma patient's CD4 T cells, this is indicative that T cell precursors reactive with FAK already exist in peripheral blood of these patients (Fig.4).

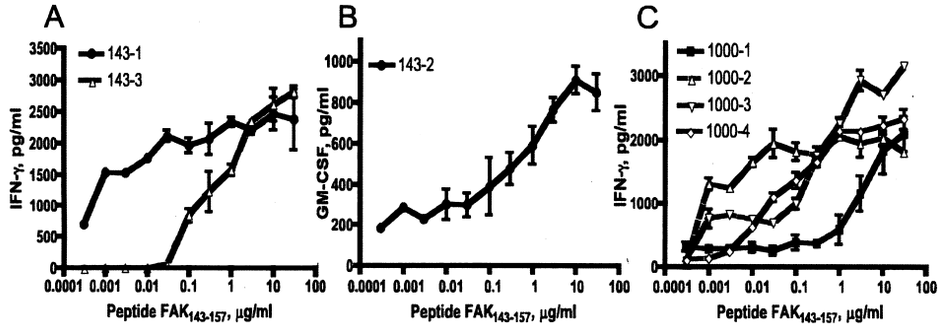

Figure 1 Induction of CD4 T helper responses using predicted peptide epitopes derived from FAK

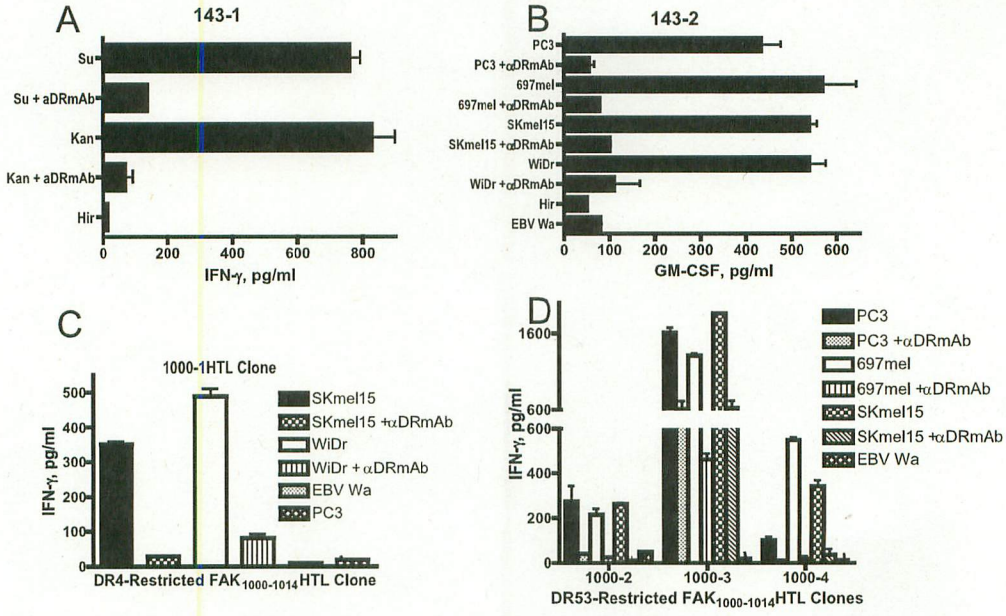

Figure 2　Direct recognition of FAK-expressing tumor cells by FAK-reactive HTL clones

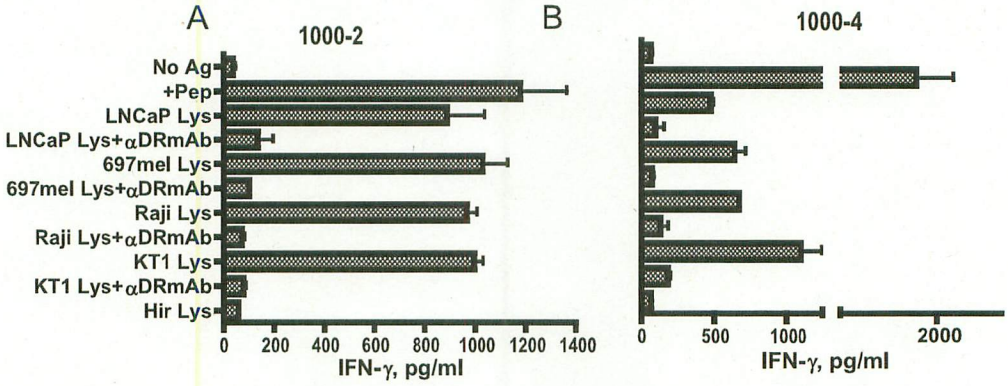

Figure 3　FAK-reactive HTL recognize naturally processed exogenous tumor lysates antigen presented by autologous DC

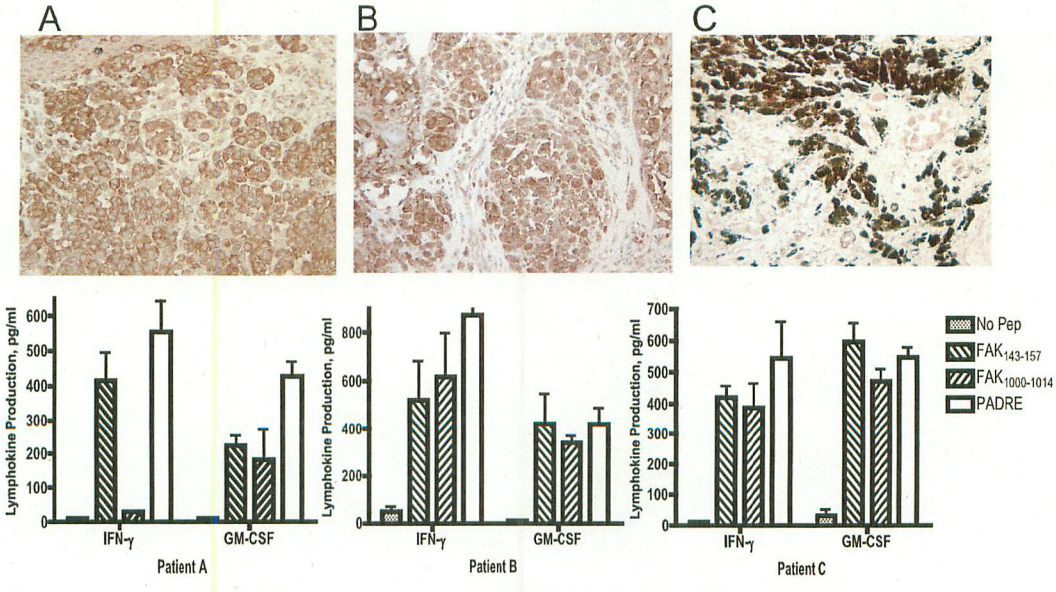

Figure 4　Assessment of T cell responses to the FAK143 and FAK1000 epitopes in melanoma patients

[Conclusions]

Our results provide evidence that FAK functions as a TAA and describe peptide epitopes that may be used for designing T cell-based immunotherapy for FAK-expressing cancers, which could be used in combination with newly developed FAK inhibitors.