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Smruti A. Desai

Roswell Park Cancer Institute, Buffalo, NY

Xinhui Wang

Roswell Park Cancer Institute, Buffalo, NY

Elvyra J. Noronha

Roswell Park Cancer Institute, Buffalo, NY

Qinwei Zhou

Roswell Park Cancer Institute, Buffalo, NY

Vera Rebmann

Institute for Immunology, University Hospital of Essen, Essen, Germany

See next page for additional authors

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Authors

Smruti A. Desai, Xinhui Wang, Elvyra J. Noronha, Qinwei Zhou, Vera Rebmann, Hans Grosse-Wilde, Franklin J. Moy, Robert Powers, and Soldano Ferrone

Structural Relatedness of Distinct Determinants Recognized by Monoclonal Antibody TP25.99 on β_2 -Microglobulin-Associated and β_2 -Microglobulin-Free HLA Class I Heavy Chains

Smruti A. Desai^{*}, *Xinhui Wang*^{*}, *Elvyra J. Noronha*^{*}, *Qinwei Zhou*^{*}, *Vera Rebmann*[†],
Hans Grosse-Wilde[‡], *Franklin J. Moy*[‡], *Robert Powers*[‡] and *Soldano Ferrone*^{*}

^{*} Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY 14263;

[†] Institute for Immunology, University Hospital of Essen, Essen, Germany; and

[‡] Department of Biological Chemistry, Wyeth-Ayerst Research, Cambridge, MA 02140

The association of HLA class I heavy chains with β_2 -microglobulin (β_2m) changes their antigenic profile. As a result, Abs react with either β_2m -free or β_2m -associated HLA class I heavy chains. An exception to this rule is the mAb TP25.99, which reacts with both β_2m -associated and β_2m -free HLA class I heavy chains. The reactivity with β_2m -associated HLA class I heavy chains is mediated by a conformational determinant expressed on all HLA-A, -B, and -C Ags. This determinant has been mapped to amino acid residues 194–198 in the $\alpha 3$ domain. The reactivity with β_2m -free HLA class I heavy chains is mediated by a linear determinant expressed on all HLA-B Ags except the HLA-B73 allospecificity and on <50% of HLA-A allospecificities. The latter determinant has been mapped to amino acid residues 239–242, 245, and 246 in the $\alpha 3$ domain. The conformational and the linear determinants share several structural features, but have no homology in their amino acid sequence. mAb TP25.99 represents the first example of a mAb recognizing two distinct and spatially distant determinants on a protein. The structural homology of a linear and a conformational determinant on an antigenic entity provides a molecular mechanism for the sharing of specificity by B and TCRs.

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