CANCER VACCINE DEVELOPMENT BASED ON MOLECULAR MIMICRY

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Background TAAs are shared wild-type cellular self-epitopes highly expressed on tumor cells and are used to develop off-the-shelf cancer vaccines appropriate to all patients affected by the same malignancy. However, they may be also presented by HLAs on the surface of non-malignant cells and affected by immunological tolerance or elicit autoimmune responses. In order to overcome such limitations, analogue peptides with improved antigenicity and immunogenicity able to elicit a cross-reactive T cell response are needed. To this aim, non-self-antigens derived from microorganisms (MoAs) may be of great benefit.

Indeed, data suggest that MoAs share sequence homology with TAAs (‘molecular mimicry’) and elicit a cross-reacting CD8+ T cell response.

Methods We looked for homology between published TAAs and non-self epitopes derived from viruses as well as microbiota species of the Firmicutes and the Bacteroidetes phyla, which together account for 90% of gut microbiota (MoAs). Blast search for sequence homology was combined with extensive bioinformatics analyses. Cross-reactive T cells were evaluated by tetramer staining as well as IFNg EliSpot assay.

Results Several pieces of evidence for homology between TAAs and MoAs have been found. Strikingly, 100% homology between paired sequences has been identified. The predicted average affinity to HLA molecules of MoAs is very high (<100 nM). The predicted structural conformation of the MoAs is, in general, highly similar to the corresponding TAA, and, in some cases, contact areas with both HLA and TCR chains are indistinguishable. Moreover, the spatial conformation of TCR-facing residues can be identical in paired epitopes, with exactly the same values of planar as well as dihedral angles. T cells cross-reactive with the paired TAAs and MoAs have been identified by tetramer staining as well as IFNg EliSpot assay, confirming the predicted sequence and conformational homology.

Conclusions The data reported in the present study show for the first time a comprehensive homology analysis between published TAAs and peptides derived from viruses as well as microbiota species. Cross-reacting CD8+ T cell responses confirm the possibility of eliciting an anti-tumor immunity by non-self peptides derived from viruses as well as microbiota species. This may have a two-fold relevance: 1) the natural T cell memory elicited by MoAs during the lifetime may turn out to be an anti-cancer T cell memory, able to control the tumor growth; 2) such non-self MoAs may be included in preventive/therapeutic cancer vaccines with a more potent anti-tumor efficacy compared to those based on TAAs.

REFERENCES


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