Phosphopeptides presented by MHC class I and class II molecules: a new category of tumor associated antigens with immunotherapeutic potential

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Antigens derived from proteins linked to growth control, survival, or metastasis are appealing targets for cancer immunotherapy, since their alteration as a means of immune escape may compromise cellular malignancy. MHC-associated peptides that are derived from phosphorylated proteins and retain the phosphate represent a new such category of cancer antigens. We have identified over 1000 phosphopeptides presented by different MHC-I and MHC-II molecules on cancer cells. Most come from proteins linked to growth control and signaling processes, many of which are disregulated in cancer cells. Most are not displayed on normal cells. T cells specific for cancer-associated phosphopeptides can be elicited in both humans and mice, and these invariably display exquisite specificity for the peptide sequence and phosphoamino acid. T cell receptors for some of these antigens have been cloned and expressed, opening the door for the development of adoptive T cell therapy approaches. Also, immune responses to some phosphopeptides in healthy individuals are surprisingly strong and due to CD8 T cells that already show a memory phenotype. Such pre-existing memory immunity in normal individuals is not generally observed to other cancer antigens, but is only evident in cancer patients, and often only after vaccination. Importantly, strong immunity to many phosphopeptides is diminished or absent in patients with leukemia and melanoma. These results suggest that prior exposure to phosphopeptides, in the absence of discernible cancer and potentially as an aspect of immune surveillance, leads to the development of phosphopeptide-specific T cell memory. Furthermore, cancer progression is associated with failure to develop this type of immunity, or its loss over time. In melanoma, responses to phosphopeptides can be enhanced through vaccination. Overall our work suggests that phosphopeptides are an important category of shared tumor associated antigens that can be targeted for therapeutic benefit.