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Proteinase-nicked IgGs: an unanticipated target for immunization therapy

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The host immune system adopts multiple mechanisms involving antibodies to confront cancer cells and bacteria. Therapeutically, anti-tumor mAbs have become mainstays in cancer treatment. However, neither host immunity nor mAb therapies appear capable of controlling tumor growth or acute infections in all cases. Structural instability of IgG has been overlooked as a contributing factor to the immunosuppressive tumor microenvironment. Recently, physiological proteinases have been identified which disable IgG effectiveness. Evidence shows that these proteinases cause localized IgG impairment by selective cleavage of a single IgG peptide bond in the hinge-region. This relatively minor alteration in the context of the overall IgG structure renders an antibody highly dysfunctional with regard to cell-killing functions (e.g. ADCC and complement). The image contains a map of the susceptible hinge region, a depiction of the proteolytic cleavage process as well the detection of cleaved IgG in a breast cancer tumor. The recognition of IgG cleavage in the tumor microenvironment and sites of infection provides opportunities for immunotherapy. Importantly, we were able to show that peptide immunization was highly protective against *S. aureus* colony growth *in vivo*. Related immunotherapeutic approaches in cancer models are also proving promising.

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