The tumor microenvironment hosts antibody-secreting cells associated with a favorable prognosis in several types of cancer. Patient-derived antibodies hold diagnostic and therapeutic potential; yet, it remains unclear how antibodies gain autoreactivity and target tumors. We found that somatic hypermutations in the immunoglobulin encoding genes of intratumoral antibody-secreting cells promote antibody tumor-reactivity against surface autoantigens in high grade serous ovarian cancer (HGSOC) patients. Tumors from many types of cancer were frequently coated with IgGs, including HGSOC. Intratumoral antibody-secreting cells were both mutated and clonally expanded, and produced antibodies that targeted matrix degrading enzymes that are abundantly expressed on the tumor cell surface. Reversion of patient-derived monoclonal-antibodies to their germline configuration revealed two types of immunoglobulin classes: one that depends on somatic hypermutations for tumor binding, and a second with germline-encoded autoreactivity. Thus, tumor-reactive autoantibodies are either naturally occurring or evolve through antigen-driven selection in patients. These findings highlight the origin and potential applicability of autoantibodies directed at surface antigens for tumor targeting in cancer patients.