Award ID:
RP150230

Project Title:
Counteracting tumor evasion of antibody immunity by a novel therapeutic strategy

Award Mechanism:
Individual Investigator

Principal Investigator:
An, Zhiqiang

Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

The natural immune responses that patients develop to their own tumors, as well as therapeutic regimens employing the latest anti-cancer monoclonal antibodies, would reasonably be expected to suppress tumor growth. Yet, a perplexing resistance to both is widespread. The ineffectiveness of the immune system to prevail in these situations suggests that cancers possess tactics to evade antibodies that could otherwise eradicate them. With a clinical context in mind, we observed that tumor-associated protein-degrading enzymes can diminish, and in some cases negate, cell killing functions by inducing a single clip in a small part of the antibody structure. The structural modification is so subtle that it had not been previously recognized and would not have been anticipated to so profoundly impair the antibody. To be able to visualize and establish if such cleavage occurred in cancer, we had to develop innovative tools (also antibodies) for that exact purpose. Indeed, the new tools readily enabled the visualization of antibody damage when incubated with cancer cells in the laboratory or within tumor tissues obtained from animals or human patients. Unexpectedly, the same antibody tools possessed the additional and remarkable property of restoring the lost functions to the damaged antibodies. The "rescue" of lost function suggested that this could be exploited as a therapy in cases where tumors cause antibody damage in order to evade our immune system. The encouraging findings must now be expanded and validated in increasingly representative models of human cancer. If confirmed, the hypothesis presented here represents a new direction in cancer immunotherapy.