'Stealth' nanoparticles could improve cancer vaccines

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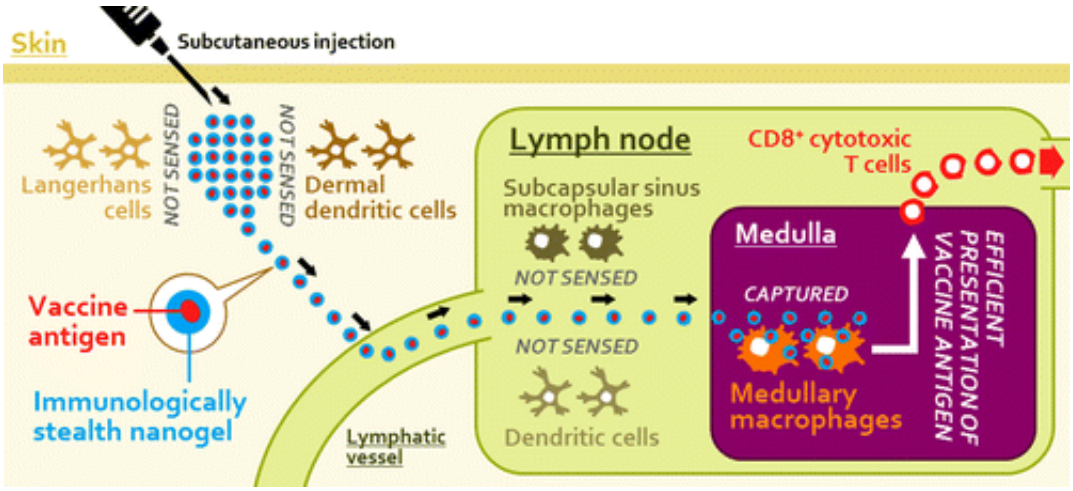

Cancer vaccines have recently emerged as a promising approach for killing tumor cells before they spread. But so far, most clinical candidates haven't worked that well. Now, scientists have developed a new way to deliver vaccines that successfully stifled tumor growth when tested in laboratory mice. And the key, they report in the journal *ACS Nano*, is in the vaccine's unique stealthy nanoparticles.

Hiroshi Shiku, Naozumi Harada and colleagues explain that most cancer vaccine candidates are designed to flag down immune cells, called macrophages and dendritic cells, that signal "killer" T cells to attack tumors. The problem is that approaches based on targeting these

generally circulating immune cells have not been very successful. But recent research has suggested that a subset of macrophages only found deep inside lymph nodes could play a major role in slowing cancer. But how could one get a vaccine to these special immune cells without first being gobbled up by the macrophages and dendritic cells circulating in the body? Shiku's team wanted to see if stealthy nanoparticles they had developed and clinically tested in patients might hold the answer.

The researchers injected the nanoparticles into mice. They found that the particles, which have no electric charge or surface molecules that would attract the attention of circulating immune cells, were able to enter the mice's lymph nodes. But once inside the lymph nodes' core, the special kind of macrophage engulfed the particles. When molecules for signaling killer T cells were put inside the nanoparticles, they hindered tumor growth far better than existing vaccines.

More information: "Nanogel-Based Immunologically Stealth Vaccine Targets Macrophages in the Medulla of Lymph Node and Induces Potent Antitumor Immunity" *ACS Nano*, 2014, 8 (9), pp 9209–9218. DOI: 10.1021/nn502975r

Abstract

Because existing therapeutic cancer vaccines provide only a limited clinical benefit, a different vaccination strategy is necessary to improve vaccine efficacy. We developed a nanoparticulate cancer vaccine by encapsulating a synthetic long peptide antigen within an immunologically inert nanoparticulate hydrogel (nanogel) of cholesteryl pullulan (CHP). After subcutaneous injection to mice, the nanogel-based vaccine was efficiently transported to the draining lymph node, and was preferentially engulfed by medullary macrophages but was not sensed by other macrophages and dendritic cells (so-called "immunologically stealth mode"). Although the function of medullary macrophages in T

cell immunity has been unexplored so far, these macrophages effectively cross-primed the vaccine-specific CD8+ T cells in the presence of a Toll-like receptor (TLR) agonist as an adjuvant. The nanogel-based vaccine significantly inhibited in vivo tumor growth in the prophylactic and therapeutic settings, compared to another vaccine formulation using a conventional delivery system, incomplete Freund's adjuvant. We also revealed that lymph node macrophages were highly responsive to TLR stimulation, which may underlie the potency of the macrophage-oriented, nanogel-based vaccine. These results indicate that targeting medullary macrophages using the immunologically stealth nanoparticulate delivery system is an effective vaccine strategy.

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