Immune cell communication key to hunting viruses,

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Immunologists at the Kimmel Cancer Center at Thomas Jefferson University in Philadelphia have used nanotechnology to create a novel "biosensor" to solve in part a perplexing problem in immunology: how immune system cells called killer T-cells hunt down invading viruses.

They found that surprisingly little virus can turn on the killer T-cells, thanks to some complicated communication among so-called "antigen presenting" proteins that recognize and attach to the virus, in turn, making it visible to the immune system. T-cell receptors then "see" the virus, activating the T-cells.

The researchers, led by Yuri Sykulev, M.D., Ph.D., associate professor of microbiology and immunology at Jefferson Medical College of Thomas Jefferson University, showed that different types of presenting proteins cooperate, spreading a signal among only a few T-cell receptors and boosting the T-cell response. This helps explain how only a few virus-infected cells can cause a killer T-cell response. They report their findings this week in an online edition of the *Proceedings of the National Academy of Sciences*.

Understanding how the immune system responds to viral threats, says Dr. Sykulev, is critical to finding better ways to manipulate it and could have implications for improved vaccine development. To better understand how proteins are recognized by killer T-cells, Dr. Sykulev and his co-workers created a biosensor out of semiconductor nanoparticles called quantum dots. These served as a unique scaffold to carry presenting proteins (called Major Histocompatibility Complex (MHC) proteins) and the attached virus portion, mimicking the clustering of MHC proteins on the surface of target cells. The researchers were able to place many MHC complexes, both with virus and non-virus fragments, and compared what was recognized by specific T-cell receptors on killer T-cells.

What they found surprised them. While the nanoparticle specifically bound to the surface of T-cells with receptors recognizing the viral-MHC complex, the control – a biosensor that carried the same MHC protein with a different peptide not recognized by the T- cells – unexpectedly also binded almost as strongly. "When we have such an arrangement of MHC proteins, we were able to see something no one had seen before – a very strong contribution of non-viral peptide-MHC interaction with a co-receptor," he says. "Such cooperativity we think can be achieved when MHC complexes are close to each other.

"We've shown that when we try to mimic the positioning of MHC protein on quantum dots, which we believe is similar to what it is on the cell membrane, we have this very strong binding. An important message is that a single virus-MHC complex recognized in the context of self-MHC complexes is sufficient to activate a T-cell response, which is amazing," he says. "That's the power of killer cells.

"We always suspected that recognition of other peptide MHCs, like self-peptide MHCs derived from normal proteins, could facilitate recognition, but it was not clear until now how this happened." Dr. Sykulev notes that this finding is not only relevant to viral infected cells, but to tumor cells as well. Both usually express very low levels of proteins that killer cells recognize.

Source: Thomas Jefferson University