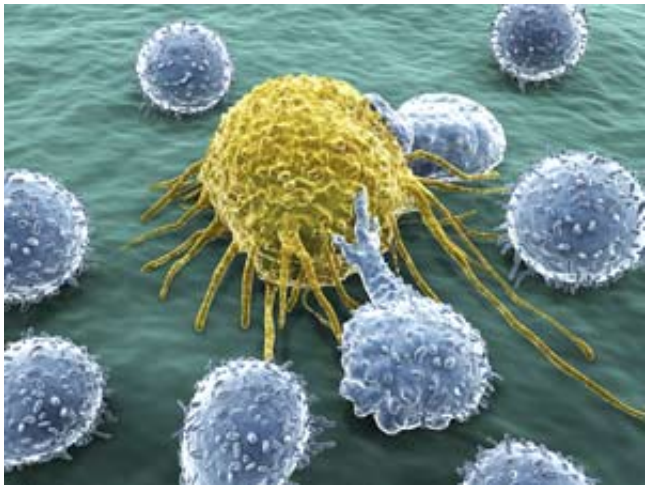
A shift in energy processing pathways occurs in immune cells that tolerate pathogens

25 September 2015



Cancer surrounded by cells of the immune system. Credit: selvanegra/iStock/Thinkstock

A fundamental metabolic shift in immune system cells has been identified by A*STAR researchers as responsible for whether they attack or tolerate disease recognized by our immune defenses. If the cells do not respond correctly, cancer and other diseases are allowed to thrive rather than being challenged by an immune response. "Targeting the metabolic switch that regulates this balance could form the basis of new and rationally designed cancer immunotherapies," says John Connolly of the A*STAR team.

The researchers at the A*STAR Institute of Molecular and Cell Biology and the Singapore Immunology Network investigated the metabolic status of dendritic cells of the immune system. These cells can be activated into immunogenic states in which they promote an immune response, or tolerogenic states in which the immune response is suppressed.

"Some of the most striking evidence for a role of these cells in human health comes from studies in cancer," Connolly says. He explains that by promoting the switch to the tolerogenic state the cancer cells appear to avoid the immune response that could destroy them. "The cancer hijacks our fundamental self-tolerance mechanisms to escape immune surveillance," he adds.

The researchers set out to identify the difference between immunogenic and tolerogenic dendritic cells. This would help them understand how the switch between the two states is controlled and how cancer cells can hijack the switching mechanism to protect themselves.

The investigation revealed fundamental changes in the metabolism of the tolerogenic cells. In particular several biochemical pathways that break down molecules to provide energy, especially those known as oxidative phosphorylation and glycolysis, were much more active in the tolerogenic cells.

Connolly said he had been surprised that something as fundamental as metabolism would play a key regulatory role in such a specialized cellular function. He is keen to make clear that helping the immune system to fight cancer is more subtle than just assisting the immune cells that attack disease. It also involves controlling the processes that instruct some immune cells to be tolerant of abnormalities.

The research team is now trying to understand the detailed molecular mechanisms by which metabolic change activates the tolerogenic program. This is already known to involve a complex range of inhibitory receptors and suppressive molecules. The ongoing research is also investigating dendritic cells in isolation from tumor samples to learn how cancer cells hijack the natural switching

mechanism. Hopefully the findings will eventually be used to prevent cancer cells from evading the immune responses that could kill them.

More information: "High mitochondrial respiration and glycolytic capacity represent a metabolic phenotype of human tolerogenic dendritic cells." *Journal of Immunology* 194, 5174–5186 (2015). dx.doi.org/10.4049/jimmunol.1303316

Provided by Agency for Science, Technology and Research (A*STAR), Singapore