N-acetyl cysteine improves efficacy of adoptive T cell immunotherapy for melanoma

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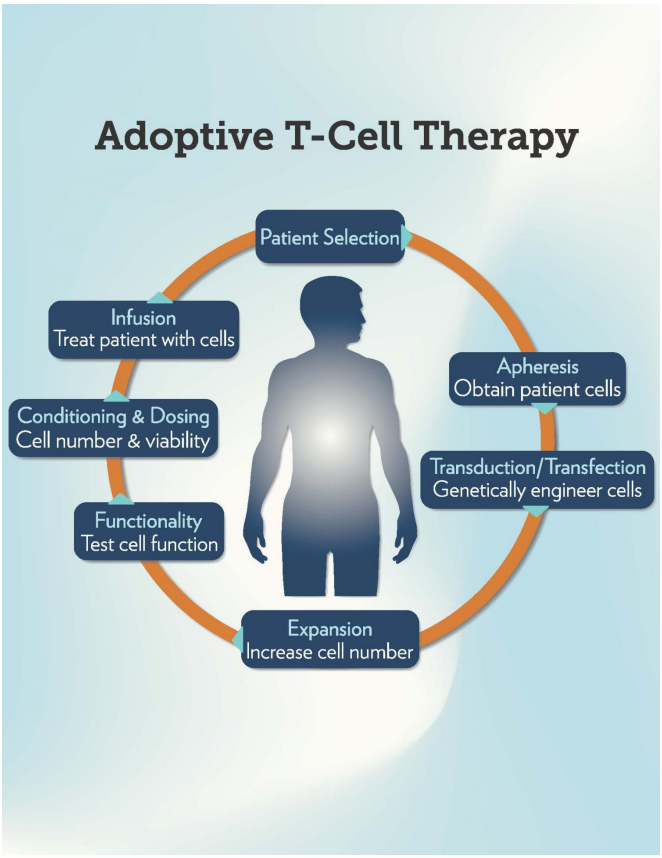

A diagram showing the steps in adoptive T cell therapy. Credit: Medical University of South Carolina

A collaborative team of investigators at the Medical University of South Carolina (MUSC) and Loyola University have demonstrated for the first time that culturing T cells in N-acetyl cysteine (NAC) before they are infused as immunotherapy improves effectiveness and outcomes in a preclinical model of melanoma. These findings were reported in the October 15, 2016 issue of *Cancer Research*.

Both incidence and mortality rates for metastatic melanoma continue to rise. Only about 15% of Stage IV melanoma patients receiving standard treatment can expect to survive for five years. By contrast, clinical trial data show that up to 40% of Stage IV melanoma patients survive for five years when treated with adoptive cell therapy (ACT), a form of immunotherapy that calls for infusion of autologous, melanoma-specific T cells.

ACT aims to boost a patient's own immune responses against the cancer. To do this, the patient's own T cells are harvested, genetically modified with a therapeutic T cell receptor, activated, and then rapidly expanded to generate large numbers of T cells for therapeutic re-infusion.

Unfortunately, patient responses vary. Better outcomes are positively correlated with persistence of the transferred cells. The rapid expansion of harvested T cells before reinfusion increases their susceptibility to activation-induced cell death (AICD), prompting the authors to hypothesize that AICD reduces ACT's overall effectiveness.

Researchers have long known that factors limiting T cell persistence also limit ACT efficacy but, until now, no one knew that something as simple as changing the culture condition by supplementing with NAC could improve survival of the reinfused T cells. The research team showed that adding NAC to the in vitro T cell expansion culture prevents increases in the DNA damage marker ?H2AX and significantly improves T cell persistence and immunotherapy outcomes, including reduced tumor growth and enhanced survival.

The team found that nearly 40% of NAC-cultured T cells were detectable in tumors after transfer compared to approximately 1.2% of standard-culture T cells. They also found that mice receiving NAC-cultured cells experienced significantly

delayed tumor growth compared to mice receiving standard-culture cells (P