A UNIQUE DENDRITIC CELL ACTIVATION STATE UTILIZES INFLAMMASOMES TO STIMULATE MEMORY T CELL RESPONSES IN HUMANS

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Background Dendritic cells (DCs) represent the primary drivers of new T cell responses that defend against cancer and infection. In order to execute this task, DCs must be stimulated in a manner that induces several T cell stimulatory activities. These activities include the ability of DCs to 1) present tumor or microbial antigens, 2) express T cell co-stimulatory molecules, 3) express cytokines that induce effector T cell differentiation, 4) migrate in high numbers to lymph nodes and 5) produce the memory T cell inducing cytokine IL-1β.

Diverse approaches have been undertaken to stimulate these DC activities in a clinical or pre-clinical setting, with common strategies targeting Toll-like Receptors, STING or inflammasomes. These approaches are based on the general concept—permeating the literature for over 30 years—that infection-like signals are sufficient to stimulate DC-mediated instruction of adaptive immunity. However, the therapeutic success of these strategies remains elusive.

Methods Herein, we demonstrate that the aforementioned approaches are unable to elicit all 5 of the aforementioned activities in human DCs. This observation may explain the ineffectiveness of these approaches in generating protective immunity to cancer. We report a distinct means of stimulating DCs, using molecular signals that mimic infection and tissue injury, that elicit all DC activities needed to stimulate adaptive immunity. We devised proprietary chemical mimics of infection and tissue injury that induce a new DC activation state termed hyperactive.

Results Primary human DCs that have been stimulated with hyperactivators far exceed the capacity of other DCs to stimulate Th1-biased memory T cell activities, by a process dependent on inflammasomes and the cytokine IL-1β.

Conclusions These studies reveal a unique DC activation state, and chemical agonists that elicit this state, as key determinants of T cell mediated immunity. DC hyperactivating chemicals represent a means to expand the opportunities in immunotherapy, and may enable durable T cell immunity to be elicited in a clinical setting.


Abstracts