Polyamine-blocking therapy reverses immunosuppression in the tumor microenvironment

Candace S Hayes[1], Allyson C Shicora, Martin P Keough, Adam E Snook, Mark R Burns, Susan K Gilmour
Affiliations Expand

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Abstract

Correcting T-cell immunosuppression may unleash powerful antitumor responses; however, knowledge about the mechanisms and modifiers that may be targeted to improve therapy remains incomplete. Here, we report that polyamine elevation in cancer, a common metabolic aberration in aggressive lesions, contributes significantly to tumor immunosuppression and that a polyamine depletion strategy can exert antitumor effects that may also promote immunity. A polyamine-blocking therapy (PBT) that combines the well-characterized ornithine decarboxylase (ODC) inhibitor difluoromethylornithine (DFMO) with AMXT 1501, a novel inhibitor of the polyamine transport system, blocked tumor growth in immunocompetent mice but not in athymic nude mice lacking T cells. PBT had little effect on the proliferation of epithelial tumor cells, but it increased the number of apoptotic cells. Analysis of CD45(+) tumor immune infiltrates revealed that PBT decreased levels of Gr-1(+)CD11b(+) myeloid suppressor cells and increased CD3(+) T cells. Strikingly, in a model of neoadjuvant therapy, mice administered with PBT one week before surgical resection of engrafted mammary tumors exhibited resistance to subsequent tumor rechallenge. Collectively, our results indicate that therapies targeting polyamine metabolism do not act exclusively as antiproliferative agents, but also act strongly to prevent immune escape by the tumor. PBT may offer a general approach to heighten immune responses in cancer.

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