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Hypoxia limits CTL functions: Lessons from live intratumoral imaging

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Poor tumor vascularization is an obstacle to immunotherapy by CTLs. It impairs tumor infiltration but also introduces hypoxia, known to interfere with T-cell migration. It is yet unknown how suboptimal vascularization affects CTL migration and function within tumors. To study this question, we combined immunohistochemistry of human melanoma samples with two-photon imaging in live mice. Orthotopically implanted B16-OVA tumors were studied after adoptive transfer of *in vitro* matured antigen-specific OT-I CTLs. In patients, CD8 T-cells concentrated around peripheral vessels in the tumor and sparsely infiltrated avascular areas. In mice, CTLs crawled rapidly in oxygenated areas within 50 μ m of flowing blood vessels. Occluding intratumoral blood vessels triggered immediate arrest of CTL motility, which was quickly reversed when flow was resumed. Immunohistology indicated that CTLs avoided hypoxic tumor areas. Live CTL imaging *in vitro* showed deceleration under hypoxic conditions and when oxidative phosphorylation was blocked. To circumvent intratumoral CTL dysfunction we attempted to increase vascular density by implanting tumors in matrices containing bFGF. bFGF-laced tumors were more easily rejected after transfer of CTLs and displayed delayed growth in untreated mice but were not affected in mice deficient in CD8 T-cells. CTLs infiltrated such tumors in normal numbers but displayed enhanced motility in highly vascular tumors, suggesting that enhanced rejection resulted from improved intratumoral CTL migration. Taken together, the results suggest that hypoxia limits CTL function away from blood vessels and that alleviating it may synergize with immunotherapy.

Biography

Tali Feferman has completed her PhD in Molecular Biology at the Macquarie University and Postdoctoral Training at The Heart Research Institute in Sydney. She has then joined the Weizmann Institute of Science in 2000. Her initial interest involved exploring the mechanism of action and immunomodulation of Myasthenia Gravis (MG) and its model experimental autoimmune MG (EAMG). In recent years her interest is mainly focused on addressing questions important for optimizing cancer immunotherapy using cutting-edge imaging microscopic techniques in live mice.

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