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Immunosuppression in tumors: Galectins cover human tumor-infiltrating lymphocytes and block their functions

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We describe a new mechanism of dysfunction of human tumor-infiltrating lymphocytes (TILs). TILs failed to secrete cytokines and lytic enzymes upon stimulation, although they were normally activated and able to produce these effector molecules inside the cell. Surprisingly, these effector molecules remained trapped inside the cell. This defect is related to the presence of galectin-3 at the TIL surface and can be relieved by agents that detach galectin-3 from the TIL surface. The normal secretion process is blocked in dysfunctional TILs, due to impaired LFA-1 mobility and actin rearrangement at the secretory synapse. This is the first observation of uncoupling between cytokine production and cytokine secretion in TILs. We also hypothesize that galectins lattices hanged on the tumor microenvironment may capture glycosylated immune factors, blocking their anti-tumor function. The presence of galectin-3 in the tumor microenvironment reduced IFNγ diffusion and ability to induce the chemokine gradient necessary to attract anti-tumor T-lymphocytes. Galectin-3 captured in vitro glycosylated IFNγ and reduces IFNγ diffusion through a collagen matrix. Inhibiting galectins enhanced the capacity of human tumor cells to express CXCL9/10 upon IFNγ treatment *in vitro*. In a humanized mouse model, human galectin-3 restricts the intratumor diffusion of IFNγ. Co-injection of IFNγ and galectin antagonists improved tumor infiltration by autologous CD8+ T cells injected intravenously and delayed tumor growth as compared with tumors injected with IFNγ alone. Our results contribute to explain why some human tumors can be considered as cold as they are poorly infiltrated by anti-tumor T-lymphocytes.

Biography

Pierre van der Bruggen has a PhD. in Agronomical Sciences. In 1988, he joined the Ludwig Institute for Cancer Research and identified in 1991 the first human gene, MAGE-1, coding for a tumor antigen recognized by cytolytic T lymphocytes. He identified over the years several other tumor antigens, which have been used in clinical trials. His group has discovered a new type of anergy of human tumor-infiltrating lymphocytes, due to the presence of galectin-3, a lectin abundant in tumors. The group is further analyzing the mechanisms by which galectin antagonists reverse the impaired T cell functions.

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