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Putting the brakes on lymphatic metastasis by utilizing plasmid vectors as priming agents

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While there has been significant progress resulting in novel, more effective targeted therapies with tumor reductive potential, metastatic disease still represents a major unmet medical need responsible for most morbidity and mortality in cancer. The process of metastasis is mediated by trafficking tumor cells that utilize the lymphatic and blood circulation to seed remote organs. This is paralleled by gradual deployment of an arsenal of immune evasion mechanisms by the cancerous process, simultaneously with a reshaping of the immune repertoire. Thus, targeted immune therapies that remove cancerous cells or curb tumor progression throughout the lymphatic system and blood circulation, should provide long-term disease control. We designed and optimized a novel platform technology to target the process of metastasis and halt disease progression through the lymphatic system, potentially applicable to measurable and minimal residual disease alike. Plasmid-mediated gene transfer to lymph nodes resulted in generation of tumor-antigen specific, MHC class I-restricted T cells with a distinguishing phenotypic and functional profile. These $CD8^+$ T cells, although not frequent, were largely dominated by $CD62L^+$ central memory cells (1). These were confined to the lymphatic system and showed increased functional avidity, persistence, polyfunctionality and a very robust proliferating capability upon heterogenic antigen-boost. Importantly, these plasmid-primed T cells failed to acquire elevated and persisting expression of co-inhibitory molecules such as PD-1 and CTLA-4, even upon differentiating to $CD62L^-$ T cells (2). This outcome could be reproduced by repeat intra-lymph node immunization with low-dose cognate peptide in presence of TLR agonist and contrasted to "highly immunogenic" regimens that resulted in considerable expansion of T cells highly susceptible to PD-1-mediated inhibition (3). Preclinical evaluation of intra lymph node immunization utilizing diverse antigens and regimens showed that the ensuing immunity could effectively clear individual target cells within blood circulation and lymphatic organs, clear or confine micrometastatic foci and even induce partial or complete regression of emerging, measurable tumors (1, 4). Nevertheless, despite effective induction, functionality within lymphatic organs and recruitment to established tumors, vaccine-induced T cells were functionally suppressed within the environment of large, established tumors, a state partially reversed by combination therapy with cyclosphosphamide (4). Interestingly, subsequent clinical evaluation of investigational agents designed on the principle of plasmid priming by intra-lymph node administration, followed by heterologous peptide boosting, showed multiple instances of disease control accompanied in several cases by evidence of tumor regression and lack of new metastases (5, 6). In a trial recently completed in patients with advanced melanoma, four out of seven subjects with inoperable metastatic disease largely confined to lymph nodes, showed durable disease control and tumor regression upon immunization (5). Evaluation of target lesions in two responding patients supported an immune-mediated confinement of the cancerous process within lymph nodes. Together, these findings challenge the view that active immunotherapy should be tested and developed mostly for minimal residual disease, having a place in advanced disease only in conjunction with other therapies. Contrary to this paradigm, our findings raise the perspective that select immunization regimens – such as those encompassing intra-lymph node plasmid priming – could generate T cells operational not only against individual tumor cells and microscopic lesions, but also against overt metastases affecting lymphoid organs. While the hypothesis that this is due to programming of T cells resilient to a range of immune inhibiting mechanisms needs to be validated in man, as the lymphatic system is an obligatory transit point for cancer dissemination, these results point to an optimal positioning of novel active immunotherapies in cancer treatment.