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Lymph node invasion by tumor cells modifies the distribution of dendritic cell subsets and memory T cell profiles in human cancer patients

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Introduction

In human breast cancer, the invasion of tumor-draining lymph nodes (TDLNs) is an important step in disease progression and has predictive value [1]. TDLN dendritic cells (DCs), which are comprised of lymphoid-organ-resident and skin-derived migratory DCs, present tumor antigens to the naïve T cells and induce their activation and polarization into different functional subsets (Th1, Th2, Th17, Th22, Tfh, regulatory T cells) that will lead to antitumor T cell responses or to tolerance [2].

Objective

Systematic comparison of the immune profile of Invaded (INV) versus Non-invaded (NI) TDLNs would help to identify those immunomodulatory mechanisms associated to the presence of the tumor that could condition the response to immunotherapy.

Material and methods

TDLNs from 70 untreated breast cancer patients undergoing surgery at Institut Curie Hospital were obtained in accordance with institutional ethical guidelines. Samples were analyzed by multi-color flow cytometry. For statistical analysis, Wilcoxon matched paired test or Mann-Whitney test was performed using Prism (GraphPadSoftware)

Results

We studied the distribution of 6 different DC subpopulations and observed in INV TDLNs a significant decrease in the percentage of BDCA1+ DCs ($P<0.05$) and a significant increase in the percentage of CD11c+HLADR+CD14+cells ($P<0.01$), including macrophages and inflammatory DCs, compared to NI TDLNs ($P<0.05$). We also found a significant lower frequency of naïve conventional and regulatory T cells in INV TDLNs ($P<0.05$). Both, in NI and INV TDLNs, memory conventional and regulatory T cells were highly polarized, mainly to the Th1 phenotype, but also to the Th2, Th17, Tfh and Th22 phenotypes, as determined by the expression of a panel of chemokine receptors and transcription factors. Notably, in INV TDLNs, a significantly higher proportion of regulatory and conventional T cells were Th1-polarized ($P<0.05$). Further functional analysis showed that after ex-vivo PMA/Iono stimulation, the Th1-polarized conventional T cells, but not the Th1-polarized regulatory T cells produced high amounts of IFN-γ, being the IFN-γ production significantly higher in INV TDLNs ($P<0.05$).

Conclusion

Overall, we observed that immune cells from metastatic TDLNs show evidence of high activation (increased proportion of inflammatory DCs and of Th1-polarized memory T cells) highlighting their potential role in the anti-tumor immune response.

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