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Lyn kinase regulates the chemotactic and inflammatory responses of tumor-associated myeloid cells

Several signals (CSF, Il-6, chemokine) to myeloid cells in the tumor microenvironment are transduced through the Src-family kinase Lyn, which is expressed as two isoforms: LynA and LynB. Total Lyn expression is negatively correlated with breast cancer patient survival, but the functional contributions of LynA and LynB in the solid tumor microenvironment have not been studied. In an E0771 orthotopic transplant model in hosts expressing or lacking LynA or LynB, we have discovered that Lyn expression in the mammary tumor microenvironment promotes the recruitment of monocytes, macrophages, neutrophils, and dendritic cells. Furthermore, Lyn promotes activation of tumor-associated macrophages. Tumors from Lyn knockout animals maintained WT-like numbers of inflammatory macrophages, but the anti-inflammatory population was reduced. Activation of WT or LynKO bone marrow-derived macrophages (BMDMs) using tumor cell-conditioned media indicated that Lyn signaling is required for response. Transplant of LynKO and WT monocytes into tumor-bearing, WT hosts confirmed that the trafficking defect created by Lyn knockout is cell intrinsic. In vitro migration experiments performed using BMDMs and isolated monocytes suggest that a cancer cell-derived chemokine is responsible for recruitment of monocytes and macrophages, and dysregulation of that pathway through Lyn knockout reduces the abundance of those cell types. Together, our findings suggest that Lyn regulates the tumor-mediated chemotactic and inflammatory signaling response of myeloid cells, which are major factors in disease progression and treatment response. Modulation of Lyn activity, or pathway constituents, is thus a potential strategy for manipulating the trafficking and anti-tumor activity of myeloid cells within breast tumors.