Emergence of B cell state heterogeneity and early immune microenvironment changes during Kmt2d-driven B cell lymphomagenesis

Gabriel Brisou[1], Sabrina Baaklini[1], Noushin Mossadegh-Keller[1], Manon Zala[1], Alicia Beyou[1], Laurine Gil[1], Lionel Chasson[1], Pierre Milpied[1], Bertrand Nadel[1], Sandrine Roulland[1]

[1] Centre d'Immunologie de Marseille Luminy, Aix Marseille University, CNRS, INSERM, Marseille, France, Mailing address, roulland@ciml.univ-mrs.fr

Abstract

Follicular Lymphoma (FL) is a prototypical example of B cell lymphoma originating from germinal center (GC) B cells. Now, single-cell transcriptomic studies from our lab and others looking at FL transcriptional heterogeneity revealed that FL cells are functionally heterogeneous, with most cells engaged in a GC-Memory continuum which is highly reminiscent of the premalignant FL ontogeny we described previously where BCL2+ memory B cells require multiple re-entries into the GC to facilitate the FL transformation process. Since FL cells frequently hijack the epigenetic machinery through inactivating mutations in histone-modifying proteins - notably the histone methyltransferase KMT2D - it is still unclear how epigenetic alterations contribute to the emergence of this intratumor heterogeneity. To address this issue, we profile single-cell transcriptomes and immune repertoires of genetically engineered mouse FL-like tumors carrying Kmt2d loss of function and BCL2 overexpression at several stages, from pre-neoplastic hyperplasia to FL-like tumors. Strikingly, mouse FL-like tumors mirrored the GC desynchronization program we observed in human FL and spanned a continuum of states from proliferating GC-like to quiescent Mem-like cell states. That GC-to-Mem axis was the main source of intra-tumor transcriptional heterogeneity with yet unknown clinical significance. Exploration of the T cell heterogeneity along disease progression revealed an early reprogramming of a tumor-supportive microenvironment establishing a link between the remodeling of a premalignant supportive immune niche and malignant cell heterogeneity. Our data suggest that early targeting of the B cell-tumor microenvironment (TME) interactions that sustain (pre)malignant B cell heterogeneity may represent a promising avenue.