Characterization of the immune microenvironment of melanoma

Halftime review seminar
February 27, 2019

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Abstract

Cutaneous melanoma is the most aggressive form of skin cancer and its advanced stages result in poor prognosis. Also, when metastasized, melanoma is difficult to treat, due to therapy resistance development. Improvements were achieved when the recent advancement of checkpoint blockade therapies (CTLA-4 and PD-L1/PD-1 inhibitors) demonstrated clinical efficacy and long-term survival in melanoma patients. However, despite the high response rate of checkpoint blockade therapy, many patients are refractory to it or acquire resistance. Identification of factors that drive or prevent effective responses to checkpoint therapy thus, remains an urgent need for understanding and expanding the use of immunotherapy in patients. Such factors may lie hidden within the tumor microenvironment or interaction between tumor cells and the cells of the immune system. This project aims to understand the role of several components of the immune microenvironment in melanoma and which clinical and molecular factors might influence this relationship.

In study I we have used a cohort of metastatic melanomas collected prior checkpoint inhibitor era and found that the presence of intra-tumoral lymphocytes is associated with improved survival. The presence of CD20+ B cells was frequently concomitant with CD3+/CD8+ T cells, indicating the formation of tertiary lymphoid structures (TLS). The TLS signature predicted clinical outcome in patients treated with immune checkpoint inhibitors. We were able to identify the presence of activated and immature B cells in these structures, which supports their functional role in melanoma tumors.

In study II we have used immune cell type associated DNA methylation based signatures on a large cohort of metastatic melanoma tumors. We found three distinct immune clusters for metastatic melanoma that significantly associates with patient survival. Additionally, these DNA methylation signatures showed prognostic implications in other solid tumor cohorts.

In study III we have investigated the presence of vasculature in melanoma tumors and found the formation of two distinct patterns with different morphological and spatial features. These differed in vessel density and, more importantly, in survival, with Pattern 2 tumors showing a better prognosis than Pattern 1 tumors. Preliminary data shows Pattern 2 tumors to be enriched in several immune cell types, such as cytotoxic lymphocytes, B-lymphocytes and monocytes.
We found somehow intriguing that a considerable number of Pattern 1 tumors are infiltrated with these cells as well, when their prognosis is so poor. Thus, we are now exploring how the two patterns differ in terms of molecular alterations and how the development of different vascularization patterns influences the immune infiltration in melanoma. Finally, in study IV, we are prospectively collecting fresh tumor tissue and after an enzymatic and physical dissociation, obtained single cells from it, to determine the extent of lymphocyte populations using BD FACSria Flow Cytometer. We will also, in a pilot study, sort cells in CD45+ and CD45− populations, on which single cell RNA sequencing will be performed. This will increase our molecular knowledge on tumor associated immune cell populations.