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PD-L1 expression in metastatic neuroblastoma as an additional mechanism for limiting immune surveillance

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Neuroblastomas (NB) are neuroectodermal tumors that account for 15% of all childhood cancer deaths. Different prognostic factors including age, stage and amplification of *MYCN* (*MYCN*^{ampl}), are critical for defining NB risk and for guiding therapeutic choices[1]. In this context, although different strategies have been approached, the prognosis of high-risk neuroblastoma (NB) remains poor due the high frequency of relapse which not only occurs at the primary tumor site but frequently arises in the bone marrow. Thus, in vivo, neuroblastoma exploits different mechanisms to escape the immune surveillance[2]. These might include the so called "adaptive immune resistance" characterized by the *de-novo* expression of Programmed Death Ligands (PD-Ls)[3] induced by IFN-γ whose storm occurs after different immunotherapeutic approaches. In the present study we analyzed the constitutive and the inducible surface expression of PD-Ls in NB cells. We showed that PD-L1 is constitutively express by virtually all HLA class I^{pos} NB cell lines, whereas PD-L2 is rarely detected. Moreover PD-L1 could be acquired/upregulated in both NB cell lines and NB engrafted nude/nude mice. Importantly, after IFN-γ stimulation, PD-L1 can be expressed by metastatic neuroblasts isolated from bone marrow aspirates of high-risk NB patients, characterized by different *MYCN* amplification status. Interestingly, in one case, metastatic neuroblasts were poorly responsive to IFN-γ stimulation, suggesting that responsiveness to IFN-γ might represent a further element of heterogeneity in metastatic neuroblasts. Finally, we documented the presence of PD-1-positive lymphocytes in NB-infiltrated bone marrow of patients. These cells are mainly represented by aβ T cells but also include small populations of gδ T cells and NK cells. Moreover, PD-1^{pos} T cells expressed higher levels of activation markers as compared to the negative counterpart. Overall our data show that a PD-L1-mediated immune resistance mechanism might occur in metastatic neuroblasts and provide a biological rationale for blocking the PD-1/PD-Ls axis in future combined immunotherapeutic approaches.

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Keywords

Anti-tumor immunity; Immune checkpoints; Neuroblastoma; Natural Killer cells; T cells; PD-1; PD-L1; PD-L2; INF-γ TNF-a.

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