Approach using « second generation » immune checkpoint inhibitors for the treatment of triple-negative breast cancer

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1. Background

Immunotherapy is revolutionizing cancer treatment. However, only a subset of patients benefit from it, the majority of them showing limited or no response. Triple-negative breast cancer (TNBC) represents 10-20% of invasive breast cancers and has no specific treatment. The blockade of novel "second generation" immune checkpoints could be promising to enhance the number of responders.

2. Aim and methods

This project aims at highlighting new immune checkpoints and studying the impact of their inhibition on TNBC progression. To this end, we selected potential immune checkpoints that showed high mRNA expression in TNBC using bioinformatic analyses. Next, we chose the targets displaying a higher protein expression in TNBC compared to the 3 other categories of breast cancer (LumA, LumB and HER2+) by using immunohistochemistry.
The proteins VISTA, sirp-a, CD47 and PVR were selected. Several murine syngeneic tumor models were used. Checkpoint expression was thoroughly investigated in 12 specific immune populations. Monoclonal antibodies against said immune checkpoints were selected.
Using syngeneic mouse models, the effect of the monoclonal antibodies on tumor growth as well as on composition of the immune tumor microenvironment was assessed.

3. Results

Tumor growth was significantly slowed down in Balb/C mice bearing 4T1 tumors treated with the anti-VISTA, anti-CD47 and anti-TIGIT (PVR ligand) antibodies, while no effect was shown in a comparable NOD-Scid model. In Balb/C mice, the anti-VISTA seems to elicit a drastic drop in CD4+ and CD8+ Treg percentage in the treated group as well as a decrease in mono-MDSCs.
In C57Bl/6 mice bearing E0771 tumors, treatment with anti-VISTA and anti-CD47 antibodies significantly slowed down tumor growth. Here, in addition to a similar effect on Tregs and mono-MDSCs, the anti-VISTA seemed to significantly decrease the proportion of M2-like macrophages in the TME.

4. Conclusion

We showed that blocking immune checkpoints such as VISTA remodelled the tumor immune microenvironment efficiently enough to slow down tumor growth in two syngeneic breast cancer models.
Further investigation will be carried out in order to highlight the activation status of the tumor resident immune cells and exact mechanisms at play.