Dysregulated expressions of inhibitory checkpoint molecules and their ligands on t-cells and blasts in aml relapses after stem cell transplantation (SCT) [Poster]

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P1309 DYSREGULATED EXPRESSIONS OF INHIBITORY CHECKPOINT MOLECULES AND THEIR LIGANDS ON T-CELLS AND BLASTS IN AML RELAPSES AFTER STEM CELL TRANSPLANTATION (SCT)

Topic: 21. Stem cell transplantation - Experimental

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Background:

Upregulation of inhibitory checkpoint molecules (ICM) on T-cells and their ligands on leukemic blasts may be a mechanism of acute myeloid leukaemia (AML) relapse after allogeneic stem cell transplantation (SCT).

Aims: Better understanding of relapse biology could improve treatment efficacy.

Methods:

We examined peripheral blood (PB) and bone marrow (BM) samples of 5 AML patients (PTs) relapsing after SCT, and PB of 5 healthy individuals (H), including 2 stem cells donors. ICM (PD-1, CTLA-4) expressions on T-cells and their ligands (CD86, PD-L1, PD-L2) on leukemic blasts were assessed through flow cytometry. PTs' PB was cultivated with and without "KitM" (GM-CSF+PGE-1) to generate leukemia-derived dendritic cells (DC_{leu}), followed by MLC, enriched by PTs' or donors' T-cells. After MLC, immune activation and functionality (degranulation, intracellular cytokine production, blast lysis) was assessed.

Results:

1. Whilst all patients showed high expressions of PD-1 on their T-Cells, additional overexpression of CTLA-4 was negatively correlated with responses to relapse treatment. Expression of ICM was low on T-cells from 4/5 healthy individuals (*Figure 1*).

2. Influence of KitM on ICM/ligand expressions on T-cells/blasts

- ICM/ligand expressions on uncultured T-cells/blasts: In contrast to H, PTs presented high co-expressions of CTLA-4 and PD-1 on PB T-cells (*Figure 1*). In addition, PTs showed high frequencies of PB/BM blasts co-expressing CD86.
- DC/DC_{leu} in PB: Generation of DC_{leu} in AML as well as generation of DC in H was successful with KitM pretreated PB vs. Control.
- ICM co-expression on T-cells after MLC with KitM pretreated PB: MLC of KitM treated PB enriched with unstimulated PTs T-cells resulted in reduced frequencies of ICM-positive T-cells in 3/5 PTs, and increased frequencies of activated (leukemia specific) T-cells in 3/5 PTs. Beyond, blast lysis was improved in 4/5 samples treated with KitM. Both findings were not observed when PB cells were cultivated in the absence of KitM.

3. Possible impact of ICM profiles on clinical outcome in a particular case

PT1 suffered from early relapse both after 1st and 2nd SCT from her healthy father. A role of ICM in relapse mechanisms was suggested by CTLA-4/PD-1 expression on her T-cells and CD86 expression on AML blasts. In addition, >90% of the healthy father's T-cells expressed CTLA-4/PD-1, which might have contributed to treatment failure. In contrast, T-cells from PT1's mother presented with low ICM levels (*Figure 1*), suggesting that the mother might have been a better donor. Stimulation of PT1's PB cells with KitM generated DCleu, decreased ICM-expressions and increased T-cell activity. KitM pretreated samples also revealed improved blast lysis after MLC.

Image:

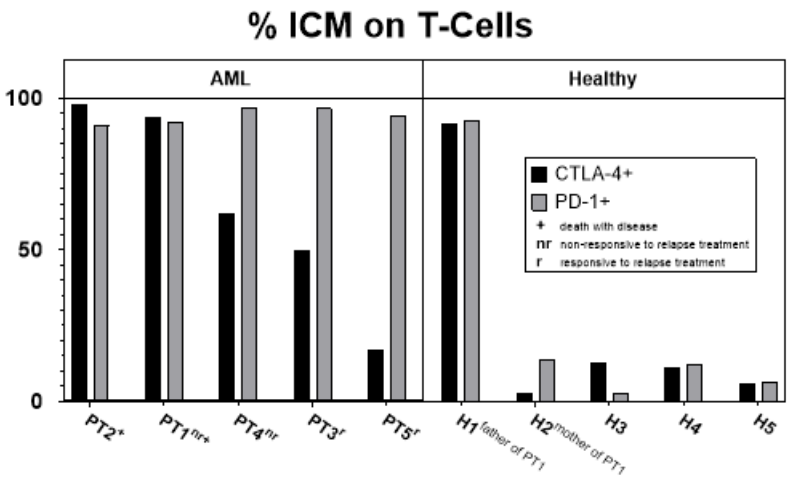

Figure 1: % Expressions of CTLA-4 and PD-1 on T-Cells in uncultivated PB of AML Patients and Healthy Individuals

Summary/Conclusion: T-cells and blasts of AML PTs relapsing after SCT uniformly co-expressed ICM and their ligands, which could be a reason for inferior immune responses. High aberrant ICM-expressions, in particular CTLA-4, on donor T-cells could be responsible for relapse after SCT by inactivating antileukemic immune reactions. Hence, checkpoint-inhibitory antibodies might represent a specific therapeutic option in these patients. Further, interactions between ICM-expressions on healthy (fresh) donor T-cells could have an impact in therapy responses and should be evaluated in donor selection. Finally, generation of DC_{leu} by treatment with KitM triggers immune responses in MLC alongside with reduced ICM-expressions on T-cells, possibly reducing their inhibitory effects and therefore improving antileukemic responses.