Resminostat, a Phase II clinical HDAC inhibitor, sensitizes tumor cells for NK cell response and synergizes with ADCC therapy

S. Hamm1, U. Parmitzke1, K. Kronthaler1, T. Wullf1
14SC AG, Martinsried, Germany

HDAC inhibitors modulate NK cell response

HDAC inhibitors were previously shown to increase the sensitivity of tumor cells to NK cell lysis in vitro by up-regulation of NKG2D ligands. However, the clinical relevance of this effect was called into question since some HDAC inhibitors were shown to inhibit NK cell viability and cytolytic function (Ogbomo et al., FEBS Letters, 581.7 (2007); Rossi et al., Journal of Leukocyte Biology, 91.2 (2012)). Resminostat, an orally available inhibitor of HDAC class I, IIb, and IV, is in Phase II clinical development. It was tested in various cancer indications (HCC, CRC, HL, NSCLC, pancreatic and biliary tract cancer), demonstrated safety in over 300 patients, and showed a survival benefit in a subgroup of patients with advanced liver cancer.

Resminostat enhances anti-tumoral NK cell response in whole blood

Isolated NK cells were treated for 48 h with resminostat and comparator compounds at indicated concentrations (left). In difference to the negative effect on isolated NK cells, resminostat did not affect the number of NK cell in vivo (BALB/c mice, treatment for 14 days, 30-60 mg/kg are clinically relevant doses; in the middle) or the function of NK cells in whole blood (on the right): labelled K562 cells were incubated with whole blood with or without resminostat, after 48 h the number of remaining K562 cells was determined by FACS, to rule out direct toxicity of resminostat K562 cells were treated with same concentrations in plasma.

Resminostat and rituximab combination efficiently kills B cell lymphoma

U2932 were pretreated with 2 µM resminostat or DMSO and incubated with PBMCs with or without rituximab (on the right representative data for one donor); the experiment was repeated with PBMCs of 4 different donors (summarized in the middle), cytotoxic effect was determined via FACS by PI staining; on the right a scheme of proposed MOA

Resminostat, a perfect combination partner for NK cell based therapy

- Under physiologically relevant conditions resminostat enhances sensitivity of NK cell to mediated cytotoxicity and synergizes with opsonizing CD20 antibody rituximab.
- This feature qualifies resminostat for combinatorial approaches with NK cell based cancer immunotherapies like opsonizing antibodies, NK cell engaging bispecific antibodies, NKG2D-CAR T cells, or adoptive NK cell transfer.

Resminostat induces NKG2D ligands on tumor cells

Tumor cells were treated with resminostat at indicated concentrations, expression of NKG2D ligands was determined after 24 h by quantitative qPCR.

Resminostat enhances NK cell mediated lysis of tumor cells

K562 cells were pretreated with DMSO or resminostat at indicated concentrations or at 2 µM and incubated with PBMCs; cytotoxic effect was determined via FACS by PI staining (left); to demonstrate NK cell dependency NK cell depleted PBMCs (middle) or isolated NK cells (98% pure; on the right) were used as effector cells.