VABILO NA PREDAVANJE / LECTURE INVITATION

Dr. Katja Srpan

Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York

Z naslovom/entitled:

PD-L1 ligation enhances NK cell anti-tumor function by inducing a metabolic shift

Sreda / Wednesday 11.9.2024 ob 14:30 uri / at 14:30

V predavalnici **P3** v drugem nadstropju Fakultete za farmacijo, Aškerčeva cesta 7 / in lecture room **P3**, second floor at the Faculty of Pharmacy, Aškerčeva cesta 7

Predavanje bo potekalo v angleščini

Vljudno vabljeni! / Kindly invited!

Več informacij / more info: irena.mlinarič@ffa.uni-lj.si

Abstract:

Katja Srpan, Kyle B. Lupo, Rosa Sottile, Gianluca Scarno, Clara Lawry, Gabryelle Kolk, Nicholas Ceglia, Brian Shaffer, Samuel A. Funt, Snehal G. Patel, Ahmed Al-Niaimi, Colleen M. Lau, Benjamin D. Greenbaum, Joseph C. Sun, Katharine C. Hsu

Programmed death ligand 1 (PD-L1) blockade is efficacious in a broad range of malignancies, intriguingly, including PD-L1neg tumors. Natural killer (NK) cells are a vital mediator of innate immunity against viral infection and malignancy and have recently been shown to express PD-L1 upon activation. Here, we elucidate the functional role of PD-L1 on circulating and tumor-infiltrating NK cells in patients with various hematologic and solid malignancies, as well as in murine tumor models. PD-L1+ NK cells can engage with therapeutic anti-PD-L1 antibody atezolizumab, soluble PD-1 or PD-1 expressed by T cells or tumor cells, and its ligation significantly enhances NK cell-mediated tumor clearance. Surprisingly, the increased anti-tumor immunity is not the result of increased NK cell degranulation, but due to improved migration into tumors via the CXCR3 chemokine pathway and cytoskeletal dynamics, enabling better synapse formation with tumor cells. Furthermore, PD-L1 ligation in NK cells induces a metabolic shift from glycolysis toward fatty acid oxidation with increased expression of CPT1A and fatty acids uptake. This metabolic shift was essential for the atezolizumab-mediated effect, as tumor-bearing mice with the NK cell-specific deletion of CPT1A failed to respond to treatment. This feature is specifically advantageous in glucose-deprived tumor microenvironments (TME) of highly glycolytic tumors, where T cell function is compromised, as we showed using the tumor model overexpressing the GLUT1 glucose receptor. Taken together, our work demonstrates that PD-L1 ligation not only enhances NK cell cytotoxic function but also increases tumor infiltration and helps overcome challenging TME conditions, resulting in a more effective anti-tumor function. These findings underscore the potential of targeting PD-L1 to augment NK cell-mediated anti-tumor responses. By enhancing NK cell function and infiltration, PD-L1-directed strategies offer promising avenues for improving cancer immunotherapy outcomes.

About the speaker:

Katja Srpan is a postdoctoral fellow at Memorial Sloan Kettering Cancer Center in New York, where she conducts translational research in Prof. Kathy Hsu's lab. She is particularly interested in better understanding NK cell biology for their optimal use in cancer immunotherapy. Katja Srpan received her Ph.D. in Immunology at the University of Manchester under the supervision of Prof. Daniel Davis. She was recently awarded a prestigious First Eagle Fellowship for her postdoctoral work.