Immune landscape of hematological malignancies and functional screening tools

Satu Mustjoki

University of Helsinki, Finland

Recent advances in the understanding of the immune response against cancer have provided novel cancer treatments, while undiscovered therapeutic potential still exists. Immune checkpoint inhibitors, particularly anti–PD-1 antibodies, have shown great potential in a variety of cancers, and are currently approved in over 15 cancer indications. CAR T cell therapies have also been approved and successfully used in B-cell malignancies. Currently emerging immuno-oncological (IO) therapies comprise antibodies targeting other immune checkpoint molecules, and various adoptive T and NK cell therapies. Despite impressive results, immunotherapy shows efficacy only in a subset of patients, and refractoriness and acquired resistance occur. As novel immunologic treatments are expensive, and severe side effects emerge, better biomarkers are needed to guide patient selection (personalized medicine) and to provide on-treatment indicators of response.

Recently we have performed an extensive immunogenomic analysis relying on large multi-omics datasets including over 8,000 transcriptomes of hematological cancers to investigate how immunological features are linked to cancer subtypes and patient survival.[1] Further, with the high-throughput profiling of over 500 drugs and genome-scale CRISPR-Cas9 loss-of-function screens we have discovered drug classes which either inhibit or potentiate CART cytotoxicity.[2]

During the presentation I will describe, how genomic features are associated with the immunogenicity of myeloid malignancies and novel immunotherapy targets can be discovered using unbiased functional screens for molecules that regulate the interaction between cancer cells and immune cells. Further, as currently approved cancer drugs may have great potential to enhance cancer immunotherapy, I will show examples how novel compounds that sensitize malignant cells to immune cell-mediated destruction can be discovered using high-throughput compound screening.

1. *Dufva O, Polonen P, Bruck O, Keranen MAI, Klievink J, Mehtonen J, Huuhtanen J, Kumar A, Malani D, Siitonen S, Kankainen M, Ghimire B, Lahtela J, Mattila P, Vaha-Koskela M, Wennerberg K, Granberg K, Leivonen SK, Meriranta L, Heckman C, Leppa S, Nykter M, Lohi O, Heinaniemi M, Mustjoki S. Immunogenomic Landscape of Hematological Malignancies. Cancer Cell. 2020;38(3):380-399 e313.*
2. *Dufva O, Koski J, Maliniemi P, Ianevski A, Klievink J, Leitner J, Polonen P, Hohtari H, Saeed K, Hannunen T, Ellonen P, Steinberger P, Kankainen M, Aittokallio T, Keranen MAI, Korhonen M, Mustjoki S. Integrated drug profiling and CRISPR screening identify essential pathways for CAR T-cell cytotoxicity. Blood. 2020;135(9):597-609.*