RESEARCH TOPIC CLI4

Single cell dissection of the tumor microenvironment in patient with urothelial bladder cancer for the identification of predictive tools and new therapies

Clinical Unit name
Department of Urology
IRCCS – Humanitas Research Hospital

Supervisor
Massimo Lazzeri
massimo.lazzeri@hunimed.eu

Abstract

Advanced Bladder Cancer (BC) represents a challenge in oncology due to its high incidence and the scarcity of therapeutic options. At first diagnosis most of the patients present a non-muscle invasive cancer (NMBC), that is treated with transurethral resection (TURBT). Intra-vescical instillation of Bacillus Calmette¿Guerin BCG also shows strong efficacy in this context. Nevertheless, a percentage of cancers eventually recur or show resistance to MMC and/or BCG, thus evolving in a muscle- invasive disease (MIBC) associated with a high mortality. Radical cystectomy (RC) with or without neo-adjuvant chemotherapy is the standard of care, but morbidity and mortality remain high. There is thus un un-met clinical need for improving the rate of care and quality of life. Importantly, RC may be applied to treat BCG-resistant NMBC but markers that can indicate rate of response and guide therapy decision making are missing. Thus, novel predictive tools are needed to guide surgery decision in this context. Also, novel therapeutics that may improve response to BCG or be applied as alternative option are strongly needed. On this regard, immunotherapies are under investigation and hold strong promise. NK adoptive cellular therapies have been tested in clinic and showed efficacy in solid tumors. Preclinical in vitro and in vivo efforts demonstrated that CAR-NK-92 cells efficiently kill urogenital cancer cells and inhibit BC growth in mice. Nevertheless, cancer exerts an inhibitory activity on infiltrating NK cells, thus partially hindering cell therapy efficacy. Here we will test the hypothesis that the composition of the TME can be used to as prognostic factor and that specific immune subsets can be targeted to prevent progression. Moreover, we will test NK cell therapies in BC preclinical models and elaborate strategies to improve efficacy. Preliminary data from the Consortium indicate that the TME strongly varies between MIBC and NMIBC. Also, we identified the CXC12-CXCR4 axis as a strategy to improve the efficacy of NK-cell therapies in urogenital cancers. We propose a single cell-based approach at the RNA and protein level to unveil the dynamics of the TME in BC during progression and in resistance to therapy. We will determine new prognostic and predictive markers and we will test novel immunotherapies in preclinical settings.

Scientific references

Advances in bladder cancer biology and therapy. Tran L., et al. Nat Rev Cancer 2021, PMID: 33268841

T1 bladder cancer: current considerations for diagnosis and management. Jordan B., Nat Rev Urol 2019, PMID: 30323201

Recurrence mechanisms of non-muscle-invasive bladder cancer - a clinical perspective. Yuen-Chun Teoh J., Nat Rev Urol 2022, PMID: 35361927

Cell Therapies in Bladder Cancer Management. Morales L., et al, Int J Mol Sci 2021, PMID: 33802203

Lipid-loaded tumor-associated macrophages sustain tumor growth and invasiveness in prostate cancer. Masetti M., et al. J Exp Med 2022, PMID: 34919143

Multimodal single-cell profiling of intrahepatic cholangiocarcinoma defines hyperactivated Tregs as a potential therapeutic target. Alvisi G., et al, J Hepatol 2022. PMID: 35738508.

CXCL12 in normal and pathological pregnancies: A review. Ao D., et al, Am J Reprod Immunol. 2020, PMID: 32485053 Hepatic stellate cells suppress NK cell-sustained breast cancer dormancy. Correia AL., et al, Nature 2021. PMID: 34079127

NF¿B-Activated COX2/PGE2/EP4 Axis Controls the Magnitude and Selectivity of BCG-Induced Inflammation in Human Bladder Cancer Tissues. Ibrahim O., et al, Cancers 2021, PMID: 33809455

Single-cell RNA sequencing highlights the role of inflammatory cancer-associated fibroblasts in bladder urothelial carcinoma. Chen Z., et al, Nat Commun 2020, PMID: 33033240

Single-cell RNA sequencing reveals the epithelial cell heterogeneity and invasive subpopulation in human bladder cancer. Lai H., et al, Int J Cancer 2021., PMID: 34480339

Predictive biomarkers of bacillus calmette-guérin immunotherapy response in bladder cancer: where are we now? Lima L., et al, Adv Urol 2012, PMID: 22919375

Type of contract

Contract for continuative and coordinated service of at least € 26.000 activated Istituto Clinico Humanitas. This sum is subject to IRPEF income tax.

Contratto collaborazione coordinata e continuativa (cococo) pari ad almeno € 26.000 annui lordi attivato da Istituto Clinico Humanitas. Importo soggetto a tassazione IRPEF.

Humanitas University
Via Rita Levi Montalcini, 4
20072 Pieve Emanuele (MI) Italy
Tel +39 0282241 - Fax +39 0282242394
info@hunimed.eu
hunimed.eu
CF 97692990159