Targeting the DNA Damage Repair Network to Promote an Innate Immune Response in ccRCC

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The network of DNA damage response (DDR) and DNA repair in cancer

Environmental factors
- IR/UV/Chemo

Endogenous factors
- Replication stress
- Metabolic stress

DNA damage

DNA damage response & DNA Repair

Adaptive immune responses
- Genome rearrangements
- Mutation burden
- Neoantigens

Innate immune responses
- Cytosolic DNA fragments
- DNA sensing pathways (cGAS-STING)
- Type I interferon response

Anti-tumor immunity

Cancer immunoprevention and immunotherapy

Anti-tumor immunity

Cancer immunoprevention and immunotherapy
Altered DNA damage response (DDR) and DNA repair in Kidney cancer

VHL loss leads to replication stress

Replication associated DNA lesions

Altered homologous recombination DNA repair in ccRCC tumors associated with disease stages and patient survival

Can we identify molecular determinants counteracting replication stress-induced DNA damage to promote the survival of VHL-deficient cells and thus the initiation/progression of ccRCC tumors driven by VHL loss?

Espana-Agusti, J. et al., Nature Commun. 2017
Dr. Eric Jonasch ccRCC patient cohorts
The linkage between DNA damage response/DNA repair and anti-tumor immune response in kidney cancer

Low mutation burden and lack of mismatch repair defects in ccRCC tumors

Preclinical mouse models of PBRM1-deficient ccRCC tumors treated with anti-PD1

Can we modulate DNA damage-dependent innate immune signaling to enhance the efficacy of immunotherapy in ccRCC tumors by targeting DDR/DNA repair network?

Liu, X. et al., Nature Commun. 2020
Alexandrov LB et al., Nature 2013
Modulating DNA damage-dependent innate immune signaling in kidney cancer
NPRL2 regulates DNA damage-dependent innate immune signaling

Clinical relevance of NPRL2 deficiency

NPRL2 deficiency in ccRCC tumors
Modulating DNA damage-dependent innate immune signaling in kidney cancer

Molecular mechanisms inducing cancer cell-intrinsic innate immune signaling

Molecular characterization of ccRCC tumors

Preclinical mouse models testing therapeutic efficacy

Clinical trials

Patient stratification & rational combination therapy
What? When? Which DDR inhibitors? How?
THANK YOU!

Peng Laboratory
Jonasch Laboratory
Collaborators
Advocators
Translational Research Partnership Award (DOD-KCRP)

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