The influence of homologous recombination deficiency on tumor immunity and immunotherapy efficacy

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Abstract**:** Genetic defects in DNA damage response pathways predispose to cancer and influence tumor immunity. Homologous recombination (HR) is a DNA repair pathway frequently altered in human cancers, but the consequences of HR defects on tumor immunity are unknown. Immune checkpoint blockade (ICB) activates the immune system to attack cancer, however its efficacy varies dramatically across patients and is influenced by the presence of specific types of DNA repair defects. Our long-term goal is to define the mechanistic basis by which HR defects influence both natural and immunotherapy-driven cancer immunity. Our preliminary data demonstrate that mutations in specific components of HR pathway are strongly associated with superior response to ICB. In a pan-cancer analysis, we found that ICB-treated patients harboring *BRCA2* mutations have longer survival than those with *BRCA1*-mutated cancers, consistent with the results from our syngeneic, isogenic models of *Brca1* or *Brca2* loss of function. The central hypothesis of this application is that defects in the “up-stream” parts of the HR pathway have distinct consequences on tumor immunity versus those that are “down-stream” (post end-resection). We will test this hypothesis in 3 specific aims. In Aim 1, we will characterize the immunologic consequences of defects in upstream versus downstream HR in human cancers and syngeneic models. In Aim 2, we will seek to elucidate the mechanism of distinct immunogenicity between *Brca1* and *Brca2* cancers in syngeneic murine models. In Aim 3, we will evaluate the impact of *Brca1* and *Brca2* mutations on natural immune surveillance.