DNA Damage Response Deficiency (DDRD) in Breast Cancer is associated with a STING-dependent Innate Immune Response

Eileen E. Parkes1, Steven M. Walker1,2, Nuala McCabe1,2, Kienan I. Savage1,2, Paul B. Mullan1,2, D. Paul Harkin1,2, and Richard D. Kennedy1,2

1Centre for Cancer Research and Cell Biology, Queens University Belfast, United Kingdom. 2Almac Diagnostics, Craigavon, Northern Ireland, United Kingdom. 3Northern Ireland Molecular Pathology Laboratory, Queens University Belfast, United Kingdom.

Abstract No: C105

DNA damage response deficient human breast cancers are associated with CD8+ and CD4+ lymphocytic infiltration.

The epithelial component of DDRD tumors releases chemokines that can account for lymphocytic infiltration.

Chemokine release is dependent on activation of the cGAS-STING-IRF3 pathway which is constitutively activated in DNA repair deficient cells, or by exogenous DNA damaging agents.

Activation of the cGAS-STING-IRF3 pathway is cell cycle specific and is associated with an accumulation of cytosolic DNA in the S-phase of the cell cycle.

Activation of the cGAS-STING-IRF3 pathway is associated with expression of the immune-checkpoint gene PD-L1 which may prevent immune-mediated tumor cell death.

This may provide a therapeutic rationale for immune-checkpoint targeted therapies in the context of DNA damage response deficiency in cancer.

Key Findings:

- DNA damage response deficient human breast cancers are associated with CD8+ and CD4+ lymphocytic infiltration.
- The epithelial component of DDRD tumors releases chemokines that can account for lymphocytic infiltration.
- Chemokine release is dependent on activation of the cGAS-STING-IRF3 pathway which is constitutively activated in DNA repair deficient cells, or by exogenous DNA damaging agents.
- Activation of the cGAS-STING-IRF3 pathway is cell cycle specific and is associated with an accumulation of cytosolic DNA in the S-phase of the cell cycle.
- Activation of the cGAS-STING-IRF3 pathway is associated with expression of the immune-checkpoint gene PD-L1 which may prevent immune-mediated tumor cell death.
- This may provide a therapeutic rationale for immune-checkpoint targeted therapies in the context of DNA damage response deficiency in cancer.

Conclusions:

- We propose a novel mechanism of immune infiltration in DDRD tumors, dependent on epithelial production of chemokines.
- Activation of this pathway and associated PD-L1 expression may explain the paradoxical lack of T-cell mediated cytotoxicity observed in DDRD tumors.
- We provide a rationale for exploration of DDRD in the stratification of patients for immune-checkpoint based therapies.