25IN The relationship between DNA damage and immune checkpoint activation in cancer

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Background: In cancer the presence of T cell immune infiltration has been recognised as a prognostic factor, however the mechanisms underpinning this response are not clearly defined. Our group and others have identified a relationship between type I Interferon immune signalling and loss of DNA repair, particularly the Fanconi Anemia pathway, in several different types of cancer. We therefore investigated the mechanism activating this immune response in the context of abnormal DNA repair.

Methods: Preclinical isogenic cell line systems and human tumours were used to identify the relationship between loss of function of DNA repair genes and activation of immune signalling. A panel of Chemoatherapeutic agents were studied for their effect on immune activation.

Results: IHC analysis demonstrated that both intra-tumoral and stromal CD8+ and CD4+ T cell infiltration were associated with DNA repair deficient breast tumors. The CXCL10 and CCL5 cytokines as well as the immune checkpoint target PD-L1 were shown to be significantly up-regulated in DNA repair deficient tumours and in tissue culture models when compared to DNA proficient tumours. Furthermore, conditioned media from DNA repair deficient cell lines stimulated inward migration of peripheral blood mononuclear cells, when compared to media from proficient cells, indicating the presence of active cytokines. We identified constitutive activation of the innate immune pathway STING/TBK1/IRF3 specifically in DNA repair deficient tumour cells when compared to proficient cells and found that binding of the DNA sensor cGAS to cytosolic DNA fragments was required for this immune response. In addition, we identified several chemo therapeutic agents that were able to activate the immune response in DNA repair proficient cell lines through DNA damage, the development of cytoplasmic DNA fragments and the consequent activation of the STING/TBK1/IRF3 immune pathway.

Conclusions: We have identified that the STING/TBK1/IRF3 immune pathway is constitutively activated by cytoplasmic DNA in DNA repair deficient cancers and may explain lymphocytic infiltration and the response to immune checkpoint based therapy. Some conventional chemotherapy agents such as doxorubicin are able to activate this
Results: We have found that PDLIM7 physically associates with MDM2 and prevents activity of CDK4 inhibitors, at least in WD/DDLS.

This supports the hypothesis that the transition from quiescence to senescence after growth arrest is a mechanism that can account for the activity of CDK4 inhibitors in liposarcoma.

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center, New York, NY, USA

Disclosure: All authors have declared no conflicts of interest.

Funding: National Cancer Institute, USA

Abstract: "The function of cyclin D-CDK4/6 kinases in cancer cell metabolism and anti-tumor immune surveillance"

Legal entity responsible for the study: Queen’s University of Belfast

Disclosure: R. Kennedy: I receive payment as the Global VP and Medical Director for Almac Diagnostics.

Funding: McClay Foundation

Abstract: "An approach to increase the efficacy of ICI is to combine them with chemotherapy, in order to achieve durable responses and improved overall survival. While immune checkpoint inhibitors (ICI) are efficacious and lead to anti-tumor immune infiltrates from MC38 tumor-bearing mice post-treatment. Conclusions: These findings suggest that transient trilaciclib-induced G1 cell-cycle arrest enhances anti-tumor activity, in combination with chemotherapy/ICI treatment.

Legal entity responsible for the study: G1 Therapeutics.

Disclosure: Employees of G1 Therapeutics.

Funding: NIH

Abstract: "Hypothesis-based combinatorial strategies may prevent these molecular feed-forward loops, and for example, the PI3K signaling pathway in DNA repair proficient cancers and may represent a logical combination with immune checkpoint targeted drugs in clinical trials.

Legal entity responsible for the study: Queen’s University of Belfast

Disclosure: R. Kennedy: I receive payment as the Global VP and Medical Director for Almac Diagnostics.

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