Cell-penetrating autoantibodies targeting DNA repair proteins may cause pediatric cancer

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Background: The etiology of pediatric cancers remains poorly understood and does not fit the classical view of cancer as an age-associated genetic disease. A paucity of somatic and germline mutations, and unusual mutation signatures in pediatric cancers suggest alternative causes that have not yet been identified.

Methods: We used native proteome arrays to profile serum autoantibodies from pediatric patients with 7 different cancer types, as well as from adult cancer patients and healthy controls. By high-resolution confocal microscopy and flow cytometry we detected penetration of autoantibodies, their subcellular localization, and impact on subcellular structures and DNA repair.

Results: We discovered significant enrichment of autoantibodies against DNA damage/repair and genome integrity maintenance pathways in pediatric patients across cancer types. We found that some autoantibodies from pediatric patients penetrate live cells in a cell cycle-dependent manner and specifically localize to the TIGER domain and, in the G2 phase, to the perinucleolar regions. TIGER-associated autoantibodies form a phase separation-like meshwork within which intracellular autoantigens are sequestered regardless of their regular subcellular localization. We further showed that serum from pediatric patients impaired DNA repair processes.

Conclusions: For the first time, we describe a property that is both unique to and shared by pediatric cancer patients. The ability of autoantibodies targeting proteins involved in DNA repair to penetrate cells and affect genome integrity may represent an autoimmune predisposition More research will be required to prove such a novel etiological mechanism, consistent with our current results.