PDIA3 as a potential bridge between immunogenic cell death and autoreactivity

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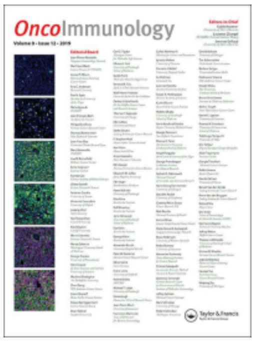

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EDITORIAL

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Antineoplastics including chemotherapeutics, targeted agents (such as tumor antigen-specific antibodies and some tyrosine kinase inhibitors) and oncolytic viruses can induce durable anticancer effects beyond therapy discontinuation. These long-term effects can be explained by the induction of immunogenic cell death (ICD), which is a modality of cell death that activates innate immune effectors (in particular dendritic cells, DCs) and culminates in an adaptive immune response against dead-cell antigens.[1] The concept of ICD has been mostly applied to immuno-oncology, where immune responses against tumor-associated/specific antigens are elicited, but is also relevant to infectious diseases, where immune responses against microbe-encoded antigens are essential for survival.[2] Both malignant cells and pathogenic microorganisms elaborate strategies to subvert the molecular mechanisms of ICD and hence to evade immune recognition.[1,3]

One of the distinctive features of ICD is the translocation of the endoplasmic reticulum (ER) chaperone calreticulin (CALR) from its normal location (ER) to the cell surface at a premortem stage. Plasma membrane-bound CALR then serves as an ‘eat-me’ signal to facilitate the phagocytic uptake of cellular antigens by DCs, allowing their cross-presentation to T lymphocytes and the induction of an antigen-specific immune response. The CALR exposure pathway is complex and involves the obligatory contribution of protein disulfide isomerase family A member 3 (PDIA3, also known as ERp57) that co-translocates with CALR to the cell surface.[4,5]

A recent paper from Laura Santambrogio’s group suggests a major implication of PDIA3 in the pathogenesis of chronic inflammatory liver diseases.[6] The authors first show that, in mice, over-eating normal chow (due to a loss-of-function mutation of leptin) or provision of high-fat and high-fructose (HFHF) diet resulted in a sustained activation of splenic DCs that exhibited changes in the MHC class II-bound immunopeptidome marked by an enrichment of epitopes from metabolism and stress response-relevant proteins. Among these HFHF diet-induced MHC class II-bound peptides, a PDIA3 epitope stood out in thus far that HFHF diet also induced autoantibodies against the very same epitope. Subsequent analyses confirmed that metabolically stressed hepatocytes exhibit increased PDIA3 levels at their surface. Moreover, an isotype switch from IgM to IgG3 of the PDIA3-specific autoantibodies occurred in mice fed with the HFHF diet. Transfer of purified anti-PDIA3 antibodies from such mice to other mice on an HFHF (but not control) diet led to liver damage. Moreover, PDIA3 epitope-specific $CD4^+$ T cells that were skewed toward a Th1 or Th17 phenotype became detectable in the livers of mice receiving the HFHF diet. Adoptive transfer of such PDIA3-specific T cells into recipients on an HFHF (but not control) diet also triggered hepatocyte death, pleading in favor of their pathogenic impact. In a final twist, the authors demonstrated that several categories of patients exhibit elevated plasma levels of PDIA3-specific autoantibodies. This applies to patients with autoimmune hepatitis, primary biliary cholangitis (PBC), or type-2 diabetes, as compared to healthy controls (Figure 1).[6]

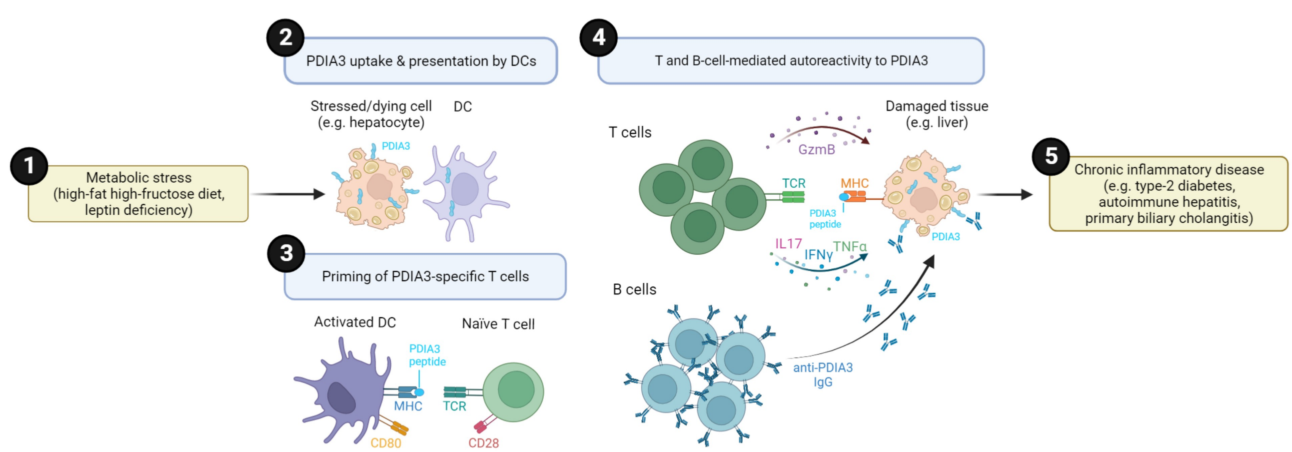

Figure 1. Role of PDIA3 in metabolic disease-related autoreactivity. In step 1, metabolic stress causes cells like hepatocytes to exhibit higher levels of the endoplasmic reticulum chaperone PDIA3 at their surface. This signal may trigger phagocytosis of damaged cells by dendritic cells (DCs). In step 2, these immune sentinels process PDIA3, present related epitopes onto MHC molecules, and then (step 3) prime naïve PDIA3-specific T lymphocytes. In step 4, such T cells differentiate into type-1 (i.e. IFN-γ and TNF-α secreting) and type-17 (i.e. IL-17A secreting) effector or cytotoxic (i.e. GzmB releasing) T lymphocytes, and favor a B cell response culminating in the production of cytopathic anti-PDIA3 IgG antibodies. The resulting autoreactivity increases the risk of developing the indicated chronic inflammatory diseases (step 5). Created with BioRender.com. GzmB, granzyme B; IFN-γ, interferon-γ; IL17, interleukin-17; MHC, major histocompatibility complex; TCR, T cell receptor; TNFα, tumor necrosis factor-α.

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The aforementioned results suggest that an ICD-relevant protein, PDIA3, can be recognized as a self-antigen, then inducing pathogenic autoreactivity in the context of liver diseases. Clinically relevant anticancer immune responses often affect non-mutated self-antigens.[7] In a mouse model, PBC protects against the development of cholangiocarcinoma.[8] The T and B cell responses associated with this autoreactive condition were mediating the clearance of malignant cholangiocytes. Such observation suggests the recognition of antigens shared between non-neoplastic and neoplastic bile duct tissues in PBC-affected hosts.[8] It will be interesting to determine whether PDIA3 is among these immunosurveillance-relevant autoantigens. Of note, previous work has identified PDIA3-specific Th1 effector cells in the immune infiltrate of colorectal cancer patients, correlating with circulating anti-PDIA3 autoantibodies.[9] Moreover, it appears that PDIA3 is overexpressed in many different cancer types, often correlating with the density of the cancer immune infiltrate. In a pan-cancer bioinformatic analysis, high PDIA3 expression predicted the clinical response to PD-L1 blockade.[10] Hence PDIA3 may play an important role in conferring immunogenicity to human cancers.

That said, the precise mechanistic links between ICD and autoreactivity are still to be elucidated. Even though PDIA3 emerges as an important autoantigen in liver disease, it is not yet clear whether autoimmune hepatitis, primary biliary cholangitis or Western style diet-induced nonalcoholic hepatosteatosis require ICD of hepatocytes and cholangiocytes to occur. Future experimentations designed to block CALR/PDIA3 exposure and other ICD-relevant pathways (such as the release of adenosine triphosphate, high mobility group B1 protein and type-I interferons) in the affected cell types must be performed to clarify this issue.

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Disclosure statement

J.G.P. is the inventor of patents covering the diagnosis, prognosis, and treatment of cancers, including patents licensed to Turstone Biologics and Therafast Bio. G.K. declares having held research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Sotio, Tollys, Vascage and Vasculox/Tioma, has received consulting/advisory honoraria from Reithera, is on the Board of Directors of the Bristol Myers Squibb Foundation France, is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio, and is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders, including patents licensed to Bayer (WO2014020041-A1, WO2014020043-A1), Bristol-Myers Squibb (WO2008057863-A1), Osasuna Therapeutics (WO2019057742A1), PharmaMar (WO2022048775-A1), Raptor Pharmaceuticals (EP2664326-A1), Samsara Therapeutics (GB202017553D0 and GB202017030D0), and Therafast Bio (EP3684471A1). All other authors declare that they have no potential conflicts of interest. The other authors declare that they have no potential conflicts of interest.

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