CANCER DISCOVERY

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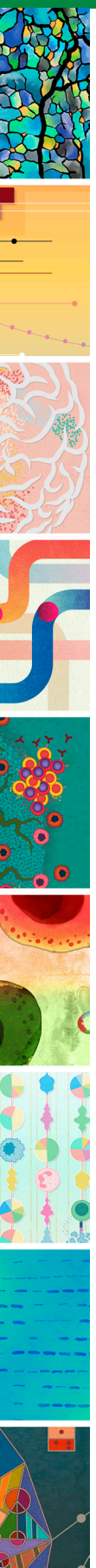

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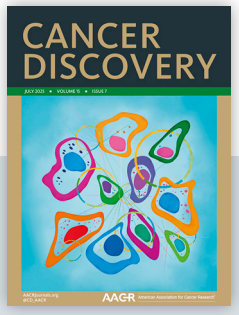

ON THE COVER Stress granules (SG) are non-membranous organelles that comprise assemblies of RNA and protein which form under cellular stress and promote cell survival. In exploring the mechanisms that govern the dynamics of SG formation in cancer cells, Redding and colleagues found that pancreatic cancer cells exhibited an unexpectedly high degree of cell-to-cell heterogeneity in SG levels in response to various stress stimuli. Fluctuation in cellular SG levels corresponded to changes in cell cycle, with SG formation peaking during G2 phase. Comparison of G2-phase synchronized versus asynchronous pancreatic cancer cells highlighted the upregulation during G2 phase of the lipid molecule 15-deoxy-delta-12,14-prostaglandin J2 (15d-PGJ2), which is a known positive regulator of SG formation. Mechanistically, the cell-cycle dependent upregulation of 15d-PGJ2 was due to the enhanced activity of the calcium-dependent phospholipase A2 (cPLA2) during G2, which was highest during G2 but otherwise cleaved by caspase-3 activity during G1 and S phases. The relationship between G2 and SG formation was confirmed in orthotopic mouse models of pancreatic cancer, and, notably, pharmacologic inhibition of cPLA2 sensitized orthotopic pancreatic tumors to oxaliplatin, a G2-arrest-inducing chemotherapy. Thus, this study highlights the interplay between cell-cycle and SG formation that gives rise to pancreatic tumor cell heterogeneity and proposes a potential strategy for pancreatic cancer treatment. For more information, see the article by Redding and colleagues on page 1437. Artwork by Bianca Dunn.

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