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Swollen Nuclei Signal from the Grave

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Eicosanoid signaling plays key pro-inflammatory roles during tissue damage. Now, Enyedi et al. show that swelling of nuclei in cell corpses activates eicosanoid signaling to recruit leukocytes to sites of tissue damage. The enhanced membrane tension in swollen nuclei directly promotes calcium-dependent translocation and activation of enzymes involved in eicosanoid biosynthesis.

Inflammation triggered by infection or tissue injury involves complex signaling networks, including through lipid molecules known as eicosanoids, which recruit leukocytes to sites of tissue damage and whose signaling is targeted by numerous anti-inflammatory drugs (Dennis and Norris, 2015). Osmotic swelling of damaged cells is known to activate inflammation, but exactly how has remained unclear. In this issue of *Cell*, Niethammer and coworkers (Enyedi et al., 2016) demonstrate that the nucleus serves as a biomechanical sensor during tissue damage-triggered inflammation.

Eicosanoid synthesis involves conversion of phospholipids into arachidonic acid (AA) by cytosolic PLA_2 ($cPLA_2$) and subsequent enzymatic action of 5-lipoxygenase (5-LOX) on AA. Calcium can trigger the translocation of soluble $cPLA_2$ to either ER or nuclear membranes. In some cells, $cPLA_2$ localizes inside the nucleus (Sierra-Honigmann et al., 1996), but the significance of nuclear localization has been uncertain. In previous work, Niethammer's team showed that, in zebrafish, damage to epithelial tissue causes osmotic swelling, calcium release, and recruitment of $cPLA_2$ to the inner nuclear membrane in cells at the wound site (Enyedi et al., 2013). In the new study, the authors unexpectedly found that phosphorylation of $cPLA_2$, which occurs during receptor activation of $cPLA_2$ (Lin et al., 1992), is not required for its translocation, indicating a novel means of $cPLA_2$ regulation. To investigate the mechanism further, they used HeLa cell nuclei as well as giant lipid vesicles and showed that membrane swelling itself causes rapid accumulation of $cPLA_2$. Remarkably, this accumulation was observed for the calcium-binding C2 domains of both $cPLA_2$ and 5-LOX, suggesting that these C2 domains directly sense membrane tension. Importantly, pro-inflammatory leukocyte recruitment in the wounded zebrafish tail fin system (buffered to prevent wound induced cell swelling) was reconstituted when HeLa cell corpses were introduced, but only if they had swollen nuclei. The study shows that osmotic swelling of the nucleus directly enhances membrane association of $cPLA_2$ and downstream 5-LOX, thus initiating eicosanoid signaling gradients to attract leukocytes (Figure 1). These findings provide the first example of a mechanochemical mechanism for sensing signals from swollen and necrotic cells and show that the nucleus is at the center of this sensing mechanism.

At the molecular level, the sensing mechanism described by Enyedi et al. appears quite simple: it requires only a Ca^{2+}-activated C2 domain and membrane under sufficient tension. The situation in a cellular context, however, may be more complicated. In cells depleted of A-type lamins, $cPLA_2$ recruitment to the nuclear membrane was enhanced, although nuclear swelling was not. Although the authors interpret the enhanced recruitment to increased tension on the nuclear membrane, depletion of A-type lamins leads to less rigid nuclei (Pajerowski et al., 2007), suggesting that the lamina or proteins interacting with it may regulate $cPLA_2$ translocation independently. It would be interesting to probe specific inner nuclear membrane proteins such as emerin to determine whether these regulate $cPLA_2$'s translocation and alter membrane bilayer structure or tension.

Enyedi et al. also show that disrupting the actin cytoskeleton leads to increased nuclear volume and $cPLA_2$ translocation. The actin cytoskeleton is intimately connected to the outer nuclear membrane through the LINC complex (Chang et al., 2015), which can act as a force sensor

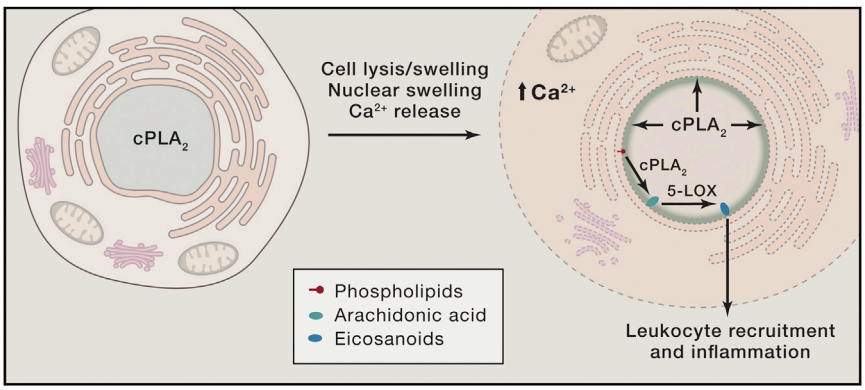

Figure 1. Ca^{2+} Release and Nuclear Swelling Trigger Translocation of $cPLA_2$
Cell lysis or swelling causes cytosolic Ca^{2+} release and nucleus swelling, both essential for $cPLA_2$ activation. Mechanical changes of the nuclear membrane allow nucleoplasmic $cPLA_2$ and 5-LOX to translocate to nuclear membrane to initiate eicosanoid biosynthesis and inflammatory responses.

to activate signaling pathways in isolated nuclei (Guilluy et al., 2014), and the nucleus is under constant actomyosin tension in cultured cells (Arsenovic et al., 2016). This raises the fascinating prospect that alterations in actin-nuclear connections may contribute to $cPLA_2$ translocation and eicosanoid signaling. Indeed, shear stress, which is imparted to the nucleus, activates $cPLA_2$ and eicosanoid signaling (Pearce et al., 1996).

As alterations in nuclear morphology are associated with numerous diseases (e.g., cancer) and mutations in proteins of the nuclear membrane and lamina cause a wide variety of diseases, it will be interesting to probe whether alterations in these mechanosensing systems contribute to the disease state.

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Mitochondria: Masters of Epigenetics

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Accumulating evidence argues that aging exerts a profound influence on epigenetics, and vice versa. A pair of studies by Merkwirth et al. and Tian et al. now provide insights on how mitochondrial stress experienced by *C. elegans* larvae propagates a specific and persistent epigenetic response that protects adult cells and extends lifespan.

Transient early life stress impacts adult health in humans and animals alike. Children of women pregnant during the Dutch "hunger winter" of 1944 were not only smaller at birth, but also more susceptible to obesity, diabetes, and cardiovascular disease throughout their lives. Not all early life stresses produce pathology, however. Several animal models of mild early stress actually generate long-lived adults. For example, in mice, increasing normal litter size by 50% extends the subsequent lifespans of the pups (Sun et al., 2009). In *C. elegans*, experimentally induced mitochondrial stress during larval development increases adult lifespan (Dillin et al., 2002). Such stress experiences are thought to anticipate future conditions that require remodeling of the adult phenotype, and the concept of epigenetic regulation has recently been thrown around like a football at a Sunday picnic. In this issue of *Cell*, the groups of Dillin and Auwerx (Merkwirth et al., 2016; Tian et al., 2016) add some beef to these arguments by describing mechanisms that persistently reprogram genome function into a long-lived alternative state (Figure 1).

Mitochondrial stress can be experimentally induced in *C. elegans* by feeding RNAi disrupting the electron transport chain (ETC) (Dillin et al., 2002) or even by expressing a polyglutamine tract-containing protein in neurons alone (Brignull et al., 2006). Once induced during development, adults express a constellation of protective genes, including mitochondrial chaperones, quality control proteases, and xenobiotic response components that comprise the mitochondrial unfolded protein response (UPR^{mt}). These adults are also long lived by a factor of almost 2-fold. Previous studies established that the induction of UPR^{mt} requires the transcription factors *atfs-1* and *dve-1*, the cofactor *ubl-5*, and the quality control protease *clpp-1*.

To understand how these responses are regulated Merkwirth et al. (2016) perform an RNAi screen spanning several chromosomes for genes required for lifespan extension in response to a knockdown of cytochrome C1 (*cyc-1*). In this way they identify *jmjd-1.2*, and using a candidate gene approach, the related *jmjd-3.1* gene. The encoded proteins belong to the family of histone lysine demethylases containing the Jumonji C domain, with overlapping specificity