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A Special Issue of *Messenger* 2016

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This special issue features a Pioneer article, three primary papers and six reviews. The Ca^{2+} mobilizing messengers, IP_3 cyclic ADP-ribose and NAADP feature throughout.

The Pioneer article by Robert ('Bob') Michel provides an absorbing historical account of the ascent of phosphoinositides in cell signaling. This journey spans the 'PI effect' described by the Hokins in the 1950s, the work leading to the influential review by Michell in the 1970s suggesting a link between receptor-mediated activation of phosphoinositide-C, turnover of inositol lipids, and Ca^{2+} elevations (Michell, 1975), the subsequent discovery of IP_3 as the key second messenger in the 1980s (see Pioneer article by Berridge (Berridge, 2012)) through to the now recognized roles of other phosphoinositides such as $\text{PI}(3,5)\text{P}_2$. This is a must read for junior scientists but perhaps also for the more seasoned investigator who may have forgotten the historical details!

The primary papers deal with the three main Ca^{2+} mobilizing messengers. First, the study by Ivanova et al characterizes the functional properties of a biotinylated analogue of IP_3 which has recently become commercially available (Ivanova *et al.*, 2016). IP_3 binds to the IP_3 receptor within the N-terminus, the structural basis of which is becoming increasingly clear (see Pioneer article by Mikoshiba (Mikoshiba, 2012)). Biotin- IP_3 should prove useful in IP_3 binding studies to determine IP_3 levels and for isolation of IP_3 receptors for biochemical analyses. Second, Morgan et al report that the anti-arrhythmic agent, carvedilol inhibits Ca^{2+} release by cyclic ADP-ribose and to a lesser extent IP_3 (Morgan *et al.*, 2016). cADPR was discovered by the Editor in Chief of *Messenger*, Hon Cheung Lee, using the trusted sea urchin egg homogenates, now somewhat of a 'gold standard' for study of IP_3 -independent Ca^{2+} mobilizing messenger action. Using this preparation, evidence is presented that carvedilol likely mediates its effects through interfering with luminal regulation of ER Ca^{2+} release channels by Ca^{2+} . This has important implications for the treatment of heart failure and points to possible roles for both cADPR and IP_3 in arrhythmogenesis.. Third, Ramakrishnan et al identify a functional role for ADP-ribosyl cyclases during development of the sea urchin (Ramakrishnan *et al.*, 2016). ADP-ribosyl cyclases, again identified by Lee, are remarkable multifunctional enzymes capable of synthesizing multiple messengers including cADPR and NAADP (Lee, 2012). The new work shows that each of the four sea urchin ADP-ribosyl cyclase isoforms display unique temporal patterns of expression through early development and that overexpression of one the isoforms (SpARC4) disrupts gastrulation. These data cement the functional importance of this fascinating enzyme family.

The review articles, introduced by Patel (Patel, 2016), focus on the roles of lysosomal Ca^{2+} signaling in neurodegeneration. This is very much a 'hot topic' at present. There is little need to stress the societal impact of neurodegenerative diseases such as Alzheimer and Parkinson given their usual late onset and thus increasing prevalence in the expanding ageing population. Understanding the causes and ultimately finding cures are key challenges. Ca^{2+} signalling through the lysosome is also very much in the limelight since the identification of NAADP-regulated TPCs which join the TRP mucolipins as endo-lysosomal Ca^{2+} -permeable channels (Grimm *et al.*, 2012). The pathophysiological importance of the latter is evident through the rare lysosomal storage disorder Mucopolipidosis Type IV (MLIV) (Bargal *et al.*, 2000). The collection of reviews marries these two research areas.

Grimm reviews the emerging pharmacology of TRP mucolipins detailing the potential utility of small molecular modifiers as novel therapeutics (Grimm, 2016). Reviews by Lloyd-Evans (Lloyd-Evans, 2016) and Feng and Yang (Feng and Yang, 2016) provide overviews of how lysosomal Ca^{2+} is dysregulated in Niemann-Pick disease type C, Alzheimer disease and several other disorders including HIV-dementia. Evidence for both gain- and loss-of-function in TRP mucolipins is discussed. Reviews by Hilfiker and colleagues (Rivero-Rios *et al.*, 2016) and Kilpatrick (Kilpatrick, 2016) cover a likely gain-of-function in two-pore channel 2 in Parkinson disease. Overall, the theme that emerges is that phenotypically disparate neurodegenerative diseases are unified by defects in endo-lysosomal membrane trafficking that can be reset through targeting lysosomal Ca^{2+} -permeable channels. These channels therefore represent novel druggable targets in neurodegeneration.

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