Mitosis, Focus on Calcium

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The transformation of a single fertilised egg into an adult human consisting of tens of trillions of highly diverse cell types is a marvel of biology. The expansion is largely achieved by cell duplication through the process of mitosis. Mitosis is essential for normal growth, development, and tissue repair and is one of the most tightly regulated biological processes studied. This regulation is designed to ensure accurate segregation of chromosomes into each new daughter cell since errors in this process can lead to genetic imbalances, aneuploidy, that can lead to diseases including cancer. Understanding how mitosis operates and the molecular mechanisms that ensure its fidelity are therefore not only of significant intellectual value but provide unique insights into disease pathology. The purpose of this review is to revisit historical evidence that mitosis can be influenced by the ubiquitous second messenger calcium and to discuss this in the context of new findings revealing exciting new information about its role in cell division.

Keywords: calcium, mitosis, GCaMP Ca2+ imaging, regulation, cytokinesis

INTRODUCTION

Since the discovery of the cyclins and their involvement in the cell-cycle, the study of mitosis regulation has focused on coordinated patterns of protein synthesis, phosphorylation, dephosphorylation, and degradation (Johnson and Walker, 1999; Nurse, 2002; McIntosh, 2016). Study of cyclin biology has demonstrated their pivotal importance during the cell cycle and mitotic cell division and, as noted by Whitaker and Larman (Whitaker and Larman, 2001), this system, in principle, does not require secondary messengers. However, cell signalling is often more complex than initially appears and for over 50 years, calcium biology researchers have suspected this multifunctional ion plays an important part in the control of mitosis (Perris and Whitfield, 1967; Luckasen et al., 1974; Berridge, 1975).

Plant and Animal Cells

These ideas were founded on early studies employing model plant (Saunders and Hepler, 1982; Hepler and Callaham, 1987; Hepler, 1994) and animal systems (Poenie et al., 1985; Silver, 1990; Whitaker, 2006a; B. Silver, 1989; Silver, 1986; Silver, 1996) where mitotic calcium signals were observed with chemical dyes (Poenie et al., 1985) or protein-based sensors of calcium such as aequorin (Keating et al., 1994). Model systems were chosen for their experimental tractability and robustness. They are often large cells and therefore easy to manipulate (microinjection, dye loading, pharmacological intervention), with minimal perturbation to the mitotic apparatus (Sluder et al., 1998; Sluder, 2016). Such studies provided consistent and promising results to link calcium with mitosis and highlighted significant correlations between calcium signals and mitotic landmarks such as nuclear envelope breakdown (NEB) (Poenie et al., 1985; Browne et al., 1996) and the metaphase → anaphase transition (Poenie et al., 1985; Hepler and Callaham, 1987) (when the spindle retracts and pulls sister chromatids towards opposite poles of what will become each new cell). Various studies
elaborated on these experimental approaches to disrupt mitotic calcium signals through the introduction (microinjection and later, by use of cell-permeant AM esterified variants) of calcium buffers such as BAPTA and showed that this inhibited mitosis progression (Miller et al., 1993). This inhibition could be relieved by addition of excess free calcium, completing the circle, and demonstrating a fundamental role for calcium in cell division (Steinhardt and Alderton, 1988; Groignon and Whitaker, 1998).

Further evidence that strengthened a role for calcium during mitosis came from related work where inositol 1,4,5 trisphosphate (IP₃) signalling was observed (Ciapa et al., 1994) and then manipulated with drugs such as heparin or introduction of antibodies directed towards the parent lipid, phosphatidylinositol 4,5 bisphosphate. These approaches were intended to suppress endoplasmic reticulum (ER) calcium release mediated by IP₃ receptors (IP₃Rs) and they altered the kinetics of mitosis (Han et al., 1992; Ciapa et al., 1994). Conversely, elevation of cytoplasmic IP₃ prematurely activated mitosis in sea urchin eggs (Whitaker and Irvine, 1984; Twigg et al., 1988). These findings indicated an important role for calcium during mitosis and highlighted the ER as the likely calcium store. They were also consistent with independently derived biochemical properties of key structures such as the mitotic spindle, that is, its disassembly in response to calcium, leading to the logical speculation that one major target of calcium during mitosis are spindle microtubules. A simple interpretation of these data would be that disruption of calcium signalling in cells, the source of which could be the ER (based on IP₃ related experiments), prevents mitosis progression through a mechanism whereby the spindle is stabilised and cannot retract as normal. Exactly how calcium is thought to modify microtubules along with more recent data in this specific area of research will be discussed in greater detail later.

Mammalian Cells

A natural extension of research into the role of calcium during mitosis was to look for corresponding signals in mammalian cells. Most of this work, but not all (Swierenga et al., 1976), employed cultured cell lines, presumably due to: 1) Ease of use and availability; 2) Technical barriers to culturing and manipulating primary cells and 3) Cultured cell lines being transformed, dividing rapidly, therefore well-suited to the study of mitosis. There are many excellent reviews that cover the work on mammalian cells, in detail, including those of Whitaker (Whitaker and Larson, 2001; Whitaker, 2006b), Hepler (Hepler, 1994), Silver (Silver, 1990; Silver, 1996) and Santella (Santella, 1998) therefore it will only be summarised here. Manipulation of calcium levels was shown to impact on mitosis (Izant, 1983) and calcium signals were observed and correlated, as for other model systems, with mitotic processes such as NEB and metaphase → anaphase transition (Poenie et al., 1986; Ratan et al., 1986). Frustratingly however there were studies, often using the same cell lines and sometimes from the same laboratories, that provided conflicting data (Ratan et al., 1986; Tombes and Borisy, 1989; Kao et al., 1990). Either calcium signals were observed but there was no discernible correlation with mitotic events or calcium signals could not be reliably detected (Tomes and Borisy, 1989). This confusion led to the view that, on balance, calcium was involved in mitosis but that the functionally relevant signals might be spatially restricted and/or temporally fleeting, rendering them difficult to reproducibly detect (Tsien and Tsien, 1990; Hepler, 1994). Sadly, this novel and potentially highly valuable area of research faded away around 15 years ago having failed to reach a consensus about the role of calcium during mitosis in mammalian cells.

RECENT RESULTS

In the intervening period, many advances have been made in relevant areas of cell biology including microscopy, molecular biology, and calcium imaging. Perhaps one of the most useful innovations to have appeared in calcium signalling has been the development of a range of genetically encoded calcium indicators (GECIs). Pioneered in the laboratory of Roger Tsien, who developed the first camelion FRET sensor calcium probes (Heim and Tsien, 1996; Miyawaki et al., 1997), but who, more importantly, forged the concept of constructing fluorescent calcium sensors using known properties of calcium binding proteins like calmodulin (CaM). This has since inspired others to develop non-FRET based sensors that have revolutionised the fields of calcium imaging in live cell systems (Akerboom et al., 2012; Akerboom et al., 2013; Chen et al., 2013; Yang et al., 2018).

Taking an idea mentioned in a review article by Tsien, that the nature of mitotic calcium signals may make them difficult to capture reproducibly (Tsien and Tsien, 1990), and by applying next generation GECIs (developed as a result of his pioneering work into conceptualising these probes) mitotic calcium has been re-examined (Helassa et al., 2019). The idea of this work was to restrict the GECI to a unique cellular location (useful if the mitotic calcium signal is spatially constrained) and to use a probe with appropriate affinity (for detection of sub-micromolar magnitude signals) and calcium binding kinetics (so that transient calcium signals would be effectively reported). The chosen reporter, GCaMP6s (Chen et al., 2013), was targeted through fusion of the coding sequence to the cytoskeletal protein actin. Actin was selected as the targeting protein with the primary goal of identifying calcium signals at the contractile actin ring (Miller, 2011), the dense actin network that constricts the centre of the dividing cell during anaphase in readiness for cytokinesis. The probe failed to report contractile ring actin calcium but, unexpectedly, did detect two persistent calcium signals located at the spindle poles during metaphase and anaphase, which were subsequently identified, through colocalization, as the centrosomes of the dividing cell. This is interesting as historical studies reported calcium signals in the vicinity of the spindle poles however these observations were never confirmed, quantified, correlated, or investigated further (Silver, 1996). This calcium signal is functionally important as its removal with a focally activated calcium chelator inhibited mitosis progression. It is also noteworthy as recent research has highlighted centrosomes nucleate actin in mitotic cells possibly to control spindle microtubule dynamics (Farina
et al., 2016; Farina et al., 2019). It seems plausible that these observations could be linked, and an exciting avenue of future investigation will be to understand how centrosomal calcium is generated and maintained and what downstream process(es) it controls. This work also observed, using transmission electron microscopy (TEM), ER close to centrosomes in mitotic cells, consistent with the historical studies examining IP₃ signalling during mitosis as discussed above. A second recent study has also examined calcium and mitosis with specific focus on the role of IP₃Rs in the orientation of the mitotic spindle (Lagos-Cabré et al., 2020). This work showed that the IP₃R3 receptor subtype was required for correct spindle geometry, but that mitosis completed normally even when all IP₃Rs were knocked-out or replaced by mutants, defective in gating calcium. It is known that cells lacking IP₃Rs can successfully complete mitosis (Ando et al., 2018) and this latest paper indicates that calcium and IP₃Rs have a relatively restricted role to play in ensuring the correct orientation of the spindle. This conservative effect on mitosis overall is at odds with the work on centrosomal calcium where suppression of the calcium signal blocked mitosis progression. This leads to the interesting possibility that the ER is not the only source of mitotic calcium and that additional mechanism(s) for generating mitosis specific calcium signals exist. Mitochondria have recently been reported to play a key role in cell division by providing ATP for the high-energy demands that this process requires. Energy production during mitosis is stimulated by a mitochondrial specific calcium signal that occurs globally during metaphase (Zhao et al., 2019) however it remains to be seen if mitochondrial calcium can influence non-mitochondrial mitosis specific processes. Indeed, from this report and a more recent, detailed characterisation of mitochondrial dynamics during mitosis (Moore et al., 2021), there is no obvious correlation between mitochondrial localisation and the spindle poles/mitotic spindles. Actin cables that are involved in the motion of mitochondria during mitosis (Moore et al., 2021) are excluded from the polar regions and therefore mitochondrial calcium signals would seemingly have to act 'at a distance' as it is unlikely, due to physical exclusion from the poles, that they could interact closely with factors controlling spindle organisation. Super-resolution confocal microscopy (SRCM) could be an interesting way to observe if a population of mitochondria do interact with the spindles through specific calcium signals or if a mitochondrial sub-population is able to access the polar regions through and alternative mechanism.
Calcium could also be provided from the extracellular environment however, a major route to calcium influx into cells, store operated calcium entry (SOCE), has been shown to be inhibited during mitosis (Smyth et al., 2009; Smyth and Putney, 2012; Yu et al., 2019). Evidence has been gathered from certain mammalian cell types showing that extracellular calcium is required for mitosis progression (Boytonto et al., 1976; Hazelton et al., 1979; Whitfield et al., 1979; Tombes and Borisy, 1989) and there are alternative calcium entry channels including those of the TRP family (Samanta et al., 2018). A comprehensive analysis of calcium entry from outside the cell during mitosis has yet to be reported and this represents another interesting avenue of investigation. A useful probe in this regard would be a GCaMP anchored to the cytoplasmic face of the plasma membrane which could report local calcium entry events during cell division. It would be simple to construct such a reporter through fusion of the GECI to an appropriate targeting motif such as the acylation consensus sequence from LCK protein tyrosine kinase (Kabouridis et al., 1997). To generate focal calcium signals from an extracellular source would require selective opening of influx channels in restricted areas of the membrane. Conceptually, this could be achieved by localised recruitment of cytoplasmic channel modulator proteins or through spatial restriction of the calcium channels in the membrane. This type of event would perhaps most likely occur where the calcium signal is required close to the inner leaflet off the membrane otherwise the calcium would have diffuse some considerable distance to its target, enhancing the likelihood of off-target effects. Examining known and hypothesised sites of focal calcium during mitosis, Figure 1, it is possible to speculate that contractile ring and intercellular bridge calcium signals would be suited to control by extracellular calcium sources. More broadly, the targeting of GECIs to specific subcellular locations, in the context of this review, those important during mitosis, represents a novel way to map in detail specific calcium signalling events during cell division. The proof of principle for such an approach, reported by our laboratory (Helassa et al., 2019), opens the doorway to generating an atlas of cell-cycle specific calcium signals which can then be functionally investigated to assess their relative contributions and importance. We can say with some confidence that calcium plays a role at NEB, metaphase → anaphase transition and now, at centrosomes throughout metaphase and into anaphase (Figure 1). It is possible that other mitosis specific calcium signals exist and the approach of selectively targeting GECIs will help to test this idea.

**Calcium Signals Exist During Mitosis, What Are the Targets?**

Calcium influences mitosis, so what are its molecular targets? The mitotic spindle has long been known to exhibit a sensitivity to calcium (Salmon and Segall, 1980; Izant, 1983) and one effect of disrupting IP$_3$Rs is to cause misorientation of spindles (Lagos-Cabrè et al., 2020) which may be due to inhibition of a key mitotic calcium signal. Calcium can exert cellular effects by directly interacting with target proteins or by binding to specific calcium sensor proteins which then convert the signal into a biological response (Burgoyne et al., 2019). The ubiquitous calcium sensor calmodulin accumulates at spindle poles, is associated with spindle microtubules during mitosis (Yu et al., 2004) and is required for mitosis progression (Rasmussen and Means, 1989; Stirling et al., 1996; Török et al., 1998; Li et al., 1999). It is therefore a strong candidate for mediating mitosis specific calcium driven events, including spindle behaviour, and its role in spindle orientation requires further investigation. Calmodulin is the primordial member of a large family of evolutionarily linked small EF-hand containing calcium sensor proteins (Burgoyne et al., 2019). Other members of this family have now been implicated in mitosis, most recently CaBP7 (also known as calneuron II, (McCue et al., 2009; McCue et al., 2010; Neumann et al., 2010; Rajamanoharan et al., 2015)), which, through its ability to regulate the phosphoinositide 4-kinase IIIβ enzyme, appears to influence a late stage of mitosis/cytokinesis (Rajamanoharan et al., 2015). This study revealed another potentially interesting facet of mitosis regulation involving lysosome function (Nugues et al., 2018) and which is linked, through CaBP7, to calcium. Although no direct evidence implicating lysosomal calcium in mitosis has been reported to date, a lysosome specific calcium channel, twopore channel 2 (TPC2), was also identified in the same high-throughput screen for proteins essential in mitosis and cytokinesis which identified CaBP7 (Neumann et al., 2010). It is well established that lysosomes act as multi-functional calcium signalling platforms (Lloyd-Evans and Waller-Evans, 2020) and this represents an exciting avenue of future research. There has been growing interest in lysosomes as druggable targets to treat human disease (Tang et al., 2020) and a lysosome specific function during mitosis could represent a new approach to targeting cell proliferation (Geisslinger et al., 2020). In addition to calmodulin and CaBP7, a variety of other small calcium sensing proteins have been linked to mitosis progression. Sorcin, a small penta-EF hand calcium sensor, exhibits mitosis specific changes in cellular localisation (Lalioti et al., 2014) and is over-expressed in multiple human cancers (Zhou et al., 2019). It has been linked to the multidrug resistant phenotype of certain cancers and is therefore of significant interest as a clinically relevant target (Pomeroy et al., 2002; Tan et al., 2003; Yokota et al., 2006; Nagpal and Das, 2007; Zhou et al., 2019). Early in mitosis, sorcin-positive vesicles associate with the spindle and later, at cytokinesis, they are found in the cleavage furrow and at the midbody (Lalioti et al., 2014). Importantly, sorcin has been shown to physically associate with, and be phosphorylated by, polo-like kinase 1 (PLK1), a key regulator of mitosis (Lee et al., 2014). It induces PLK1 autophosphorylation and depletion of sorcin promotes cytokinesis failure and the appearance of multi-nucleate cells reminiscent of the phenotype observed with CaBP7 knockdown (Neumann et al., 2010). These loss-of-function observations from two independent small calcium sensing proteins suggests that cytokinesis is particularly sensitive to calcium. This is further consistent with a calcium dependent process such as exocytosis (Burgoyne and Morgan, 1993; Barclay et al., 2005) operating
during cell scission (Goss and Toomre, 2008). Identification of specific focal calcium signals at the final stage of cell division will be an important future line of enquiry.

The S100 proteins are another family of conserved EF-hand containing calcium binding proteins with a wide range of physiological functions. S100A6 (also known as Calcycin, (Donato et al., 2017)) is upregulated in proliferating cells (Nowotny et al., 2000) and is associated with the midbody during cell division (Skop et al., 2004). Disruption of S100A6 function causes defects in chromosome segregation (Ai and Skop, 2009) and inhibits cell proliferation (Breen and Tang, 2003) indicating that it has important functions during mitosis. S100 proteins interact with annexins to mediate recruitment to cellular membranes (Rintala-Dempsey et al., 2008) and this family of proteins have also been implicated in cell division.

The annexins are a large family of calcium dependent phospholipid binding proteins (Gerke et al., 2005) that are involved in a range of physiological processes including cell division. There are at least 12 different annexin proteins expressed in humans (Gerke and Moss, 2002) and some of these have been directly linked to roles in mitosis. Annexin 11 exhibits complex mitosis related trafficking first leaving the nucleus and associating with the spindle poles (consistent with our findings of a focal calcium signal at centrosomes) and later, accumulating at the intercellular bridge (Tomas et al., 2004). Importantly, depletion of annexin 11 inhibits midbody formation with daughter cells unable to complete cytokinesis (Tomas et al., 2004). A second member of the family, annexin A2, associates with the equatorial cortex during mitosis and its depletion, like annexin 11, inhibits cytokinesis albeit through a different mechanism that disrupts normal recruitment and function of the key GTPase RhoA thereby preventing normal contractile actin ring assembly (Benaud et al., 2015). As mentioned above, there is interplay between annexins and sorcins, and understanding this and how it links to localised calcium signals, that must be present to mediate the specific recruitment of these proteins, is a fertile area of future research.

DISCUSSION

An overarching theme of calcium regulation during mitosis is the use of focal signals to recruit specific calcium binding proteins which we then speculate execute mitosis and cytokinesis specific functions. There is much interesting research to complete in this area, first, a directed calcium sensing toolkit of localised probes to identify sites of focal calcium needs to be developed. The first such probe has revealed a centrosome calcium signal however there is good reason to believe that other focal signals exist, at the nucleus, equatorial cortex and midbody, based on historical observations of calcium signals and the localisation of calcium binding proteins involved in mitosis during cell division (Figure 1). The second is to understand what these signals control and how. This will require identification of the specific calcium binding proteins that respond to each focal signal and, in turn, what effectors they interact with to control downstream events. Understanding how calcium controls cell division is becoming increasingly important with more and more reports of dysregulated calcium signalling and aberrant expression of calcium binding proteins linked to human diseases including cancer. New insights in this area of cell biology could provide future targets for specific control of cell proliferation and lead to the development of new classes of anticancer drugs (Sansregret and Swanton, 2017).

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REFERENCES

Ai, E., and Skop, A. R. (2009). Endosomal Recycling Regulation during Cytokinesis. Commun. Integr. Biol. 2 (5), 444–447. doi:10.4161/cib.2.5.8931
Akerboom, J., Carreras Calderón, N., Tian, L., Wabnig, S., Prigge, M., Tolö, J., et al. (2013). Genetically Encoded Calcium Indicators for Multi-Color Neural Activity Imaging and Combination with Optogenetics. Front. Mol. Neurosci. 6, 2. doi:10.3389/fnmol.2013.00002
Akerboom, J., Chen, T.-W., Wardill, T. J., Tian, L., Marvin, J. S., Mutlu, S., et al. (2012). Optimization of a GCaMP Calcium Indicator for Neural Activity Imaging. J. Neurosci. 32 (40), 13819–13840. doi:10.1523/jneurosci.2601-12.2012
Ando, H., Hirose, M., and Mikoshiba, K. (2018). Aberrant IP3 Receptor Activities during cell scission. Cell Calcium 38, 343–353. doi:10.1016/j.ceca.2005.06.012
Benaud, C., Le Dez, G., Mironov, S., Galli, F., Reboutier, D., and Prigent, C. (2015). Annexin A2 Is Required for the Early Steps of Cytokinesis. EMBO Rep. 16 (4), 481–489. doi:10.15222/embr.201440015
Berridge, M. J. (1975). Control of Cell Division: a Unifying Hypothesis. J. Cycl. Nucleotide Res. 1 (5), 305–320.
Boynton, A. L., Whitfield, J. F., and Isaacs, R. J. (1976). The Different Roles of Serum and Calcium in the Control of Proliferation of RALB/c 3T3 Mouse Cells. Vitro 12 (2), 120–123. doi:10.1007/bf02796358
Breen, E. C., and Tang, K. (2003). Calcycin (S100A6) Regulates Pulmonary Fibroblast Proliferation, Morphology, and Cytoskeletal Organization In Vitro. J. Cell. Biochem. 88 (4), 848–854. doi:10.1002/jcb.10398
Browne, C. L., Creton, R., Karplus, E., Mohler, P. J., Palazzo, R. E., and Miller, A. L. (1996). Analysis of the Calcium Transient at NEB during the First Cell Cycle in Dividing Sea Urchin Eggs. Biol. Bull. 191 (1), 5–16. doi:10.2307/1543056
B. Silver, R. (1989). Nuclear Envelope Breakdown and Mitosis in Sand Dollar Embryos Is Inhibited by Microinjection of Calcium Buffers in a Calcium-Reversible Fashion, and by Antagonists of Intracellular Ca2+ Channels. Dev. Biol. 131 (1), 11–26. doi:10.1016/s0012-1606(89)80034-x
Lagos-Cabrè, R., Ivanova, A., and Taylor, C. W. (2020). Ca2+- Release by IP3 Receptors Is Required to Orient the Mitotic Spindle. Cell Rep. 33 (11), 108483. doi:10.1016/j.celrep.2020.108483

Lalioti, V. S., Ilari, A., O’Connell, D. J., Poser, E., Sandoval, I. V., and Colotti, G. (2014). Sorcin Links Calcium Signaling to Vesicle Trafficking, Regulates Polo-like Kinase 1 and Is Necessary for Mitosis. PLoS One 9 (1), e85438. doi:10.1371/journal.pone.0085438

Lee, S.-Y., Jang, C., and Lee, K.-A. (2014). Polo-like Kinesins (Plks), a Key Regulator of Cell Cycle and New Potential Target for Cancer Therapy. Dev. Reprod. 18 (1), 65–71. doi:10.1271/dr.2014.18.1.068

Li, C., Heim, R., Lu, P., Pu, Y., Tsien, R. Y., and Chang, D. C. (1999). Dynamic Redistribution of Calmodulin in HeLa Cells during Cell Division as Revealed by a GFP-Calmodulin Fusion Protein Technique. J. Cell Sci. 112 (Pt 10), 1567–1577. doi:10.1242/jcs.112.10.1567

Lloyd-Evans, E., and Waller-Evans, H. (2020). Lysosomal Ca2+ Homeostasis and Signaling in Health and Disease. Cold Spring Harb. Perspect. Biol. 12 (6), doi:10.1101/cshperspect.a035311

Luckasen, J. R., White, J. G., and Kersey, J. H. (1974). Mitogenic Properties of a Calcium Ionophore, A23187. Proc. Natl. Acad. Sci. U.S.A. 71 (12), 5088–5090. doi:10.1073/pnas.71.12.5088

McCue, H. V., Burgoyne, R. D., and Haynes, L. P. (2009). Membrane Targeting of the EF-Hand Containing Calcium-Sensing Proteins CaBP7 and CaBP8. Biochem. Biophysical Res. Commun. 380 (4), 825–831. doi:10.1016/j.bbrc.2009.01.177

McCue, H. V., Haynes, L. P., and Burgoyne, R. D. (2010). Bioinformatic Analysis of CaBP/calcineurin Proteins Reveals a Family of Highly Conserved Vertebrate Ca2+-Binding Proteins. BMC Res. Notes. 3, 118. doi:10.1186/1756-0500-3-118

McIntosh, J. R. (2016). Mitosis. Cold Spring Harb. Perspect. Biol. 8 (9), doi:10.1101/cshperspect.a023218

Miller, A. L. (2011). The Contractile Ring, Curr. Biol. 21 (24), R976–R978. doi:10.1016/j.cub.2011.10.044

Miyawaki, A., Llopis, J., Heim, R., McCaffrey, J. M., Adams, J. A., Ikura, M., et al. (1999). Dynamic Cation of Differentially Expressed Genes in Tobacco Chewing-Mediated Oral Cancer by Differential Display/polymerase Chain Reaction. Eur. J. Clin. Invest 37 (8), 658–664. doi:10.1111/j.1365-2362.2007.01841.x

Neumann, B., Walter, T., Hériché, J. K., Bulkescher, J., Ehrle, J., Conrad, C., et al. (2010). Phenotypic Profiling of the Human Genome by Time-Lapse Microscopy Reveals Cell Division Genes. Nature 464 (7328), 721–727. doi:10.1038/nature08869

Novotny, M., Bhattacharya, S., Filipak, A., Krezel, A. M., Chazin, W., and Kuznicki, J. (2000). Characterization of the Interaction of Calcyckin (S100A6) and Calcybindin-Protein. J. Biol. Chem. 275 (40), 31179–31182. doi:10.1074/jbc.M01622200

Nugues, C., Nordine, H., and Haynes, L. P. (2018). Lysosomal Exocytosis Is Required for Mitosis. bioRxiv. preprint. 375816. doi:10.1101/375816

Nurse, P. (2002). Cyclin Dependent Kinases and Cell Cycle Control (Nobel Lecture) Copyright the Nobel Foundation, 2002. We Thank the Nobel Foundation, Stockholm, for Permission to Print This Lecture. Chembiochem 3 (7), 596–603. doi:10.1002/1439-6733(20020703)3:7<596::AID-CHBIOCHEM>3.0.CO;2-u

Peris, A. D., and Whitfield, J. F. (1967). Calcium and the Control of Mitosis in the Mammal. Nature 216 (5122), 1350–1351. doi:10.1038/2161350u

Poenie, M., Alderton, J., Steinhardt, R., and Tsien, R. (1986). Calcium Rises Abruptly and Briefly throughout the Cell at the Onset of Anaphase. Science 233 (4766), 866–889. doi:10.1126/science.3755550

Poenie, M., Alderton, J., Tsien, R. Y., and Steinhardt, R. A. (1985). Changes of Free Calcium Levels with Stages of the Cell Division Cycle. Nature 315 (6015), 147–149. doi:10.1038/315147a0
Pomeroy, S. L., Tamayo, P., Gaasenbeek, M., Sturla, L. M., Angelo, M., McLaughlin, M. E., et al. (2002). Prediction of Central Nervous System Embryonal Tumour Outcome Based on Gene Expression. Nature 415 (6870), 436–442. doi:10.1038/415436a0

Rajamanoharan, D., McCue, H. V., Burgoyne, R. D., and Haynes, L. P. (2015). Modulation of Phosphatidylinositol 4-phosphate Levels by CaBPs Controls Cytokinesis in Mammalian Cells. MBBc26 (8), 1428–1439. doi:10.1091/mbc.e14-07-1243

Rasmussen, C. D., and Means, A. R. (1989). Calmodulin Is Required for Cell-Cycle Progression during G1 and Mitosis. EMBO J. 8 (1), 73–82. doi:10.1002/j.1460-2075.1989.tb03350.x

Ratan, R. R., Shelanski, M. L., and Max, L. (1996). Calcium, BOBs, QEDs, Microdomains and a Cellular Decision: Control of Mitotic Cell Division in Sand Dollar Blastomeres. Nat. Rev. Mol. Cell Biol. 1 (2), 161–170. doi:10.1038/sj.nrm.4200143

Rintala-Dempsey, A. C., Rezvanpour, A., and Shaw, G. S. (2008). S100-annexin Complexes - Structural Insights. FEBS J. 275 (20), 4956–4966. doi:10.1111/j.1742-6658.2008.06543.x

Salmon, E. D., and Segall, R. R. (1980). Calcium-labile Mitotic Spindles Isolated from Sea Urchin Eggs (Lytechinus variegateus). J. Cell Biol. 86 (2), 335–365. doi:10.1083/jcb.86.2.355

Silver, R. B. (1990). Calcium and Cellular Clocks Orchestrate Cell Division. Ann. N. Y. Acad. Sci. 592 (1), 125–136. doi:10.1111/j.1749-6632.1990.tb21681.x

Silver, R. B. (1996). Calcium, BOBs, QEDs, Microdomains and a Cellular Decision: Control of Mitotic Cell Division in Sand Dollar Blastomeres. Cell Calcium 20 (2), 161–179. doi:10.1016/s0960-9822(98)70105-0

Silver, R. B. (1986). Mitosis in Sand Dollar Embryos Is Inhibited by Antibodies Directed Against the Calcium Transport Enzyme of Muscle. Proc. Nat. Acad. Sci. U.S.A. 83 (12), 4302–4306. doi:10.1073/pnas.83.12.4302

Steinhardt, R. A., and Alderton, J. (1988). Intracellular Free Calcium Rise Triggers Nuclear Envelope Breakdown in the Sea Urchin Embryo. Nature 332 (6162), 364–366. doi:10.1038/332364a0

Stirling, D. A., Rayner, T. F., Prescott, A. R., and Stark, M. J. (1996). Mutations Which Block the Binding of Calmodulin to Spc110p Cause Multiple Mitotic Defects. J. Cell Sci. 109 (Pt 6), 1297–1310. doi:10.1242/jcs.109.6.1297

Swierenga, S. H. H., MacManus, J. P., and Whitaker, M. (2006). Calcium at Fertilization and in Early Development. J. Cell Sci. 119 (Pt 6), 1297–1307. doi:10.1242/jcs.109.6.1297

Tang, T., Yang, Y.-y., Wang, D., Yang, X.-y., Wang, J., Li, L., et al. (2020). The Role of Lysosomes in Cancer Development and Progression. Cell Biosci. 10 (1), 131. doi:10.1186/s13578-020-00489-x

Tomas, A., Futter, C., and Moss, S. E. (2004). Annexin 11 Is Required for Midbody Formation and Completion of the Terminal Phase of Cytokinesis. J. Cell Biol. 165 (6), 813–822. doi:10.1083/jcb.200311054

Tormo, A., Grujic, M., Groigno, L., Patel, R., and Whitaker, M. (1998). Imaging the Spatial Dynamics of Calmodulin Activation during Mitosis. Curr. Biol. 8 (12), 692–700. doi:10.1016/s0960-9822(98)70275-1

Tsien, R. W., and Tsien, R. Y. (1990). Calcium Channels, Stores, and Oscillations. Annu. Rev. Cell Biol. 6, 715–760. doi:10.1146/annurev.cb.06.110190.003435

Twigg, J., Patel, R., and Whitaker, M. (1988). Translational Control of InsP3-Induced Chromatin Condensation during the Early Cell Cycles of Sea Urchin Embryos. Nature 332 (6162), 366–369. doi:10.1038/332366a0

Whitaker, M. (2006). Calcium Microdomains and Cell Cycle Control. Cell Calcium 40 (5–6), 585–592. doi:10.1016/j.ceca.2006.08.018

Whitaker, M. (2006). Calcium at Fertilization and in Early Development. Physiol. Rev. 86 (1), 25–88. doi:10.1152/physrev.00023.2005

Whitaker, M., and Irvine, R. F. (1984). Inositol 1,4,5-trisphosphate Microinjection Activates Sea Urchin Eggs. Nature 312 (5995), 636–639. doi:10.1038/312636a0

Whitaker, M., and Larman, M. G. (2001). Calcium and Mitosis. Seminars Cell & Dev. Biol. 12 (1), 53–58. doi:10.1016/s0271-9258(00)00217-4

Whitfield, J. F., Boynton, A. L., Macmanus, J. P., Sikorska, M., and Tsang, B. K. (1979). The Regulation of Cell Proliferation by Calcium and Cyclic AMP. Mol. Cell Biochem. 27 (3), 155–179. doi:10.1007/bf00215364

Yang, Y., Liu, N., He, Y., Liu, Y., Ge, L., Zou, L., et al. (2018). Improved Calcium Sensor GCaMP-X Overcomes the Calcium Channel Perturbations Induced by the Calmodulin in GCaMP. Nat. Commun. 9 (1), 1504. doi:10.1038/s41467-018-03719-6

Yu, F., Hubrakk, S. Z., Chakraborty, S., Sun, L., Alcantara-Adap, E., Kulkarni, R., et al. (2016). Identification of Histological Markers for Malignant Gliona by Genome-wide Expression Analysis of Dynein, a-PIX and Sorcin. Acta Neuropathol. 111 (1), 29–38. doi:10.1007/s00401-015-1085-6

Yu, Y.-T., Chen, Y., Dai, G., Chen, J., Sun, X.-M., Wen, C.-J., et al. (2004). The Association of Calmodulin with Central Spindle Regulates the Initiation of Cytokinesis in HeLa Cells. Int. J. Biochem. Cell Biol. 36 (8), 1562–1572. doi:10.1016/j.biocel.2003.12.016

Zhou, X., Wu, X., and Chen, B. (2019). Sorcin: a Novel Potential Target in Therapies of Cancers. Cancers 11, 7327–7336. doi:10.3390/cancers11111177

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