Another decade of advances in research on primary cilia, porosomes and neosis: some passing thoughts at 70

Denys N. Wheatley
Editor-in-Chief

Abstract

This editorial contains some of my reflections on a career spanning almost 50 years in biomedical research at the cellular level and over 12 years as Editor-in-Chief of *Cell Biology International*, at the time of my 70th birthday. It is gratifying that I have been involved in some of the more important organelles and processes that have come to the forefront of cell research today, and I have chosen just three examples to illustrate this point.

Discovery of the porosome

It is pleasing to find that over the last decade and more, *Cell Biology International* has been the venue in which several important, and now fully recognized, organelles and cellular activities have been reported. In two recent reviews, Jena and co-workers (Potoff et al., 2008; Jena, 2009) gives us a full account of the porosome, which he discovered in the same year that I became Editor-in-Chief of *Cell Biology International* (Jeong et al., 1998) (see Table 1). This minute structure has been resolved in nanoscale detail, but of particular relevance are the backup studies that show how the organelle works in regulating the manner in which secretion from cells allows small amounts of exocytosed material to be released from each vesicle, not in “quantal amounts” (i.e. whole vesicle emptying in one go), which was the received wisdom. Much of the work that substantiates this discovery and the physiological behaviour of the porosome has been published as primary research articles in *Cell Biology International* (Table 1).

Primary cilium: an early discovered organelle of great importance

We have also devoted a considerable number of pages for much more than a decade to primary cilia, one of my abiding interests since I first set eyes on a remarkable specimen in 1965 (reviewed in Wheatley, 2008a) (see Table 2). The primary cilium is an organelle that so many cell biologists suddenly (since 2000) ‘rediscovered’, despite investigations that have gone on for well over a century – much longer than for most other cell organelles (see the review by Broggio, 2010) (Table 2). It could not unequivocally be called a sensory organelle until Schwartz et al. (1997) and subsequently Praeftorius and Spring (2001) (Table 2) established that it sent signals (Ca²⁺ transients) to the cell body in response to environmental changes (physical and later chemical). But the implication had always been there since the very first speculation of Zimmerman (Broggio, 2010, offers a highly informative discussion on this matter). In the interim, others – notably Poole and co-workers – made a very good case for a sensory function (see Table 2). But we now know that many primary cilium membranes respond to a vast range of external factors, which can be seen from the short reviews by Ong and Wheatley (2003) (relating to medicine), and by Satir et al. (2010) and others in more academic contexts (referenced in Table 2). The cilium is an antenna of such importance that its absence can lead to a plethora of disorders, some trivial and others grave. But, it occurred to me recently that many of the antennae we see around us these days in the world of telecommunications can have a dual role, both receiving and transmitting signals. Comparisons may be odious, but I decided it was worth taking this one step further.

Receivers and transmitters

Now that it is generally accepted that primary cilia are complex signal-receiving organelles, their membranes studded with receptors of many different kinds sensing a wide variety of ligands...
that elicit responses in the cells through their second messenger pathways, could it be that they also act as transmitters (emitters), sending signals back out into their environments, perhaps even in response to signals that have come via the main cell body rather than the primary cilium itself? I am not aware of any evidence to support this idea, but I see no reason why they should not work both ways. These thoughts led me on further. I wondered whether these two organelles, the porosome and the primary cilium, have a closer connection. For example, are the membranes of primary cilia rich in porosomes, perhaps more so than on the rest of the cell membrane? It seemed to me that we might indeed have porosomes in primary cilia, perhaps in modified membrane patches, whereby they could emit (exocytose) signals back from them. Far-fetched, you may say, but today's crazy notion often becomes tomorrow's received wisdom. Since so many (most?) cell biologists had considered the primary cilium to be an unimportant 'vestigial' appendage, the notion that they have important functions must have appeared equally crazy. The dictum that I have frequently espoused that nothing a cell does should be seen as trivial or irrelevant has been adequately vindicated by the extent to which the pathology of disturbances of primary cilium formation and function has become one of the most highly researched organelles in the past 10-15 years, as presaged in Wheatley (1995) (see Table 2). This surge has not been driven so much by academic pursuit of knowledge, but because there have been so many instances in which the primary cilium is key to, or heavily involved in, the aetiology of a whole variety of medical conditions, from polycystic kidney disease to situs inversus.

Restitutive divisions and the regrowth of cancers

And finally in this editorial, written at the time of my 70th birthday, and after 12 years of being in charge of Cell Biology International, I would also like to 'reflect' on another seminal area of research that has gratifyingly opened up in its pages, in this case even more recently than the other two topics. This relates to the process that has been termed by some protagonists 'neosis' because of its relationship with mitosis and meiosis, but it has also been referred to as restitutive division (references in Table 3). The experts are neither entirely agreed on its name nor on the actual details of the process(es) that takes place, but in outline the following occurs. A cell (referring usually to a tumour cell) sometimes indulges in endopolyplody, grows large and becomes relatively resistant to different forms of cytotoxic treatment on account of its 'out-of-cycle' status. These 'giant cells' often survive when diploid or quasi-diploid tumour cells around them are being destroyed by radiation or cytotoxic agents, in a situation that has been referred to as mitotic catastrophe. The received wisdom is that these giant cells are terminal and hence no longer pose a significant problem. But they can and do undergo restitutive division, spawning in some cases quasi-diploid cells that repopulate a shrunken tumour, allowing it to regrow, and rendering it more resistant to subsequent therapeutic attacks. The reduction of polyplody to diploid cells with full growth potential as a new population is widespread in nature, which makes it odd that this quite natural process has been overlooked in tumour biology. Is it another example, like the primary cilium, where the old literature and research work of stalwarts in the past will suddenly be rediscovered?

The emergence of ideas on neosis and repopulation of tumour (stem?) cells, and much of the evidence for the process (which is becoming too persuasive to ignore), can be found in the references given in Table 3, of which well over half of the most seminal and relevant ones have been published in Cell Biology International.

Concluding remarks

On these three counts and many others, the future of Cell Biology International looks bright and healthy. Submissions are six times higher per annum than when I took over in 1998. In the absence of a 'cherry picking' philosophy, rife in other high-flying cell biology journals, I believe it has quietly blazed trails that few other journals devoted to cell biology can match, and remains a major achievement of the International Federation for Cell Biology, of which it is the official Publication. In the hands of Portland Press Limited, it will undoubtedly continue to flourish.

References


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