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Review

Peroxisystem: Harnessing systems cell biology to study peroxisomes

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In recent years, high-throughput experimentation with quantitative analysis and modelling of cells, recently dubbed systems cell biology, has been harnessed to study the organisation and dynamics of simple biological systems. Here, we suggest that the peroxisome, a fascinating dynamic organelle, can be used as a good candidate for studying a complete biological system. We discuss several aspects of peroxisomes that can be studied using high-throughput systematic approaches and be integrated into a predictive model. Such approaches can be used in the future to study and understand how a more complex biological system, like a cell and maybe even ultimately a whole organism, works.

Introduction

One of the biggest challenges in biology today is to understand a complete biological system up to the level where we can predict its behaviour under any given condition or perturbation. In recent years, high-throughput experimentation with quantitative analysis and modelling have been added to the cell biology toolkit creating a new methodology to study the organisation and dynamics of a cell – recently coined systems cell biology (Mast et al., 2014). Unfortunately, even in the simplest and best-studied eukaryotic cell, the baker's yeast *Saccharomyces cerevisiae*, we are still far from being able to achieve an ability to predict its functional outputs given a certain biological input. Hence, to start getting insights into the works of a complete biological system, one option is to use a model system that is smaller than a cell – an organelle.

Similar to a cell an organelle is a dynamic biological system that responds to diverse stimuli, has different fates and communicates with other biological systems. However, due to the simplicity of an organelle compared to a whole cell, it is more feasible to use it in order to study an entire system in an integrated manner – from signal detection, through organelle assembly and function, up to its communication with other biological systems such as other cellular components.

Peroxisomes, fascinating organelles that are found in almost all eukaryotes, have the potential to be a great model for the analysis of a system. Peroxisomes participate in central pathways of cellular metabolism such as β-oxidation of fatty acids, amino acid catabolism and detoxification of reactive oxygen species (Wanders and Waterham, 2006) as well as in recently identified non-metabolic processes such as antiviral innate immunity (Dixit et al., 2010; Odendall et al., 2014). Peroxisomes have complex biogenesis and degradation possibilities (Till et al., 2012; van der Zand and Tabak, 2013; Veenhuis and van der Klei, 2014), are actively distributed during cell division and possess their own targeting and translocation machineries (Hasan et al., 2013). Additionally, peroxisomes are remarkably diverse in shape, size, number and content. This diversity depends on the cell type and environment, and can be rapidly regulated in response to diverse signals (Smith and Aitchison, 2013). Interestingly, unlike other organelles peroxisomes are not essential for the viability of some cells such as yeast at specific growth conditions (Knoops et al., 2014). Hence, peroxisomes represent a dynamic and complex system that has biological 'inputs' and whose biological processes could be modelled with enough information to predict 'outputs'.

Another reason that peroxisomes are an attractive system to understand is their central cellular roles

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Abbreviations: ER, endoplasmic reticulum; ERMES, ER-mitochondria encounter structure; GFP, green fluorescent protein; MCS, membrane contact sites; PPI, protein–protein interaction; PTS, peroxisomal targeting sequence.

and their emerging developmental and medical importance. A large number of peroxisomal disorders with dramatic phenotypes have been described (Steinberg et al., 2006; Wanders and Waterham, 2006) and malfunctions in peroxisomes contribute to the etiology of Alzheimer's and Parkinson's diseases (Islinger et al., 2012; Lizard et al., 2012), aging, cancer and type 2 diabetes (Beach et al., 2012; Fransen et al., 2013).

In this review, we will focus on several aspects of peroxisomes that can be studied using systems cell biology approaches in an attempt to understand a complete biological system.

Mapping the constituents of peroxisomes

In order to understand any biological system, it is essential to first find out its full molecular composition. For an organelle such a compendium would include the entire spectrum of proteins (proteome), lipids (lipidome), ions (ionome) and the complete array of small molecules (metabolome).

Proteins

The peroxisome proteome is diverse in different cell types (Odendall et al., 2014), dynamic under different conditions (Zhang et al., 2013; Odendall et al., 2014) and different subpopulations of peroxisomes might exist in the same cell (Huybrechts et al., 2009; Islinger et al., 2012). Hence, one of the biggest challenges in defining their complete proteome is their plastic and dynamic nature. To try and tackle this complexity, many systematic efforts have been taken over the years to define the proteome of peroxisomes in different organisms. The various approaches are as follows.

Comprehensive genetic screens

Collections of yeast mutants were assayed for loss of the ability to grow on oleic acid or myristic acid as a sole carbon source (Smith et al., 2006; Lockshon et al., 2007). These screens identified mutants that were compromised in β-oxidation of fatty acids as well as mutants with a complete loss of peroxisomes. Obviously such screens could not pick up proteins required for other peroxisomal functions.

Biochemical fractionations followed by mass spectrometry

Mass spectrometry was used in fungi (Schafer et al., 2001; Yi et al., 2002; Marelli et al., 2004; Managadze et al., 2010), plants (Fukao et al., 2002; Reumann et al., 2007, 2009; Eubel et al., 2008) and mammalian cells (Kikuchi et al., 2004; Islinger et al., 2007; Wiese et al., 2007; Gronemeyer et al., 2013). Such assays gave a wealth of information about potential peroxisomal proteins and more work is required to differentiate between real peroxisomal proteins and contaminations from closely sedimenting organelles. Future efforts that will perform such mass spectrometry mapping under a wide variety of conditions might uncover more, condition specific, proteins.

Computational predictions of peroxisomal proteins

Computational predictions have given high-quality lists of peroxisomal proteins. These predictions were based on homology searches relative to known peroxisomal proteins, or sequence analysis to uncover the presence of peroxisomal matrix targeting sequences 1 or 2 (PTS1/2) using different predictors (Emanuelsson et al., 2003; Kamada et al., 2003; Neuberger et al., 2003; Reumann, 2004; Schluter et al., 2010; Lingner et al., 2011; Camoes et al., 2015). Interestingly, it was recently found that a PTS1 sequence can also occur as a result of ribosomal read-through or alternative splicing (Freitag et al., 2012; Schueren et al., 2014) adding to the list of peroxisomal proteins and to the complexity of analysing this system.

Despite the great power of these methodologies, they also harbour several intrinsic restrictions. First, peroxisomal membrane proteins have a much less defined targeting sequence and so predictors of matrix targeting sequence have been less helpful in discovering such proteins. Another limitation stems from the observation that matrix proteins not always rely on the classical targeting sequences as some proteins 'piggyback' on PTS1-containing proteins, or directly interact with the receptor protein Pex5 in a PTS1-independent fashion (van der Klei and Veenhuis, 2006; Islinger et al., 2009; Hasan et al., 2013; Schueren et al., 2014). Additionally, some PTS-containing proteins are not localised to peroxisomes under any condition examined (Jung et al., 2010).

High-content imaging-based screens

With the emergence of systematic green fluorescent protein (GFP) libraries (Huh et al., 2003) and high-content screening platforms, it was possible to perform systematic screens to either directly look for peroxisomal proteins or to search for modulators of

peroxisome size/number or targeting efficiency. Such screens uncovered new peroxisomal effectors, some of which may be *bona fide* peroxisomal proteins (Saleem et al., 2008, 2010; Wolinski et al., 2009; Cohen et al., 2014).

Due to the various restrictions of each methodology, it is not surprising that none of these approaches yielded a complete overlapping set of proteins and that new peroxisomal proteins are still being discovered. This implies that, although having come a long way by combining various systematic and unbiased approaches, we do not yet know the entire protein content of this organelle. In the future, it would be interesting to further use high-throughput methods to characterise the protein content of peroxisomes in different cell types (*e.g.* from different organisms, different tissues and different pathological states) under different conditions/triggers and upon numerous genetic perturbations. Such knowledge would also enable a richer modelling of how external perturbations affect the internal composition of a biological system.

Metabolites

In addition to identifying the full peroxisome proteome, it is important to remember that peroxisomes also contain a unique content of lipids, ions and metabolites. Notably, the peroxisomal membrane of mammals appears to be freely permeable to solutes with molecular mass lower than about 300–400 Da (Antonenkov and Hiltunen, 2012), and thus some metabolites are assumed to diffuse across the membrane while others require specific transporters. Would this mean that most small metabolites are in equilibria with the cytosol? Or are there active mechanisms to create gradients despite the diffusible barrier – there is much more yet to discover. We also do not know whether peroxisomal membrane permeability is the rule in other organisms. Thus, it is intriguing to identify the lipid and ion content and the metabolome of peroxisomes.

In recent years, different methods have been developed to characterise the ionome (Eide et al., 2005; Yu et al., 2012), lipidome (da Silveira Dos Santos et al., 2014) and metabolome (Cooper et al., 2010) of the cell. These methods can potentially be used to specifically determine the content of peroxisomes. The biggest challenges for such analysis at present are the difficulties in creating biochemically pure peroxisomal preparations due to cellular contaminants and that the fractionation steps create lesions in the membrane nullifying attempts to characterise ionic content. The creation of novel chemical and genetic probes for peroxisomes (Bonekamp et al., 2012; Elbaz-Alon et al., 2014) might solve these problems by measuring the content of peroxisomes *in vivo* (Rimon and Schuldiner, 2011). Identifying the full peroxisome content will serve as a first step in characterising this exciting biological system.

Charting the functional organisation of peroxisomes

When attempting to describe the effect of a protein on a biological system in which it resides, it is necessary to assign function to each individual protein, obtain information on how proteins are organised into complexes and pathways and describe how the pathways intersect (Breker and Schuldiner, 2009). Despite intense investigation, the function of a large number of peroxisomal proteins is still unknown, and new functions for studied proteins are continuously being uncovered. This is one of the arenas where traditional biochemistry, genetics and cell biology are essential in moving the field forward. However, systems cell biology approaches can be utilised to unravel the functional organisation of peroxisomes on several levels.

Physical interactions

Discovering the physical organisation of peroxisomal proteins by creating a protein–protein interaction (PPI) map of peroxisomal proteins is essential for understanding the interplay between the various components.

Heroic efforts to chart the complete PPI network of a cell have been made in different organisms including humans (Rual et al., 2005; Stelzl et al., 2005; Ewing et al., 2007; Rolland et al., 2014), flies (Giot et al., 2003), nematodes (Li et al., 2004) and yeast (Ito et al., 2001; Ho et al., 2002; Gavin et al., 2006; Collins et al., 2007). It is possible to reanalyse the available data or, preferably, perform more tailored systematic experiments to specifically identify the comprehensive PPI network of the peroxisomal proteome.

Protein-fragment complementation assays have recently been perfected for high throughput in

S. cerevisiae (Pu et al., 2011; Sung et al., 2013) and can be used for this goal. Complementation assays are based on the formation of a reporter protein when its two non-functional fragments are brought into proximity by interaction of two proteins; each fused to one fragment of the reporter protein (Michnick et al., 2011). Examples for intensely used yeast complementation approaches are the dihydrofolate reductase and bimolecular fluorescence complementation assays. Theses experimental systems can be specifically used for peroxisomal proteins because they can work *in organello* and preserve local interactions.

Functional relationships

To identify functional dependencies between proteins, it is possible to create and analyse genetic interaction maps. Such maps involve measuring fitness of single- and double-mutant combinations of all desired genes and deriving the degree of functional dependence for them. Genetic interactions have proven to be an extremely useful way to uncover protein function and have been made for a variety of organelles in yeast (Schuldiner et al., 2005; Collins et al., 2007; Aguilar et al., 2010; Hoppins et al., 2011). Moreover, with the development of RNAi-based strategies (Bassik et al., 2013; Kampmann et al., 2013, 2014) as well as the extensive development of genome engineering with programmable nucleases (Kim and Kim, 2014), it is likely that these experimental systems would be further used for identifying genetic interaction maps in metazoans. It would be interesting to identify the genetic interaction map of peroxisomal proteins in different eukaryotic cells as a genetic interaction map of peroxisomes has never been created.

Uncovering the functional organisation of the peroxisome will unravel another level of complexity of this biological system.

Discovering the rules underlying peroxisome dynamics

Peroxisomes are remarkably diverse and dynamic in their shape, abundance, size and content (Smith and Aitchison, 2013). Additionally the biogenesis, inheritance and degradation of peroxisomes are complex processes that are still not fully understood and are the subject of intense debate (Hettema et al., 2014).

Beautiful transcription-based models were previously developed to describe and predict the gene expression changes in yeast peroxisomes in response to different stimuli (Koerkamp et al., 2002; Smith et al., 2007; Ratushny et al., 2008, 2011, 2012; Danziger et al., 2014). However, in order to develop cell biological models that can predict peroxisome dynamics, it is necessary to accumulate more data beyond the transcriptional level such as protein abundance and modifications, lipids, ions and metabolites content, peroxisomes size and number under different conditions and so forth.

Several strategies have been recently taken to further study peroxisomes dynamics in yeast including condition-specific subcellular protein distribution and abundance (Jung et al., 2013), phosphoproteomics analysis under growth in the presence of oleic acid (Saleem et al., 2010) as well as imaging-based high-content strategies to identify proteins that affect peroxisomes size and inheritance (Niemisto et al., 2006; Saleem et al., 2010).

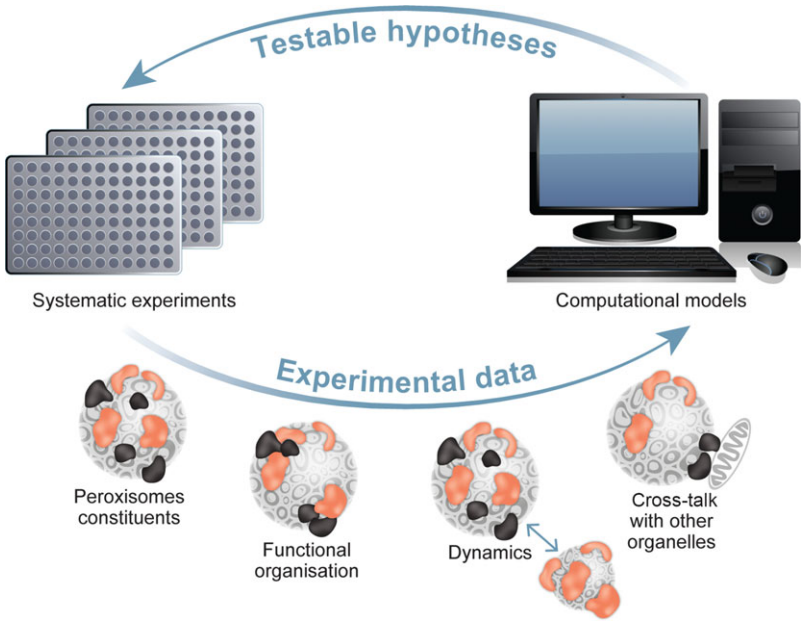
Furthermore, computational models were recently harnessed to study peroxisome dynamics. In one study, a computational model was developed to identify which mechanism, *de novo* formation or fission, governs peroxisomes biogenesis in yeast. Interestingly, the model brought forward an integrated view in which both mechanisms operate depending on the cellular state and the current need of peroxisomal functions (Mukherji and O'Shea, 2014). In another study, a computational analysis nicely showed how transient interactions between peroxisomes can contribute to the homogenisation of peroxisome populations in mammalian cells (Bonekamp et al., 2012).

Systems cell biology approaches should be further harnessed in yeast and metazoan cells to study peroxisome dynamics and to develop a comprehensive model that can predict behaviour under different growth conditions and cell states.

Revealing the cross-talk of peroxisomes with other organelles

No living system is an island: organisms, cells and organelles all communicate with each other enabling the creation of complex behaviours. Hence, another level in understanding a biological system is its interaction with the surrounding environment.

Figure 1 | Harnessing systems cell biology to study peroxisomes
Diverse high-throughput systematic approaches can be used to study different aspect of peroxisomes such as constituents, functional organisation, dynamics and cross-talk with other organelles. Then, a model that integrates and interprets the collected data can be developed, and further experiments will be performed to test and refine the model. Ultimately, after several iterations between experimental and computational work, a model that can predict the function of peroxisomes under any growth condition, cell state or perturbation could be available.



Communication between organelles is essential for coordinating cellular functions. An enormous amount of work has been published on the cross-talk of peroxisome proliferation with different signalling pathways that coordinate cellular functions (Misra et al., 2013). Communication can also occur through direct interactions in membrane contact sites (MCS), where two organelles come into close apposition (Elbaz and Schuldiner, 2011; Prinz, 2014), or through indirect communication, for example, by vesicle-mediated transport of molecules from one organelle to another.

The past few years have brought about a flurry of information on interactions between peroxisomes and other organelles highlighting the complexity of these routes and how much more there is yet to uncover. First, mitochondrial-derived vesicles were demonstrated to travel between mitochondria and peroxisomes in mammalian cells (Neuspiel et al., 2008). In addition, using a systematic high-content screen we recently uncovered that peroxisomes are juxtaposed to the endoplasmic reticulum (ER)/mitochondria MCS defined by the ER-mitochondria encounter structure (ERMES) complex (Cohen et al., 2014). It was also demonstrated that peroxisomes cooperate and cross-talk with other cellular organelles (Schrader et al., 2013) such as the ER (Thoms et al., 2009) and lipid droplets (Binns et al., 2006; Pu et al., 2011). Since peroxisomal communication with other organelles is an emerging field, we believe that a combination of traditional and systematic approaches holds the promise to provide further clarity.

Uncovering the full extent of peroxisomes cross-talk with other organelles, the effectors of this communications as well as their physiological role are essential for characterising the 'inputs' and 'outputs' of the system and enabling a more realistic modelling ground for the function of this organelle.

Challenges and future directions

Understanding a complete biological system, even a relatively defined one such as an organelle, up to the level where we can predictively model it is a great

challenge but one, that if accomplished, will provide a revolution in the way that we understand a living system. Here, we suggest that the fascinating and dynamic peroxisomal organelle can be used as a good model system. Using available systems cell biology methods together with developing new experimental tools will shed light on the function and regulation of peroxisomes in various eukaryotic organisms.

Peroxisomes were discovered last amongst the organelles, as late as the middle of the previous century (De Duve and Baudhuin, 1966). An exciting era of biochemistry spearheaded this field and provided essential information on the enzymes that reside in peroxisomes. Followed by a dynamic era of genetic studies that armed us with the constituents allowing biogenesis, inheritance and size control of these organelles. Now, we have the tools and framework to use systematic approaches coupled with computational modelling capacities to acquire data on the level of a functional system and use it to further understand peroxisomes, and predict the effects of different perturbations on their function. One can even imagine that one day our understanding of peroxisomes will reach a level that will enable us to create artificial organelles that will be implanted in cells to treat pathological conditions. Although this sounds like a dream, the first steps in this direction have already been taken (Tanner et al., 2013).

Despite the increasing speed at which scientific discoveries are made, it is impossible to imagine that we will ever be able to measure all the components of a biological system under any possible condition in which the system might function. Here, comes the power of computational models – such models would use, integrate and interpret collected data and make predictions on how the system should react in a new, untested environment. Such predictions can then be tested experimentally, and any deviation from the prediction can be used to improve the model (Figure 1). In the future, relying on the principles that we learn in small biological systems and utilising similar approaches should enable us to understand how a more complex biological system, like a cell or maybe even a whole organism, works.

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Conflict of interest statement

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