Studies on peroxisome biogenesis

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SUMMARY

Peroxisomes are subcellular organelles, which house a very diverse set of enzymes in order to fulfil a variety of functions in cellular metabolism. The importance of peroxisomes is emphasised by the existence of inheritable peroxisomal disorders in man which are generally presented with severe mental and growth retardation and which are often fatal in early infancy. With the aim of tracing all peroxisomal disorders prenatally (and hopefully of finding cures) the genetics and mechanisms of peroxisome biogenesis and function are studied in detail. Ever since the discovery of peroxisomes scientists have been wondering about the origin of these organelles and have been considering the possibility that the endoplasmic reticulum (ER) might play a role in the formation of these organelles.

At present 23 proteins, which are essential for peroxisome biogenesis, called peroxins, are known. This is in part thanks to studies in the model organism Saccharomyces cerevisiae (bakers yeast). In this organism overproduction of one of the peroxins, Pex15p, leads to the formation of a tremendous network of ER membranes. This phenomenon is one indication on a growing list that the ER might be involved in peroxisome biogenesis. However, our attempts to prove that Pex15p travels to peroxisomes via the ER failed due to incomplete knowledge (of the unfolded protein response and of karmellae formation) at that time (chapter 2). These investigations led us to a sidetrack (regulation of INO1 expression, addendum to chapter 2) because we noticed that the carbon source used in growth media (glucose versus oleate) influenced the outcome of experiments dealing with the unfolded protein response.

In the meantime a remarkable observation was made in mouse dendritic cells which provides a strong indication that the ER is actually involved in peroxisome formation (chapter 3). In these cells a peroxisomal marker, the integral peroxisomal membrane protein Pex13p, could be traced by immuno electron microscopy. It was found to be present not only in membranes of mature peroxisomes, but also in a peroxisomal reticulum, in tubular membrane structures and in tubular membrane structures which were continuous with (a specialised region of) the ER. This way the (possible) route of peroxisome formation could be visualised: from the ER to mature peroxisomes.

The function of S. cerevisiae Pex15p was studied (chapter 4) and a link
was found with Pex6p, an ATPase. Pex15p is thought to be the peroxisomal membrane anchor of Pex6p, while the ATP hydrolysis dependent release of Pex6p from Pex15p seems to provide energy for one of the mechanisms underlying peroxisome biogenesis. There are indications that the release of Pex6p from Pex15p triggers membrane fusion (chapter 4) and/or recycling of a key player in peroxisomal matrix protein import (Pex5p, addendum to chapter 4).

Because we noticed that methods to determine the membrane association of peroxisomal membrane proteins differed from those of membrane proteins of other organelles, we systematically compared the extraction behaviour of membrane proteins from different organelles by several methods (chapter 5). The results confirmed our concern. We observed that the extraction behaviour of membrane proteins is not only specific for the type of protein but also for the membrane it is extracted from. Thus, care should be taken in assigning the membrane association of (peroxisomal) membrane proteins.

**Conclusion**

Although we were unable to show whether Pex15p passes the ER en route to the peroxisome in *S. cerevisiae*, further research on this peroxin revealed an interesting link with Pex6p which provided insight in one of the mechanisms underlying peroxisome biogenesis in this organism. The results obtained with studies on mouse dendritic cells clearly indicate that the ER plays a major role in providing membranes for peroxisomes. If this is true, we can assume that a similar mechanism lies at the basis of peroxisome biogenesis of other higher eukaryotes, including man.