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EDITORIAL

In focus in HCB

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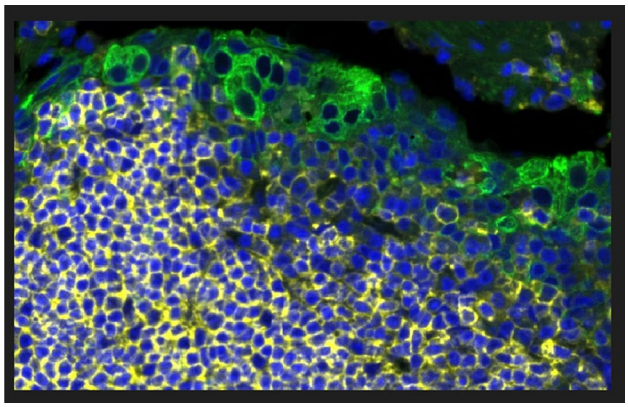

In this month's editorial, we will highlight a review updating recent research into the cell biology and pathology of peroxisomes, and two original contributions describing studies aimed at (1) determining the membrane topology of the catalytic sites of peroxisomal acyl-CoA synthetases and (2) the potential therapeutic benefits of treating burn wounds with bone marrow-derived mesenchymal stem cells. We hope you enjoy these highlights, as well as the full articles published in this issue.

The peroxisome: mystery version 3.0

An equally intriguing and fascinating cell biology story began 70 years ago when Rhodin (1954) observed single membrane-limited bodies in mice kidney proximal tubules by electron microscopy which he named microbodies, and then subsequently were renamed peroxisomes by De Duve and Baudhuin (1966). Here, Schrader and colleagues (Kumar et al. 2024) present version 3.0 of their "mystery" series on peroxisomes (Schrader and Fahimi 2008; Islinger et al. 2012, 2018). Their present review consists of eight parts covering realities and enduring mysteries of peroxisome organization and morphology, peroxisomal metabolism, matrix protein import, the shapers, movers, and regulators of peroxisome dynamics, peroxisome–organelle membrane contact sites, as well as components and functions of peroxisome-organelle cooperation, roles for peroxisomes in immune and defense mechanisms, the peroxisome physiology and pathology as it relates to specific cell types and different tissues, and finally closes with loss-of-function peroxisomal disorders. This highly comprehensive and state-of-the-art review is well illustrated and contains highly instructive tables. The last figure of the review presents an overview of some "mysteries" of peroxisome biology yet to be solved, and as an outlook the authors promise to provide a future update on mysteries 4.0. So, make sure to stay tuned!

Peroxisomal acyl-CoA synthetases: Janus duality of the catalytic sites

A main function of peroxisomes is lipid metabolism (Kumar et al. 2024; Wanders et al. 2023). To accomplish this function, the various types of fatty acids must be activated in the cell cytosol to coenzyme A (CoA) esters by acyl-CoA synthetases for subsequent importation into peroxisomes by specific peroxisomal transporter proteins, the ABCD transporters. The latter have thioesterase activity and hydrolyze acyl-CoA esters to yield free fatty acids and CoA. Inside the peroxisome, free fatty acids must be reactivated to CoA esters by acyl-CoA synthetases for subsequent degradation (van Roermund et al. 2012; Kawaguchi et al. 2021). Currently, four different mammalian acyl-CoA synthetases with distinct, nonetheless overlapping substrate specificities are

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known. They are transmembrane proteins, and conflicting reports exist regarding the membrane topography of their catalytic sites, either being exposed to the cytosol (Mannaerts et al. 1982; Pahan and Singh 1995) or to the peroxisomal lumen (Smith et al. 2000). Here, Chornyi et al. (2024) report in cellulo studies to answer this question by a microscopy-based method using the self-assembling split superfolder GFP (sfGFP) methodology of Cabantous et al. (2005). In this method, two nonfluorescent portions of sfGFP, namely GFP (1–10) and GFP11, are used to label proteins of interest, which upon self-assembly become fluorescent. In a first step, the current authors verified the suitability of the sfGFP methodology to study the topography of peroxisomal membrane proteins facing the cytosol such as ABCD1 or the peroxisomal lumen such as SLC25A17 (alias PMP34). Of note, they observed that the methodology was less suited to investigate soluble peroxisomal proteins by studying the acyl-CoA oxidase 1 (ACOX1). For the catalytic sites of both acyl-CoA synthetases SLC27A2 and SLC27A4, they determined a lumenal location, which was interpreted to suggest that both enzymes are involved in the reactivation of their respective substrates. On the other hand, a cytosolic orientation was detected for ACSL1, which was taken as evidence for the activation of long-chain fatty acids prior to peroxisomal import. No peroxisomal localization could be verified for the fourth analyzed acyl-CoA synthetase, namely ACSL4. From a methodological point of view, the authors emphasize that the high sensitivity of their approach is critically important when proteins are shared by various organelles, with only a fraction localized to peroxisomes.

Potential role of mesenchymal stem cells in burn wound healing

Mesenchymal stem cells (MSCs) have been proposed as cell-based therapies for a number of diseases and wound healing processes (Guillamat-Prats 2021; Mazini et al. 2020). These multipotent stem cells are typically isolated from bone marrow or adipose tissues, with the ability to differentiate into multiple cell types important for tissue regeneration and wound healing (Guillamat-Prats 2021). In the current issue of the journal, El-Sayed et al. (2024) have performed experiments to evaluate the potential role of mesenchymal stem cell therapy to assist in the wound healing process in a rat burn model. For these experiments, they cultured MSCs from rat bone marrow, and then characterized them by flow cytometry analysis after three passages in culture. The MSCs were found to stain positively for the cell surface markers CD73, CD105, and CD90, and to be negative for CD34, in accordance with the standard identification parameters for MSCs (Consentius et al. 2018). Rats were subjected to a 20-mm circular skin burn on the left and right dorsal sides, with the right side treated with transplanted bone marrow-derived MSCs around the wound. Animals were then killed 7, 14, 21, and 28 days following MSC transplantation, and tissue analyzed for histopathology and pro- and anti-inflammatory cytokines determined in serum blood. By gross pathology and microscopic analysis the results showed that (1) treatment with MSCs led to enhanced wound closure over all time points compared to the untreated contralateral side wound and (2) MSC treatment induced enhanced collagen deposition and assembly, neovascularization, and epithelial regeneration, all required for complete wound healing and tissue regeneration. Analysis of cytokine expression in the blood serum revealed that (1) compared to control animals, elevated levels of growth and pro-inflammatory cytokines GM-CSF, TNFα, IFNα, and IL-6 were observed in animals at 7 days following burn, but then declined through 28 days post-burn; (2) levels of the immunomodulatory and inflammatory cytokines IL-10 and TGFβ decreased at 7 days post-burn, followed by increases through 28 days post-burn; and (3) MSC treatment led to increased levels of both pro-inflammatory cytokines and the anti-inflammatory cytokine IL-10. All together, the results suggest that in the rat burn model, treatment with bone marrow-derived MSCs resulted in a more rapid regeneration of skin tissue components, suggesting that such treatment may benefit human patients with burns as well.

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