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Review

Peroxisomes and cancer: The role of a metabolic specialist in a disease of aberrant metabolism

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ABSTRACT

Cancer is irrevocably linked to aberrant metabolic processes. While once considered a vestigial organelle, we now know that peroxisomes play a central role in the metabolism of reactive oxygen species, bile acids, ether phospholipids (e.g. plasmalogens), very-long chain, and branched-chain fatty acids. Immune system evasion is a hallmark of cancer, and peroxisomes have an emerging role in the regulation of cellular immune responses. Investigations of individual peroxisome proteins and metabolites support their pro-tumorigenic functions. However, a significant knowledge gap remains regarding how individual functions of proteins and metabolites of the peroxisome orchestrate its potential role as a pro-tumorigenic organelle. This review highlights new advances in our understanding of biogenesis, enzymatic functions, and autophagic degradation of peroxisomes (pexophagy), and provides evidence linking these activities to tumorigenesis. Finally, we propose avenues that may be exploited to target peroxisome-related processes as a mode of combatting cancer.

1. Introduction: from microbody to malignancy

Peroxisomes, initially termed "microbodies", were first observed using electron microscopy and described in the 1954 thesis of Johannes Rhodin, as single membrane entities, approximately 0.1–1 μM in diameter [1]. These structures were further defined by Christian de Duve, the 1974 Nobel Laureate (shared with Claude and Palade) in physiology or medicine, and Pierre Baudhuin, with the use of density centrifugation to purify microbodies from rat livers. This led to the biochemical identification of microbody-specific enzymes such as urate oxidase, *L* and *D*-amino acid oxidases, and the hydrogen peroxide-decomposing enzyme, catalase [2]. Such findings indicated that microbodies were not empty organelles, as once believed [3], but likely served biologically relevant cellular functions. Due to the ability to metabolize hydrogen peroxide via catalase, de Duve coined the term peroxisome, to appropriately replace "microbody" [4].

For approximately twenty years following their discovery, the significance of peroxisomes remained unknown, until a series of

Abbreviations: AA, arachidonic acid; ABCD, ATP-binding cassette (ABC) transporters subfamily D; ACOX, Acyl Coenzyme-A oxidase; AGPS, alkyl-glycerone phosphate synthase; AMACR, α-Methylacyl-CoA racemase; ATO, arsenic trioxide; BAK, BCL2 antagonist/killer; CAT, catalase; CAF, cancer-associated fibroblast; CHO, Chinese hamster ovary; DEPP, decidual protein induced by progesterone; DHA, docosahexaenoic acid; DHAP, dihydroxyacetone phosphate; DLP1, dynamin-like protein-1; ER, endoplasmic reticulum; ERG, erythroblast transformation-specific related gene; FAR1, fatty acyl Co-A reductase 1; FIB, fibroblast; FIS1, mitochondrial fission protein 1; GNPAT, glycerone phosphate *O*-acyltransferase; HDACi, histone deacetylase inhibitor; HER2, human epidermal growth factor receptor 2; IFN, interferon; MAVS, mitochondrial-antiviral signalling protein; MFF, mitochondrial fission factor; NBR1, neighbor of BRCA1 gene 1; PBD, peroxisome biogenesis disorders; PBD-ZSD, Zellweger spectrum disorders; PHYH, phytanoyl-CoA 2-hydroxylase; PMP, peroxisomal membrane protein; PPAR, peroxisome proliferator-activated receptor; PTM, post-translational modification; PTS1, peroxisomal targeting signal-1; PTS2, peroxisomal targeting signal-2; ROS, reactive oxygen species; RCDP, rhizomelic chondrodysplasia punctata; SMAC, second mitochondrial-derived activator of caspases; SQSTM1/p62, sequestosome 1; TAM, tumor-associated macrophage; TCGA, The Cancer Genome Atlas; TRIM37, tripartite motif 37; VDAC2, voltage-dependent anion-selective channel protein 2; VHL, Von Hippel-Lindau syndrome; VLCFA, very-long chain fatty acid; vMIA, viral mitochondria-localized inhibitor of apoptosis

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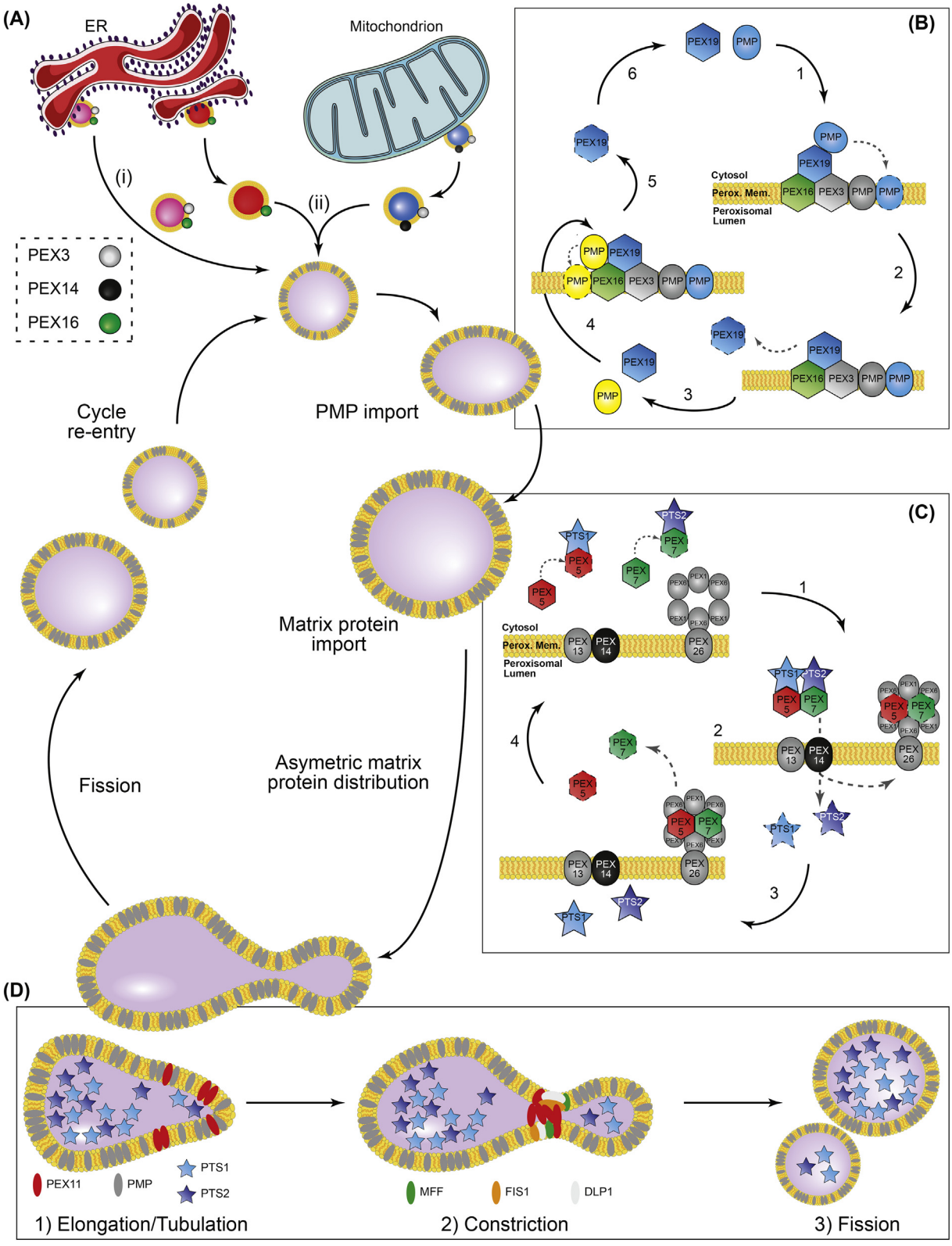

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