Joint guest lecture of the
Philipps-Universität Marburg and
Max-Planck-Institute for Heart & Lung Research

19th of April 2018

Guests are welcome

JULIA GROSS

University Medical Center Götti
and Center for Molecular Biosciences (GZMB)

"The secrete side of Wnt signaling: Understanding the sorting and signaling of Wnts on Extracellular Vesicles"

Wnt signaling is an important in development and adult homeostasis. An additional layer of regulating the Wnt pathway is the secretion and release of Wnts. Together with its cargo receptor Evi, Wnts are transported to the plasma membrane to induce short-range signaling. Moreover, Wnt/Evi complexes are sorted onto extracellular vesicles for long-range secretion. Extracellular vesicles (EVs) are membrane particles secreted from cells into all body fluids. Several EV populations exist differing in size and cellular origin (e.g. exosomes and microvesicles (MV)). How Wnts are sorted into these trafficking pathways is not fully understood. I will present different examples of fine-tuning Wnt secretion on extracellular vesicles:

(1) We have investigated the role of SNARE protein Ykt6 in exosomal Wnt secretion and identified conserved phosphorylation sites in the SNARE domain of Ykt6. These can block cycling of Ykt6 from the membrane to the cytosol. In Drosophila wing imaginal discs, time-controlled RNAi of Ykt6 in the posterior compartment blocks Wg secretion resulting in adult wing notches, which is rescued by expression of wildtype and non-phosphorylatable, but not phosphomimetic Ykt6. Microscopic analysis of loss and gain of function mutants confirm the evolutionary conserved regulation of Ykt6 in Wnt trafficking into Multivesicular bodies and onto exosomes.

(2) In addition, neutral sphingomyelinase (nSMase) inhibition has been shown to inhibit exosome release from cells and has since been used to study their functional implications. We investigated how SMPD2/3 impact different EV populations. SMPD2/3 inhibition by GW4869 or RNAi decreases secretion of exosomes, but also increases secretion of MVs from the plasma membrane. Both populations differ significantly in metabolite composition and Wnt proteins are specifically loaded onto MVs under these conditions. Our data reveal a novel regulatory function of SMPD2/3 in vesicle budding from the plasma membrane and clearly suggest that - despite the different vesicle biogenesis - the routes of vesicular export of Wnts are adaptable. Interestingly, these enzymes are differentially expressed in different tumor entities.

In conclusion, fine-tuning of long-range Wnt secretion on extracellular vesicles is evolutionary conserved from flies to human and also impacts the progression of diseases, such as cancer, when deregulated.

5:00 pm
Fachbereich 17
Großer Hörsaal

Philipps Universität Marburg

Max-Planck-Institut
für Herz- und Lungenforschung
W.G. Kerckhoff-Institut

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**University Medical Center Göttingen
and Center for Molecular Biosciences (GZMB)**

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Philipps Universität Marburg

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