SCIENTIFIC SEMINAR

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Nutrients and the Rag GTPases, metabolic switches for cancer and aging

Cellular nutrients activate the mechanistic target of rapamycin complex 1 (mTORC1) via the Rag family of GTPases. This cascade, evolutionarily conserved in all eukaryotes, is key to couple the availability of building blocks and energy to the execution of the energetically onerous processes: protein synthesis, transcription, lipid synthesis and proliferation. Under plentiful levels of cellular nutrients, an obligate heterodimeric complex formed by RagA or B and RagC or D binds mTORC1 and recruits it to the outer lysosomal surface, an essential step for allowing mTOR kinase activation that occurs in a growth-factor dependent manner.

Mutations in components of the Rag GTPase pathway are puzzlingly low in human cancer, with the exception of activating mutations in RagC in B-cell lymphomas. We have engineered the mouse genome to knock-in some of these mutations and found that full-body RagCmut/+ mice have accelerated lymphomagenesis when bred to the follicular lymphoma prone strain VavP-Bcl2. Strikingly, cells are only permissive to a subtle increase in Rag GTPase signaling, while stronger deregulation of the pathway is deleterious, consistently with the absence of mutations leading to overt activation of the pathway in human cancer. Without a lymphoma-prone genetic background, RagCmut/+ mice exhibit a surprising reduction in the spontaneous tumorigenesis that occurs at old ages, and a shortened longevity with multiple features of premature aging. We have generated the first genetic proof of increased nutrient signaling and mTORC1 driving aging in mammals, and our data supports a two-component model in which increased nutrient signaling drives parenchymal damage, and myeloid inflammation further precipitates organ deterioration and accelerated aging.

I will discuss some of these findings and current efforts focused in understanding how deregulated nutrient signaling and metabolism contribute to aging-related diseases.

CIC bioGUNE
MEMBER OF BASQUE RESEARCH & TECHNOLOGY ALLIANCE

EXCELENCIA SEVERO OCHOA

Friday
December 13
Atrio 800
12:00H

BRTA
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