PROGETTO

Supervisore::	SIMONE CENCI
Titolo/*Title*:	**ComBATaging: exploring the biological bases of the exceptional longevity of bats.**
Curriculum:	CMB (Biologia Cellulare e Molecolare/*Cellular and Molecular Biology*)
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	https://research.hsr.it/en/divisions/genetics-and-cell-biology/age-related-diseases/simone-cenci.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

In the last decade, bats (Chiroptera) have emerged as an unorthodox, powerful model for inquiring the biological mechanisms of human aging and age-related diseases. Bats outperform other mammals in longevity, being capable of living up to 10 times more than expected for their size. The only flying mammals, bats require formidable energy supply, making their exceptional lifespan even more surprising and a challenge to most current theories on aging. Notably, bats are also virtually exempt from age-related diseases, including cancer. Since bats are wild and hardly encountered, their basic cell biology is still virtually unexplored.

Rationale and hypothesis

Aging is associated with a progressive decline of autophagy, the bulk cellular strategy devoted to clearance of damaged organelles, protein aggregates and intracellular pathogens to maintain cellular homeostasis. Building on phylogenomic evidence of evolutionary pressure and on preliminary expression data in bat cells, we hereby hypothesize that bats evolved superior, life-enduring autophagy as a crucial stress-adaptive cellular homeostatic strategy against harsh metabolic requirements, with longevity as a side evolutionary effect.

Objectives and specific aims

Supported by AIRC and the European Commission, we set out to investigate, for the first time, the cell biology of bats deploying a reductionist, systematic comparative approach. Exploiting established protocols and a special EU license, we will sample, culture, analyze and manipulate bat tissues and cells, adopting cutting-edge hypothesis-driven approaches and

comprehensive technologies to define unique biological features that underlie the exceptional longevity of bats. The candidate scientist will undertake an innovative comprehensive investigation on the cellular, organellar and molecular determinants of bats' unique evolutionary adaptations, by comparison with human and murine counterparts, with special focus on autophagy as a prime protein and organelle homeoostatic strategy. In particular, the project will aim at quantitating overall autophagic activity and characterizing its impact on organelle renewal and proteome plasticity. Genetic and pharmacologic manipulation of specific mechanisms in primary cells will offer a powerful reductionist strategy to identify key biological features underlying bats' disease resistance and longevity.

Expected outcomes

Our project holds groundbreaking potential as the first evolution-based inquiry of pro-longevity mechanisms in mammals. Unlike canonical scientific research approaches, where the hypothesis is tested on pre-clinical models that recapitulate disease, here we take the opportunity to learn from what naturally evolved across millions of years in an unbiased fashion on the molecular basis of longevity. Any data that will be generated within this study might contribute to a new understanding of pro-longevity adaptations in mammals, paving the way for future functional applications in humans. Our preliminary data raise confidence that this framework may generate powerful insights to understand, contrast, and possibly reverse human aging and age-related diseases.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

During her/his training, the student will acquire the following skills:
- Molecular (qRT-PCR, FACS, IB), imaging (IF, TEM, IHC) and functional (proliferation, energy metabolism, apoptosis) assessment of gene and protein expression of homeostatic pathways;
- Functional characterization of adaptive responses;
- Morpho-functional characterization of mitochondrial function;
- Genetic and pharmacologic manipulation of proteostatic pathways;
- Genetic engineering of primary cells and cell lines;
- Critical analysis of experimental data;
- Experimental design, including contingency plans;
- Critical presentation of data in internal seminars, national and international meetings.

Bibliografia essenziale

Locatelli AG, Cenci S. *Autophagy and longevity: Evolutionary hints from hyper-longevous mammals.* **Front Endocrinol. 2022** Dec 20;13:1085522.

Locatelli AG, Kacprzyk J, Hughes GM, Huang Z, Clarke M, Gorbunova V, Sacchi C, Stewart GS, Teeling EC. *Evolution of mammalian longevity: age-related increase in autophagy in bats compared to other mammals.* **Aging** (Albany NY) **2021**; 13(6):7998-802

Jebb D, Huang Z, Pippel M, Hughes GM, Lavrichenko K, Devanna P, Winkler S, Jermiin LS, Skirmuntt EC, Katzourakis A, Burkitt-Gray L, Ray DA, Sullivan KAM, Roscito JG, Kirilenko BM, Dávalos LM, Corthals AP, Power ML, Jones G, Ransome RD, Dechmann DKN, Locatelli AG, Puechmaille SJ, Fedrigo O, Jarvis ED, Hiller M, Vernes SC, Myers EW, Teeling EC. *Six reference-quality genomes reveal evolution of bat adaptations.* **Nature 2020**;583(7817):578-584