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**Mitochondrial Plasticity in Aging and Disease**

**Aging and numerous age-related diseases are associated with defects in mitochondria, which serve as metabolic and cellular signaling hubs. Our group analyses molecular mechanisms determining the functional plasticity and dynamic behavior of mitochondria.**

***„Mitochondria are fascinating organelles, highly dynamic with diverse functions. Understanding the molecular mechanisms driving their functional plasticity holds the promise to find new paths to tackle aging and age-related diseases.“***

**Research Focus**

Mitochondrial deficiencies have long been recognized as hallmarks of ageing but how they contribute to the multifactorial ageing process remains still enigmatic. Many studies in the past were based on the restricted view of mitochondria as sources for cellular energy or damaging reactive oxygen species. However, mitochondria are multifaceted metabolic organelles with cell- and tissue-specific functions, and dynamically adapt to altered physiological demands, which is essential to ensure cell survival under stress, to maintain stem cell pluripotency and to allow immune cell activation.



Superresolution microscopy of the mitochondrial network stained with mitoOrange in MEFs.

To understand the consequences of mitochondrial defects in ageing and age-associated diseases, it is necessary to take the functional plasticity of mitochondria into account. The group studies mechanisms shaping the mitochondrial proteome in response to stress, during ageing or in age-related diseases, focusing on mitochondrial proteases as key determinants of mitochondrial plasticity. Metabolic reprogramming of mitochondria by these proteases drives adaptation to stress, limits inflammation and suppresses ferroptosis. While proteolytic rewiring can support progression of diverse cancers, loss-of-function mutations in protease-encoding genes are associated with neurodegenerative disorders and cardiomyopathy.

#### Goals

* The group uses multiple proteomic, lipidomic and metabolomic approaches combined with genome-wide genetic screens and mouse models to define the mechanisms determining mitochondrial plasticity.
* They succeeded to demonstrate that phospholipid signaling drives proteolytic rewiring and metabolic repurposing of mitochondria by the mitoprotease YME1L to support pyrimidine synthesis. Metabolic reshaping of mitochondria supports growth of pancreatic ductal adenocarcinoma cells, while tissue-specific loss of YME1L in mice causes heart failure, axonal degeneration and depletion of adult neural stem and progenitor cells.
* The group revealed an intimate link between nucleotide metabolism and inflammation, demonstrating that nucleotide imbalance induces the release of mitochondrial DNA to the cytosol and innate immune signaling.

Other research lines analyze regulatory roles of mitoproteases for mitochondrial dynamics, stress signaling and protection against neurodegeneration and ferroptosis, a cell death modality associated with lipid peroxidation and membrane rupture. Understanding how cells regulate mitochondrial function and its adaptation during stress, aging and in disease holds the promise to open up new therapeutic interventions.

#### Key Publications

1. Deshwal, S., Onishi, M., Tatsuta, T., Bartsch, T., Cors, E., Ried, K., Lemke, K., Nolte, H., Giavalisco, P. and **Langer, T.** (2023). Mitochondria regulate intercellular coenzyme Q transport and ferroptotic resistance via STARD7. Nat Cell Biol. 25, 246-257. doi:10.1038/s41556-022-01071-y.
2. Rivera Meijias, P., Narbona-Perez, A.J., Hasberg, L., Kroczek, L., Bahat, A., Lawo, S., Folz-Donahue, K., Schumacher, A.-L., Ahola, S., Mayer, F.C., Giavalisco, P., Nolte, H., Lavandero, S. and **Langer, T.** (2023). The mitochondrial protease OMA1 acts as metabolic safeguard upon nuclear DNA damage. Cell Reports 42,112332. doi:10.1016/j.celrep.2023.112332.
3. Ahola, S., Rivera Mejias, P., Hermans, S., Chandragiri, S., Giavalisco, P., Nolte, H. and **Langer, T.** (2022). OMA1-mediated integrated stress response protects against ferroptosis in mitochondrial cardiomyopathy. Cell Metab. 34(11), 1875-1891. doi: 10.1016/j.cmet.2022.08.017.
4. Sprenger, H.G., MacVicar, T., Bahat, A., Fiedler, K.U., Hermans, S., Ehrentraut, D., Ried, K., Milenkovic, D., Bonekamp, N., Larsson, N.G., Nolte, H., Giavalisco, P. and **Langer, T.** (2021). Cellular pyrimidine imbalance triggers mitochondrial DNA-dependent innate immunity. Nat. Metabol. 3, 636-650. doi:  10.1038/s42255-021-00385-9.
5. MacVicar, T., Ohba, Y., Nolte, H., Mayer, F.C., Tatsuta, T., Sprenger, H.-G., Lindner, B., Zhao, Y., Li, J., Bruns, C., Krüger, M., Habich, M., Riemer, J., Scharzer, R., Pasparakis, M., Henschke, S., Brüning, JC., Zamboni, N. and **Langer, T.** (2019). Lipid signalling drives proteolytic rewiring of mitochondria by YME1L. Nature 575(7782), 361–365. doi: 10.1038/s41586-019-1738-6.