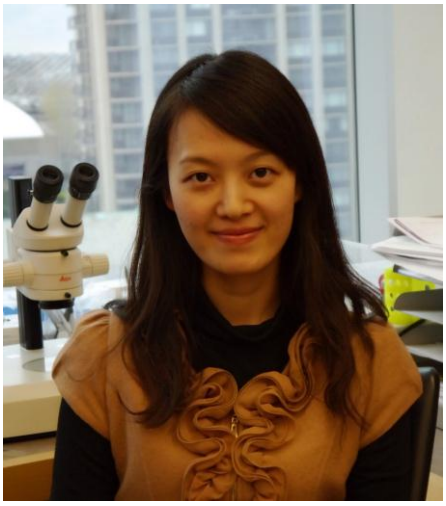
北大刘颖组在肿瘤发生及衰老调节研究方向取得重要进展

Liuying Group of Peking University has Made Important Progress in the Research of Tumorigenesis and Aging Regulation



刘颖研究员

2018 年 5 月 16 日，北京大学分子医学研究所、北大-清华生命科学联合中心刘颖课题组在《Nature》杂志发表题为“KLHL22 activates amino-acid-dependent mTORC1 signaling to promote tumorigenesis and ageing”的论文，发现 KLHL22 E3 泛素连接酶对氨基酸依赖的 mTORC1 调控具有重要作用。同时证明 KLHL22 能够影响乳腺癌发生和机体衰老进程。该研究具有潜在的临床应用价值，KLHL22 可能成为乳腺癌治疗和干预机体衰老的新靶点。

mTORC1 是细胞代谢调控的中枢。多种生理信号（如细胞内氨基酸浓度）精确调控 mTORC1 活性，从而协同合成代谢和分解代谢以维持机体内稳态。mTORC1 失控会引起多种代谢疾病，同时也会导致肿瘤发生和机体衰老。

该研究发现，KLHL22 在细胞内氨基酸充足时离开细胞核并富集到溶酶体上，泛素化修饰 mTORC1 的抑制蛋白 DEPDC5 并促使其降解，从而活化 mTORC1。论文同时报道了 KLHL22 的重要生理作用：抑制 KLHL22 可以促进秀丽线虫的寿命延长；33 例乳腺癌病人样品中 KLHL22 均高表达，敲除乳腺癌细胞的 KLHL22 可抑制裸鼠移植瘤的发生。

KLHL22 activates amino-acid-dependent mTORC1 signalling to promote tumorigenesis and ageing

KLHL22 激活氨基酸依赖性 mTORC1 信号传导以促进肿瘤发生和衰老

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The mechanistic target of rapamycin complex 1 (mTORC1) is a master regulator of cell growth that responds to a diverse set of environmental cues, including amino acids. Deregulation of mTORC1 has been linked with metabolic diseases, cancer and ageing. In response to amino acids, mTORC1 is recruited by the Rag GTPases to the lysosome, its site of activation. The GATOR1 complex, consisting of DEPDC5, NPRL3 and NPRL2, displays GAP activity to inactivate Rag GTPases under amino-acid-deficient conditions. However, it is unclear how the inhibitory function of GATOR1 is released upon amino acid stimulation. Here we find that in response to amino acids, the CUL3–KLHL22 E3 ubiquitin ligase promotes K48-linked polyubiquitination and degradation of DEPDC5, an essential subunit of GATOR1. KLHL22 plays a conserved role to mediate the activation of mTORC1 and downstream events in mammals and nematodes. Depletion of MEL-26, the Caenorhabditis elegans orthologue of KLHL22, extends worm lifespan. Moreover, KLHL22 levels are elevated in tumours of breast cancer patients, whereas DEPDC5 levels are correspondingly reduced. Depletion of KLHL22 in breast cancer cells suppresses tumour growth in nude mice. Therefore, pharmacological interventions targeting KLHL22 may have therapeutic potential for the treatment of breast cancer and age-related diseases.