Novel oncogenic driver gene *DEPDC5* in human gastrointestinal stromal tumors

With the support by the National Natural Science Foundation of China and the Chinese Academy of Sciences, the research team led by Prof. Wang YueXiang (王跃祥) at the CAS Key Laboratory of Tissue Microenvironment and Tumor, Shanghai Institute of Nutrition and Health, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, uncovered a novel druggable driver gene in one of the human deadly cancers, which was published in *PNAS* (2019, 116(45): 22746—22753).

Sarcomas, cancers that arise from transformed cells of mesenchymal original, are quite deadly. Gastrointestinal stromal tumors (GISTs) are the most common human sarcoma and are initiated by activating mutations in the *KIT* receptor tyrosine kinase. Although sharing the same *KIT* mutations, micro-GISTs have a limited growth potential and hence are restrained at the subcentimetre level. The fact that micro-GISTs are common in general individuals, found in one third of the general population, without clinical symptoms indicates additional genetic alterations contribute to the progression of clinical GISTs. Chromosome 22q deletions are frequent chromosomal abnormalities in human GISTs, occurring in ~50% GISTs, and are thought to contribute to the pathogenesis of this disease. However, the crucial gene in 22q has been unknown for decades.

To identify the causative gene in chromosome 22q, Wang's team performed whole exome sequencing and reported recurrent genomic inactivated *DEPDC5* gene mutations in GISTs. They showed that DEPDC5 is a chromosome 22q-targeting tumor suppressor, silenced by mutations in GIST specifically. The team further provided evidence that DEPDC5 inactivation promotes GIST cell proliferation through activating the mTORC1 signaling pathway and subsequently inhibits cell cycle arrest. Finally, the team demonstrated that DEPDC5 modulates the sensitivity of GIST to KIT inhibitors, and the combination therapy with the mTOR inhibitor and KIT inhibitor may work better in GIST patients with DEPDC5 inactivation. These findings of recurrent genomic alterations, together with functional data validate the DEPDC5 as a *bona fide* tumor suppressor contributing to GIST progression and a biologically relevant target of the frequent chromosome 22q deletions. The *DEPDC5* inactivated mutations are prognostic in that they are associated with aggressive GISTs where they promote GIST progression and reduce sensitivity to KIT inhibitors. The intriguing discovery of DEPDC5 also shows that biologic mechanisms of focal epilepsy (note that genetic *DEPDC5* inactivation is responsible for focal epilepsy) are relevant in tumorigenesis, and thereby highlight that recent therapeutic developments for focal epilepsy (eg DEPDC5 agonists) could also serve as anti-cancer drugs.

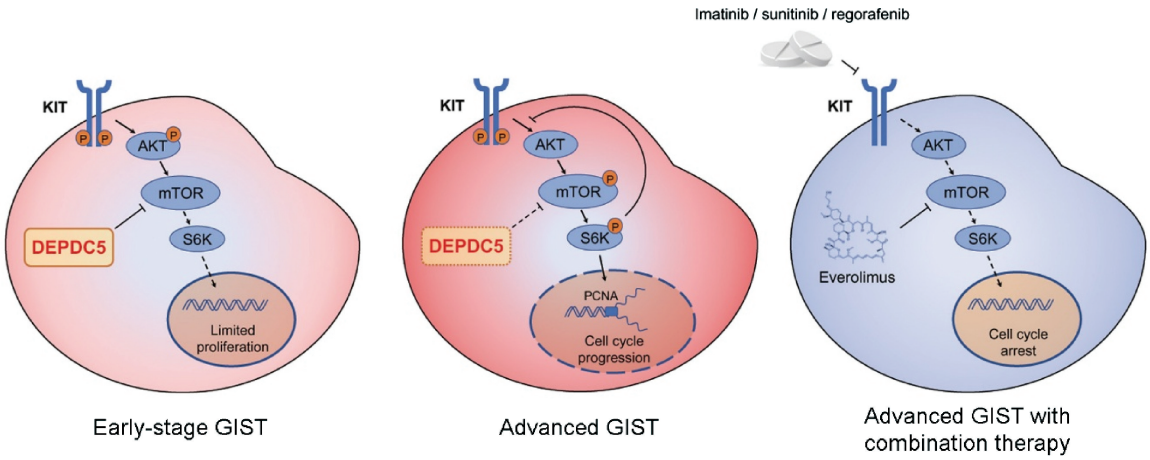

Figure *DEPDC5* inactivation promotes gastrointestinal stromal tumor (GIST) progression. Left: Limited proliferation capacity in DEPDC5 intact, early-stage GIST; middle: *DEPDC5* inactivated mutations promote GIST cell proliferation, leading to tumor progression; right: combination therapy with the mTOR inhibitor and KIT inhibitor works better in GIST patients with DEPDC5 inactivation.