

Discovery of novel cancer signalling mechanism



Active mutations in KIT tyrosine kinase, a signalling receptor protein that plays a crucial role in the growth and survival of different types of cells, are found in several cancers such as acute myeloid leukemia (AML). However, it remains unclear whether KIT transduces cancer-specific signals from intracellular compartments of AML cells. One of the major active KIT mutations in AML is *N822K*, however, the signalling platform and mechanisms of *N822K* are relatively unknown. Scientists from Japan funded by AMED* investigated the relationship between the localisation of KIT^{N822K} (KIT protein carrying the *N822K* mutation) and its activation in an AML cell line. Scientists found that in AML cells, KIT^{N822K} mislocalised to, and accumulated in the endolysosome. Using immunofluorescence experiments they showed that KIT was activated in the Golgi, a finding observed in other leukemia cells that have KIT mutations. Additionally, when they treated cells with brefeldin A (BFA) or 2-methylcoprophilinamide (M-COPA), compounds that block intracellular transport of proteins, KIT was retained in the ER. This also decreased the auto-phosphorylation of KIT and thereby its downstream signalling. Whereas suppression of Golgi export of KIT using monensin did not suppress the KIT signals, which told the scientists that mutated KIT carries out cancer signalling specifically at the Golgi.

So, what are the future applications of this study? Small

molecule tyrosine kinase inhibitors and antibodies against receptor tyrosine kinases have been developed to suppress cancer proliferative signalling using mechanisms similar to the ones described above. According to Prof. Shiina (co-author of the research article, based at TUS#), this study reveals that the novel compound M-COPA can be used to block transport of KIT from the ER to the Golgi (where it is activated and carries out downstream oncogenic signalling). The scientists say that the compound M-COPA has applications such as treatment of patients with AML, improved prognosis for these patients, and improvement in the quality of life of these patients. Prof. Shiina concludes by stating, “Currently, the synthesis of various M-COPA analogs is progressing every day at our university, and their inhibitory effects against hematological cancers and solid cancers (stomach cancer, lung cancer, ovarian cancer, etc.) are being verified.”

Journal Article: Obata et al., 2019. [N822K- or V560G-mutated KIT activation preferentially occurs in lipid rafts of the Golgi apparatus in leukemia cells](#). Cell Communication and Signaling

Article provided by Indrani Das, summarised by Cheleka Mpande

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