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Signalling protein may unleash the potential of drug-based therapies to treat hyperparathyroidism

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Signaling protein Sema3d' which prevents parathyroid glands from being hyperactive, controls the cancer-promoting signaling pathway, encouraging anti-cancer drug-based therapeutic strategies and reducing the burden of surgery in elderly hyperparathyroidism patients



Researchers at Duke-NUS Medical School, Singapore have discovered “Sema3d”, a signalling protein that appears to protect parathyroid glands from excessive activity providing insights for drug development to treat hyperparathyroidism – a condition currently treatable only through surgery. The briefing on the study was done on 28 May 2019, in Singapore by Assistant Professor Manvendra Singh, the study’s corresponding author from the Cardiovascular and Metabolic Disorders Programme at DukeNUS Medical School.

The parathyroids are four small glands located in the neck, behind the larger thyroid, and are responsible for maintaining healthy blood calcium levels through the secretion of parathyroid hormone (PTH). Primary hyperparathyroidism a condition in which these glands produce excessive PTH elevates blood calcium levels, and leads to kidney stones, neuropsychiatric disorders and bone abnormalities, particularly among elderly women.

The research team discovered that semaphorin3d (Sema3d), a signalling protein secreted by developing parathyroid glands, helps to prevent excessive growth. Sema3d was found to reduce signalling within the EGFR/ERBB signalling pathway, which is responsible for parathyroid cell growth and is also known to mediate cancer growth and survival.

Assistant Professor Manvendra Singh said: “Not many molecules are known to inhibit parathyroid growth and there are no drugs available in the market to treat the condition. Surgery is the most common treatment for hyperparathyroidism. However, re-operative surgery for persistent or recurrent hyperparathyroidism remains technically challenging due to

fibrotic scarring and distorted anatomy that make it more difficult to identify abnormal parathyroid glands. Patients are also at increased risk for laryngeal nerve injury, cervical bleeding and postoperative hypocalcemia.”

In a transgenic model lacking the gene that codes for Sema3d, EGFR signalling was activated, leading to parathyroid cell proliferation and the development of primary hyperparathyroidism. Turning off EGFR signalling with a known anti-cancer drug caused some of the parathyroid tissue to return to normal. The finding suggests Sema3d and drugs that can similarly inhibit EGFR signalling could treat hyperparathyroidism.

The research team further believes Sema3d’s protective role in restricting parathyroid cell proliferation, by suppressing the EGFR/ERBB signalling pathway, could be relevant to other tumour types as well. Further investigations could lead to the development of anti-tumour treatments employing genetically engineered Sema3d or other drugs that target the protein’s downstream pathways, the researchers conclude.