Signaling protein discovery may lead to drug-based therapies to treat hyperparathyroidism

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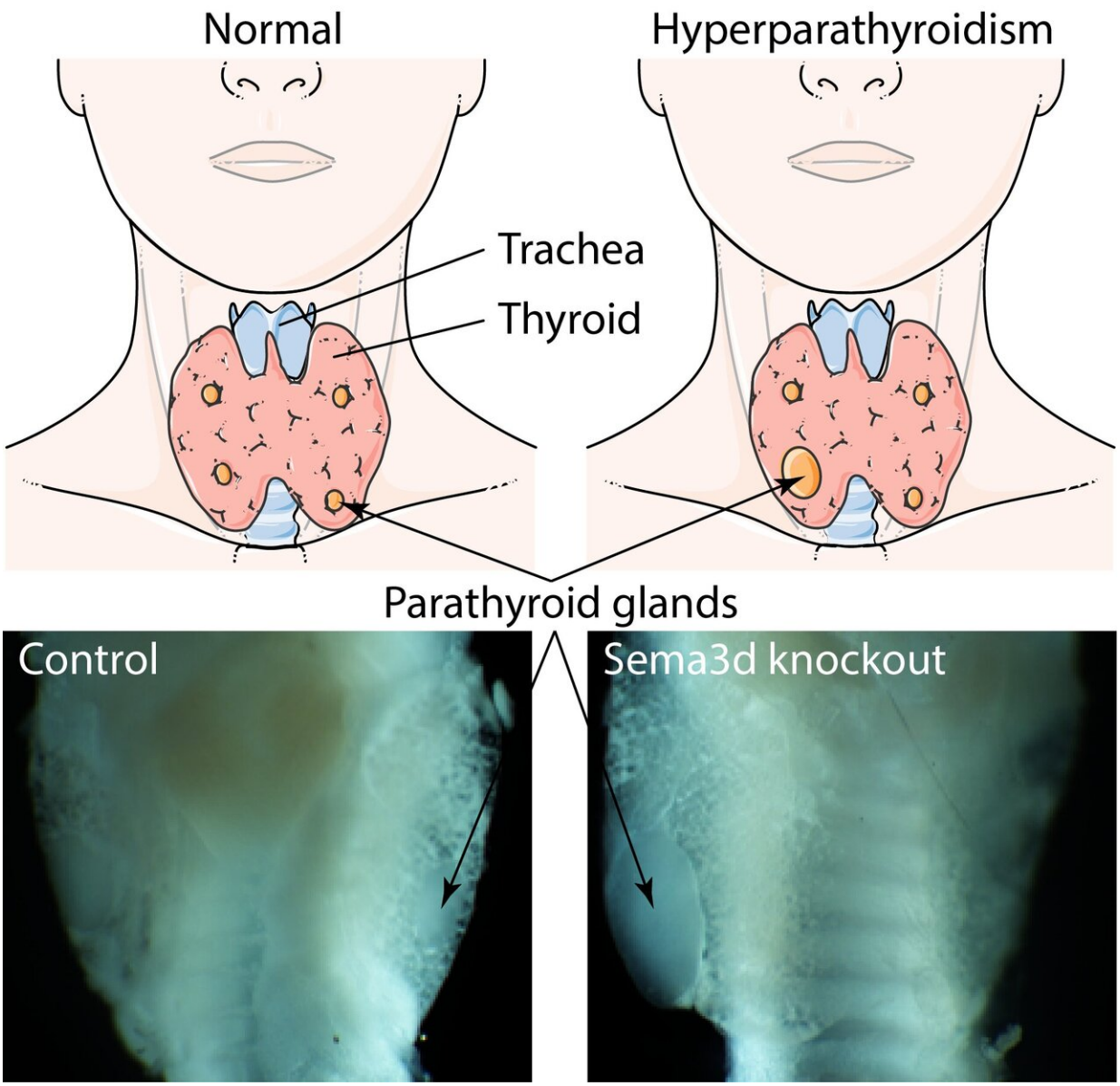

Four small parathyroid glands located in the neck behind the larger thyroid are responsible for managing healthy blood calcium levels. Primary hyperparathyroidism is marked by excessive parathyroid hormone secretion due to parathyroid hyperplasia, which leads to increased serum calcium levels and causes kidney stones, neuropsychiatric disorders and bone abnormalities. Researchers in Singapore and India, led by Duke-NUS Medical School, found that a signalling protein required for parathyroid gland development, called semaphorin3d (Sema3d), protects the glands from excessive growth by inhibiting cell proliferation. Credit: Duke-NUS Medical School

Overactive parathyroid glands,which control the body's blood calcium levels, can lead to kidney stones, neuropsychiatric disorders and bone abnormalities, particularly among elderly women. Researchers led by Duke-NUS Medical School have discovered a signaling protein that appears to protect these glands from excessive activity, providing insights for drug development to treat hyperparathyroidism—a condition currently treatable only through surgery.

"Not many molecules are known to inhibit parathyroid growth and there are no drugs available in the market to treat the condition," said Assistant Professor Manvendra Singh, the study's corresponding author from the Cardiovascular and Metabolic Disorders Programme at Duke-NUS Medical School. "Surgery is the most common treatment for hyperparathyroidism. However, reoperative 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."

The parathyroid 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 too much PTH, elevating blood calcium levels, can lead to kidney stones, neuropsychiatric disorders and bone abnormalities.

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

In a transgenic model lacking the gene that codes for Sema3d, EGFR signaling was activated, leading to parathyroid cell proliferation and the development of primary hyperparathyroidism. Turning off EGFR signaling 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 signaling could treat hyperparathyroidism.

"This discovery is a potential game-changer in the treatment of hyperparathyroidism," said Prof Patrick Casey, Senior Vice Dean for Research at Duke-NUS. "Considering the condition is common in the elderly, possible drug-based therapeutic options in the future would reduce the burden of surgery and associated risks in these elderly patients."

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

More information: Singh, A., Mia, M., Cibi, D., Arya, A., Bhadada, S., & Singh, M. (2019). Deficiency in the secreted protein Semaphorin3d causes abnormal parathyroid development in mice. *Journal Of Biological Chemistry*. DOI: 10.1074/jbc.ra118.007063

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