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DEHAL1 DEFICIENCY DISRUPTS THYROGLOBULIN HOMEOSTASIS AND IMPAIRS IODINE STORAGE.

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Iodine deficiency disorders (IDD) are caused the chronic shortage of iodine intake. However, this definition neglects the influence of genetic factors modulating the individual capacity for iodine handling, including storage and build-up of reserves. Under iodine deprivation, *Dehal1*KO mice develop hypothyroidism in a surprisingly short time, suggesting abnormal iodine storage, but the intrinsic mechanisms have not been investigated.

Aims: To study the impact of Dehal1 deficiency on iodine storage *in vivo*.

Methods The peripheral thyroid status and the thyroid glands from *Wt* and *Dehal1*KO mice were investigated under sufficient amount of dietary iodine (5.8 µg I/day) for 28 days. Changes in thyroid weight, microarchitecture, cell morphometry and thyroglobulin (Tg) abundance, conformation and excretion were analyzed by histology, immunohistochemistry and ELISA. Gene expression involving iodine handling and Tg-metabolism was monitored by RT-qPCR. TSH, MIT, DIT, T3, T4 were determined by RIA and LC-MS-MS.

Results At 28 days, *Wt* and *KO* mice were both euthyroid by serum logTSH (*Wt*: 1.45±0.05 mU/L *vs KO*: 1.45±0.2 mU/L; p>0.05), T4 (*Wt*: 51±1 ng/ml *vs KO*: 49.7±1.5 ng/ml; p>0.05) and T3 levels (*Wt*: 0.5 ng/ml *vs KO*: 0.47±0.02; p>0.05). Dissected glands were macroscopically similar. However, cuboidal (*vs* flatenned) thyrocytes and reduced follicular diameters were detectable in *KO* glands, suggesting a hypermetabolic state. Gene expression of iodine handling genes like *Slc5a5*(Nis) and *Dio1* was upregulated by 27 and 2-fold in *KO* mice. *Tg* and mRNAs involved in Tg-processing, structural conformation at the follicle (*P4hb*-Pdi, *Sult1a1),* receptor-mediated metabolism (*Flot1, Asgpr,* but not *Cav*) and transcytosis (*Lrp2*-Megalin, *Rap*) were also 2-10-fold overtranscribed, suggesting a failure of the expected (TSH-independent) thyroid autoregulation by iodine. Importantly, Tg immunodetection revealed clumps of dense Tg aggregates at the periphery of follicles in *KO* glands, leaving a pale center, suggesting the active use of follicular iodine reserves. Furthermore, plasma Tg concentration was higher in *KO* than in *Wt* mice (673 pg/ml *vs* 418 pg/ml; p<0.05), suggesting enhanced transcytosis and excretion from the thyroid gland. In contrast to peripheral euthyroidism, *KO* mice showed reduced T4 content in the thyroid (141 ng/g vs 48 ng/g; p<0.05) with preservation of T3 (2-fold lowerT4/T3 ratio), suggesting local ID.

Conclusions Despite correct iodine nutrition, the thyroids of *Dehal1*KO mice show typical signs of iodine deficiency. The vulnerability of *Dehal1*KO mice towards hypothyroidism can be mediated by a profound dysregulation of Tg homeostasis, the scaffold for iodine storage at the follicle, interfering the efficient build-up of iodine reserves.