曼氏血吸虫甲状腺激素受体的分子表征

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时间：2025.5.28

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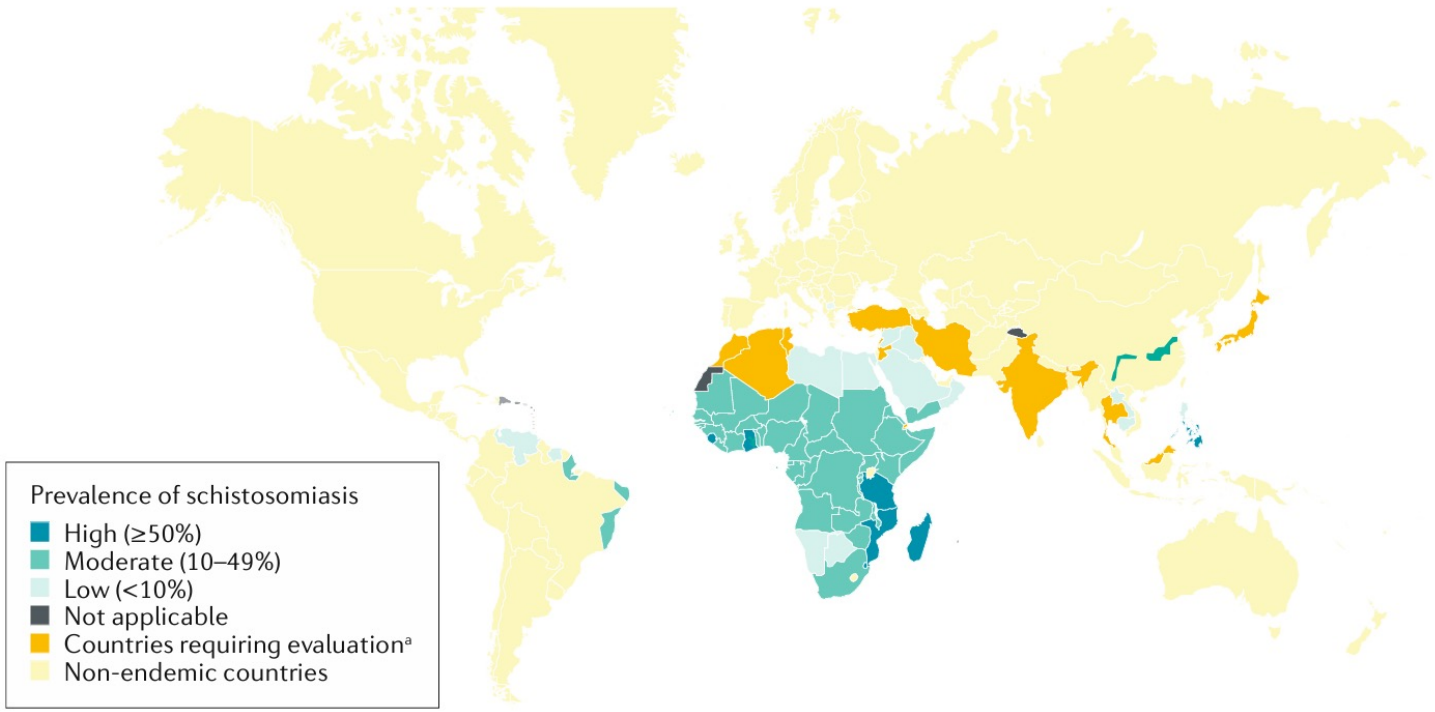
研究背景：血吸虫病



McManus DP, *et al* (2018). *Nat Rev Dis Primers.*

流行病学：

- 全球78个国家地区流行
- 感染人数超过2亿
- 8亿人面临感染风险

主要病原：

曼氏血吸虫、日本血吸虫、埃及血吸虫

药物治疗：

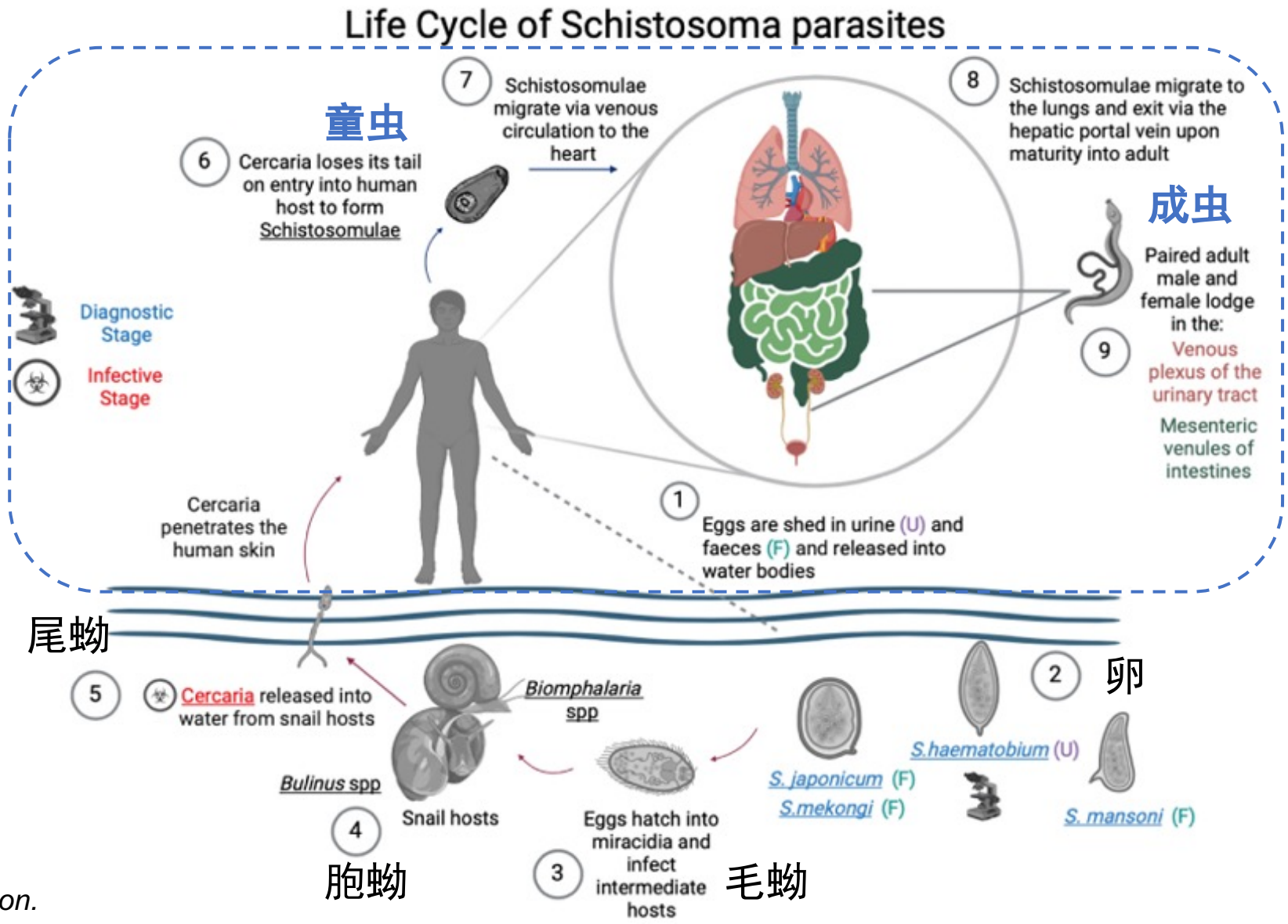
吡喹酮（耐药性）

研究背景：血吸虫的生活史

人类等终宿主

淡水介质

螺类中间宿主



血吸虫成虫可在人体内存活数十年

Ekloh W, *et al* (2024). *Heliyon.*

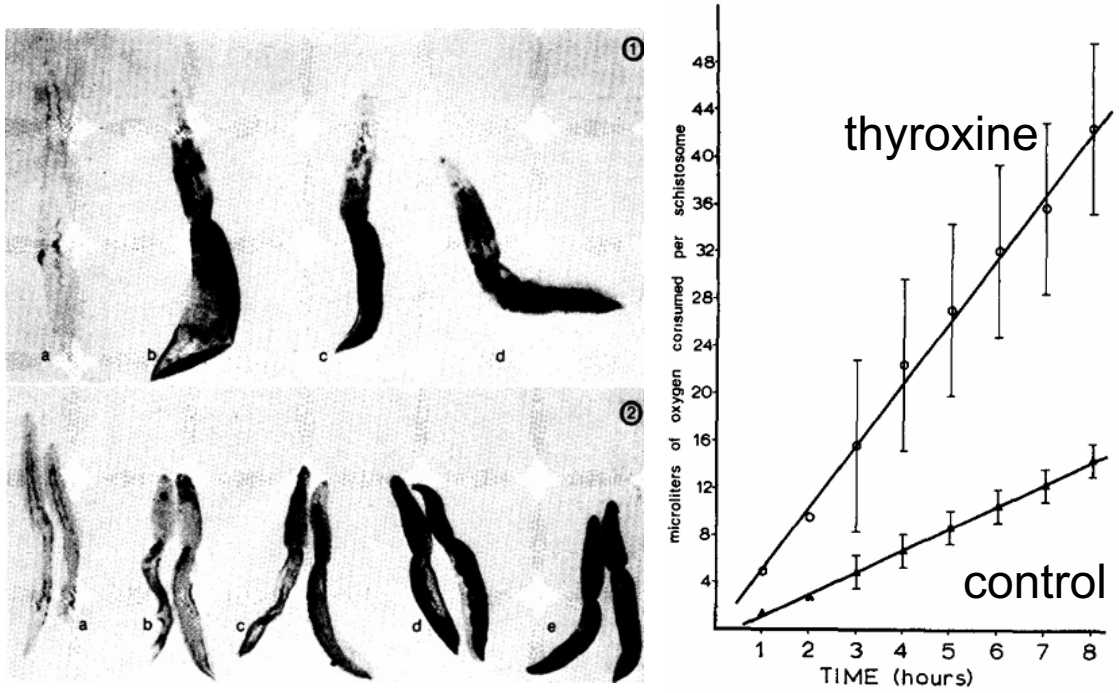
研究背景：甲状腺激素对血吸虫的调控

不同甲状腺功能小鼠中的血吸虫感染情况：

Group	Time from exposure to cercariae (weeks)	No. of mice	No. (± SE) of cercariae penetrating out of 40	Mean no. of worms ± SE	Mean no. of worm pairs ± SE	Mean length of worms (in mm) ± SE (no. measured)	
						Males	Females
Control	0	20	35.6 ± 0.24	...	...	...	...
	5	10	...	14.6 ± 1.2	3.1 ± 0.5	7.0 ± 0.3 (29)	7.1 ± 0.3 (25)
	8	10	...	15.6 ± 0.3	7.0 ± 0.9	12.0 ± 0.2 (20)	14.5 ± 0.5 (20)
Euthyroid	0	20	34.9 ± 0.38	...	...	...	...
	5	8	...	12.8 ± 2.0	2.6 ± 0.6	6.6 ± 0.4 (33)	7.3 ± 0.3 (26)
	8	9	...	13.6 ± 1.2	5.3 ± 0.7	11.5 ± 0.3 (18)	14.1 ± 0.4 (18)
Hypothyroid	0	20	33.5 ± 0.67	...	...	...	...
	5	8	...	13.4 ± 0.3	2.1 ± 0.5	5.2 ± 0.2 (32)	7.2 ± 0.4 (14)
	8	9	...	14.1 ± 1.5	5.8 ± 0.8	10.2 ± 0.2 (18)	13.2 ± 0.4 (18)
Hyperthyroid	0	20	34.7 ± 0.35	...	...	...	...
	5	7	...	16.3 ± 1.2	4.7 ± 0.8	7.9 ± 0.2 (37)	9.0 ± 0.3 (33)
	8	8	...	14.9 ± 1.6	6.4 ± 0.9	12.7 ± 0.2 (20)	15.5 ± 0.3 (20)

在甲状腺功能衰退的小鼠中血吸虫发育不良
在甲状腺功能亢进的小鼠中血吸虫成熟更早

甲状腺素对血吸虫生命活动的影响：



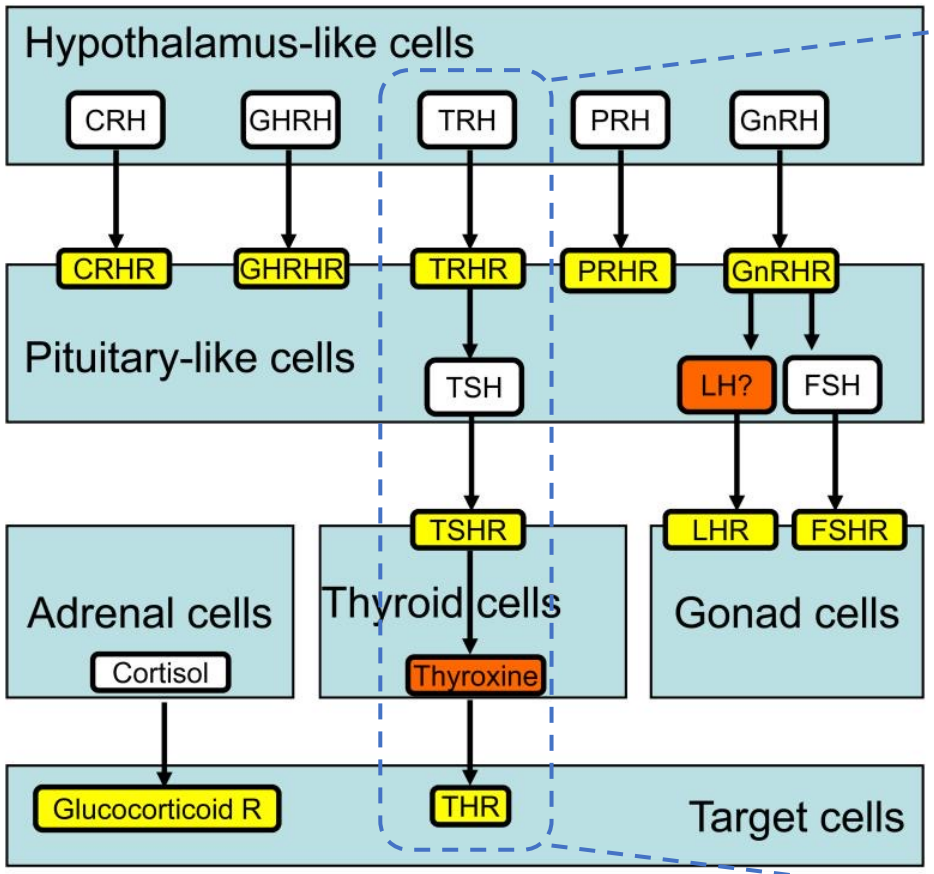
体外的甲状腺素（T4）处理引起虫体代谢变化

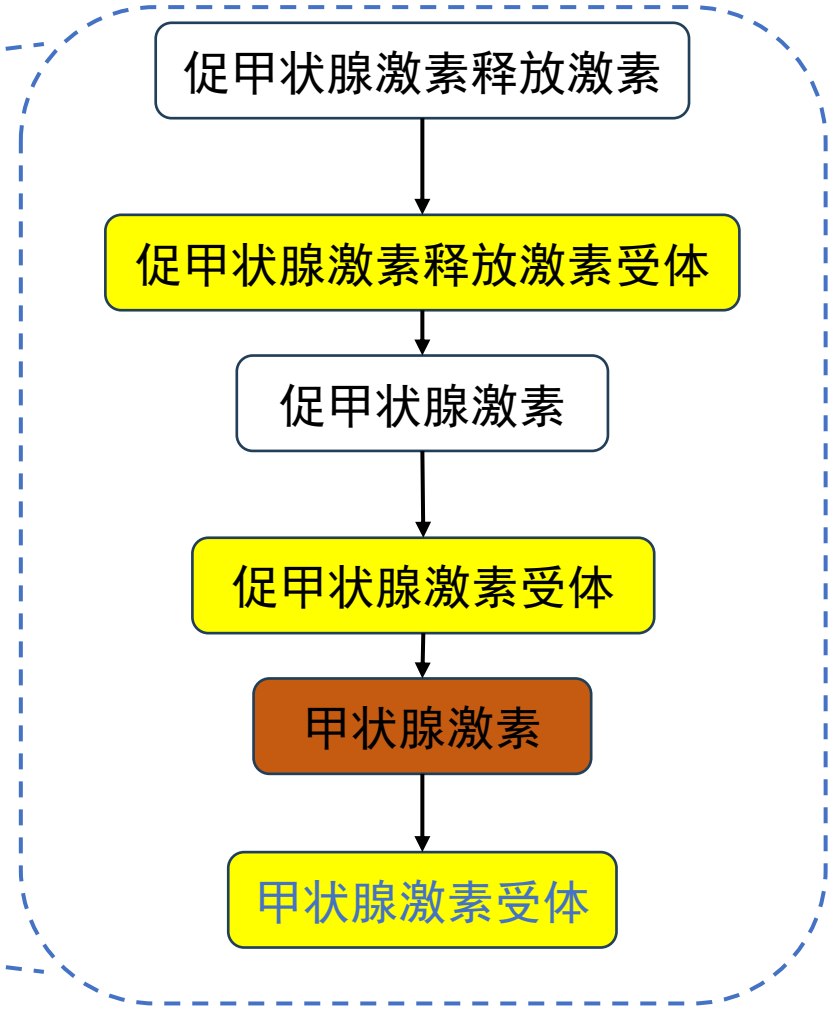
Wahab MF, *et al* (1971). *J Infect Dis*.

Cornford EM (1974). *Exp Parasitol.*

研究背景：血吸虫的下丘脑—垂体—甲状腺轴

血吸虫中推测的内分泌系统：





合成甲状腺素、活性三碘甲状腺原氨酸以及脱碘的完整系统

Schistosoma japonicum Genome Sequencing and Functional Analysis Consortium (2009). *Nature*.

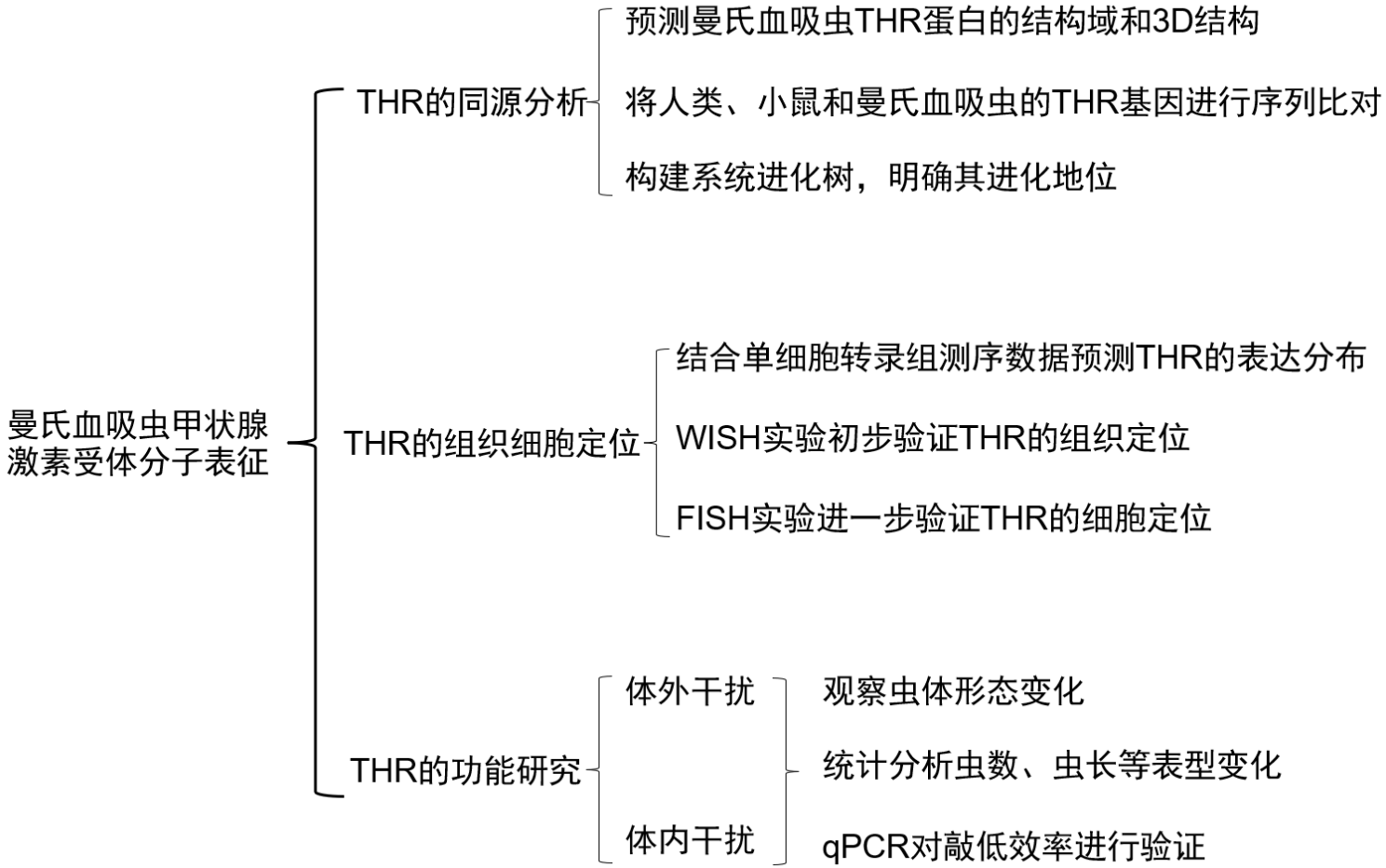
科学问题

宿主甲状腺激素信号是否通过血吸虫的甲状腺激素受体调控其生长发育过程？

实验内容和技术路线

实验内容：从同源分析、表达定位和功能研究三个角度对曼氏血吸虫的甲状腺激素受体进行分子表征

技术路线：



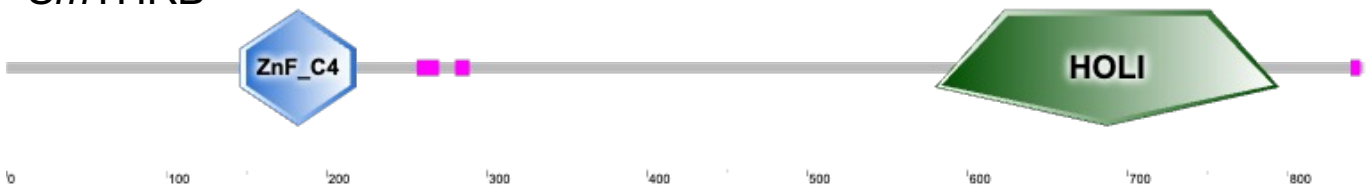
研究结果：*Sm*THR的序列结构分析

曼氏血吸虫中两个潜在甲状腺激素受体基因（*Smthr*）：

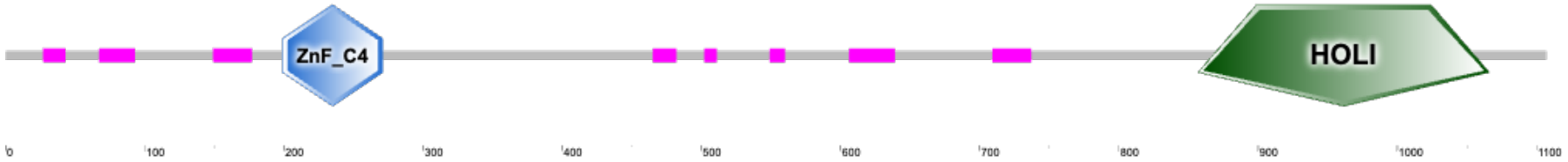
Smp_174260 / *Smthrb* → *Sm*THRB

Smp_134490 / *Smthra* → *Sm*THRA

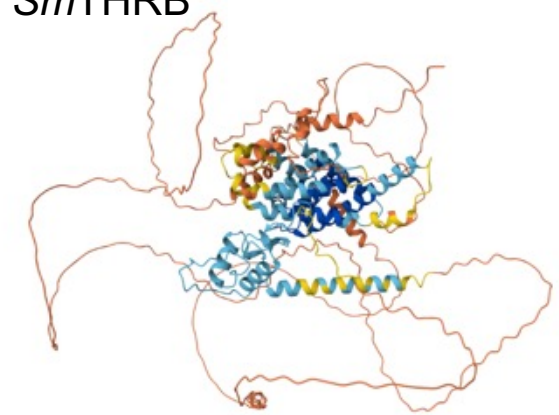
*Sm*THRB



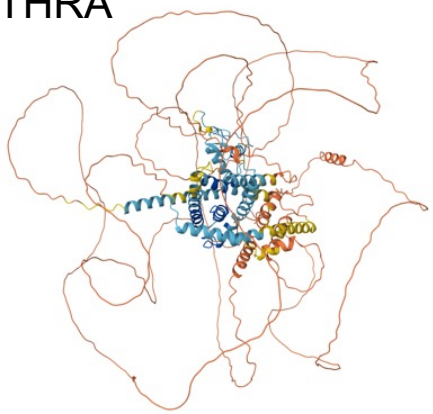
*Sm*THRA



*Sm*THRB



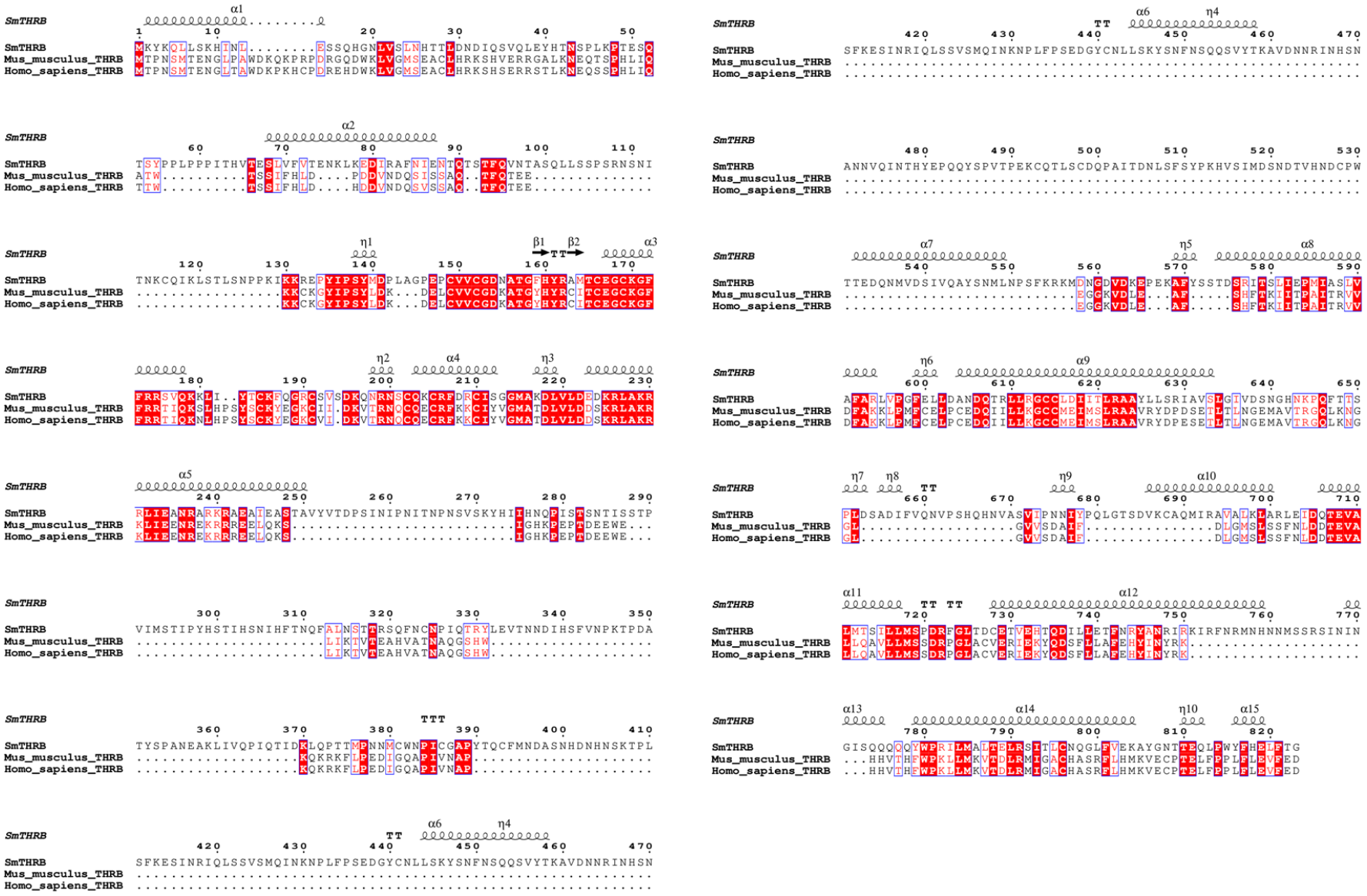
*Sm*THRA



研究结果： *Sm*THRB的保守性分析

THRB的序列比对：

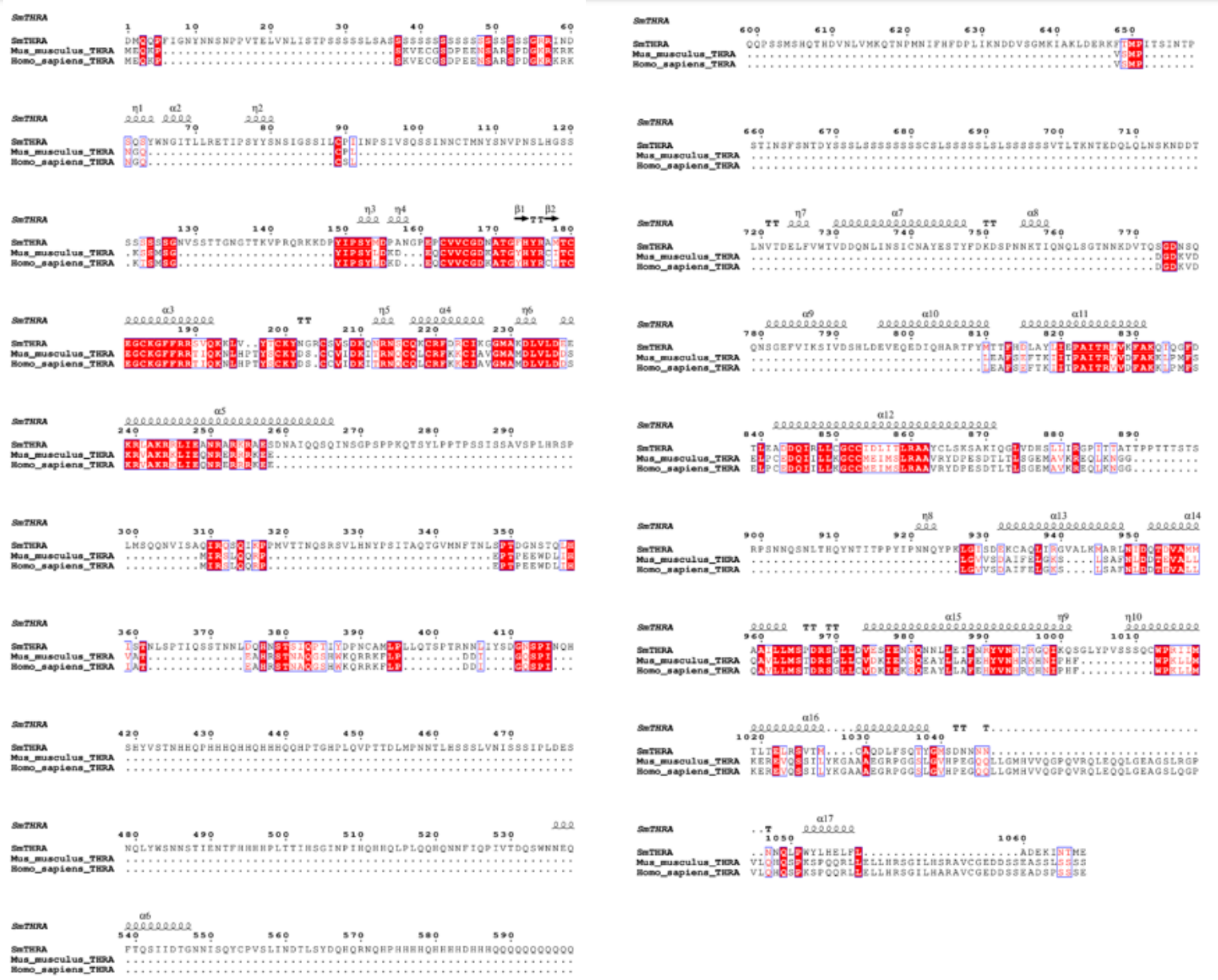
*Sm*THRB具备典型的功能结构域序列保守性，且与宿主同源性较低



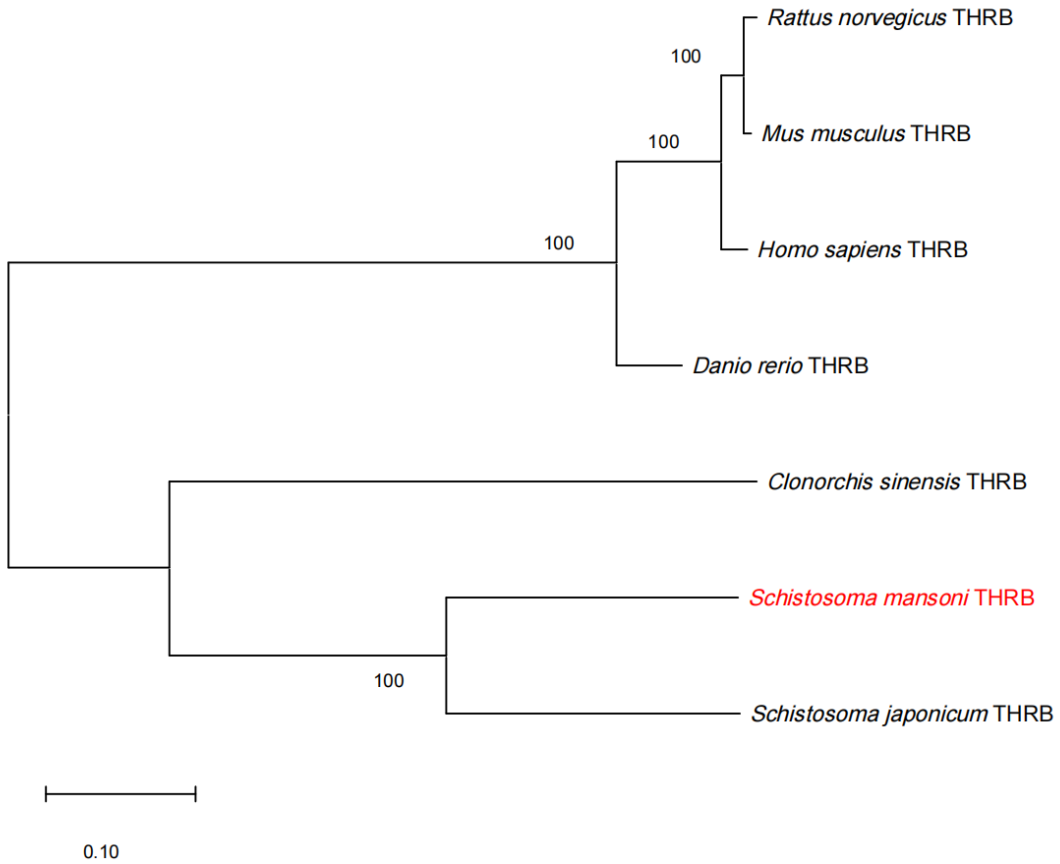
研究结果： *Sm*THRA的保守性分析

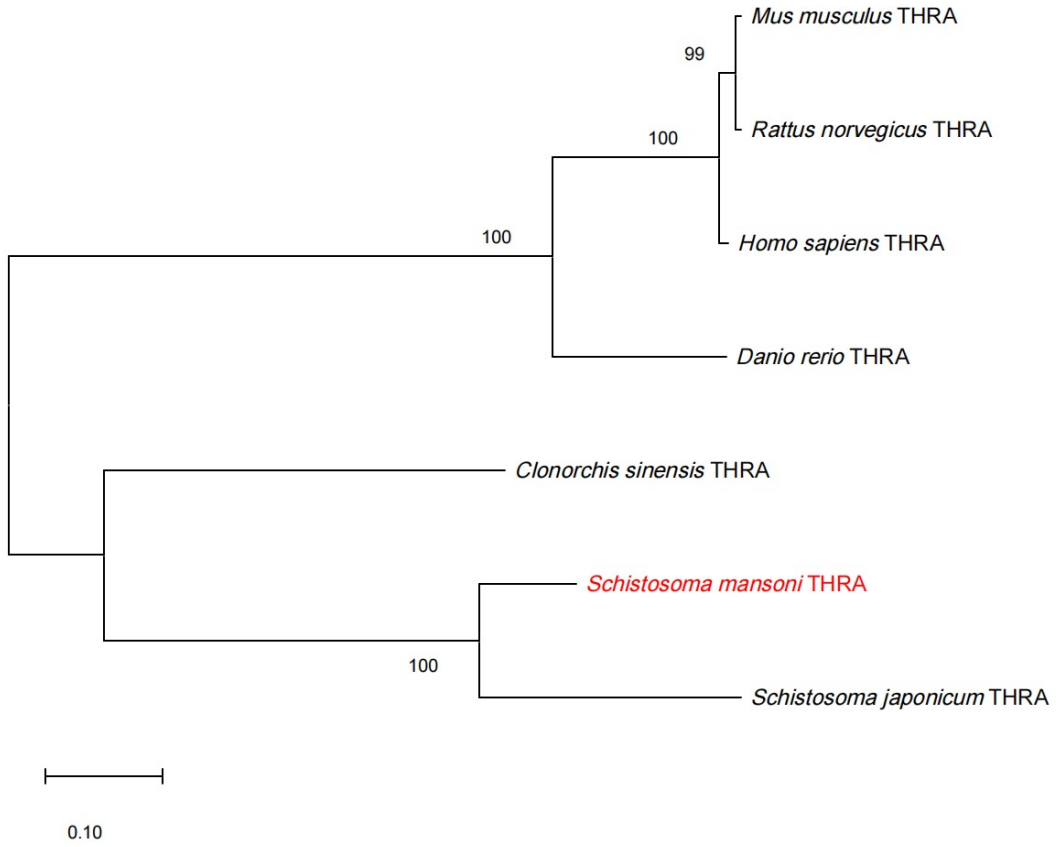
THRA的序列比对：

*Sm*THRA具备典型的功能结构域序列保守性，且与宿主同源性较低



研究结果：*Sm*THR的同源分析

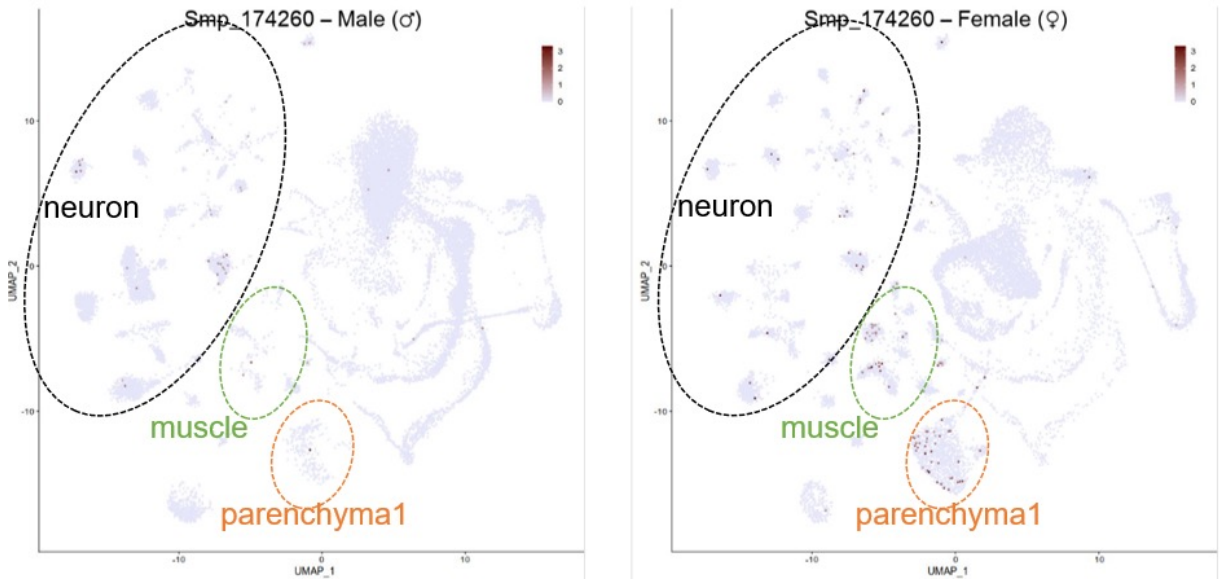


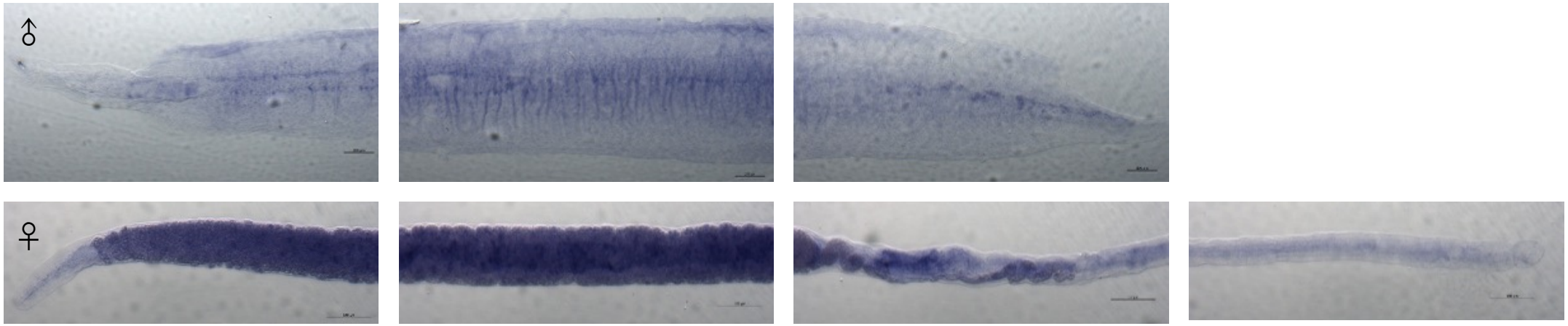


SmTHR在吸虫中具备一定保守性

研究结果：*Smthr*的组织定位—WISH

Smthrb

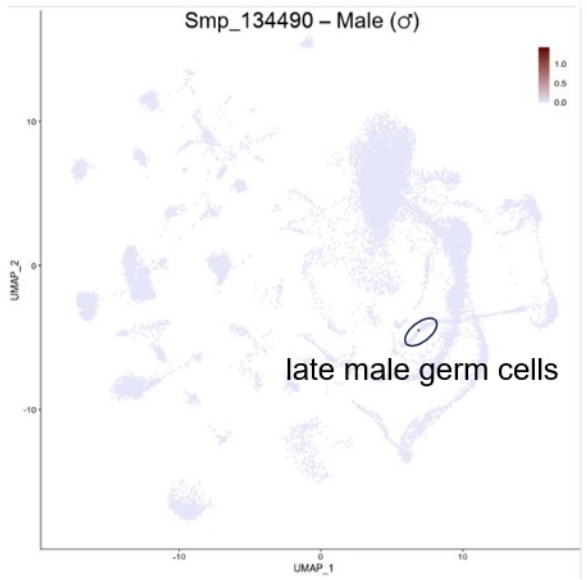


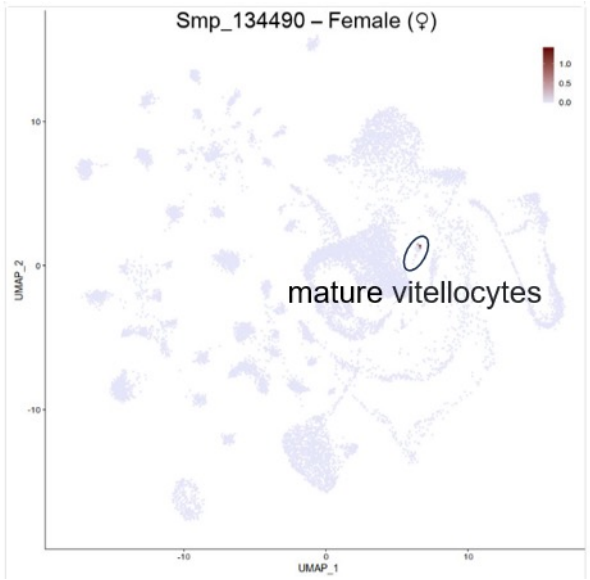


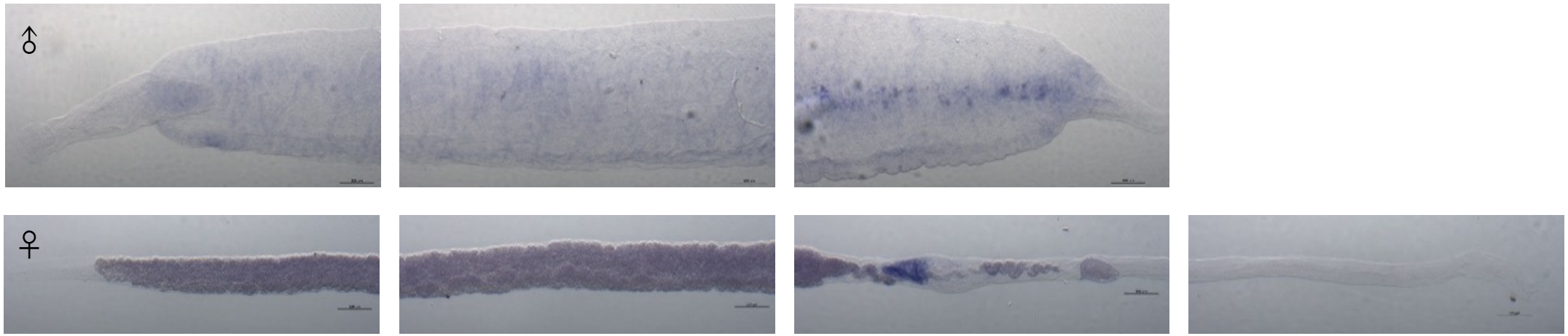
***Smthrb*在单细胞图谱所示细胞类型和肠道富集表达**

研究结果：*Smthr*的组织定位—WISH

Smthra

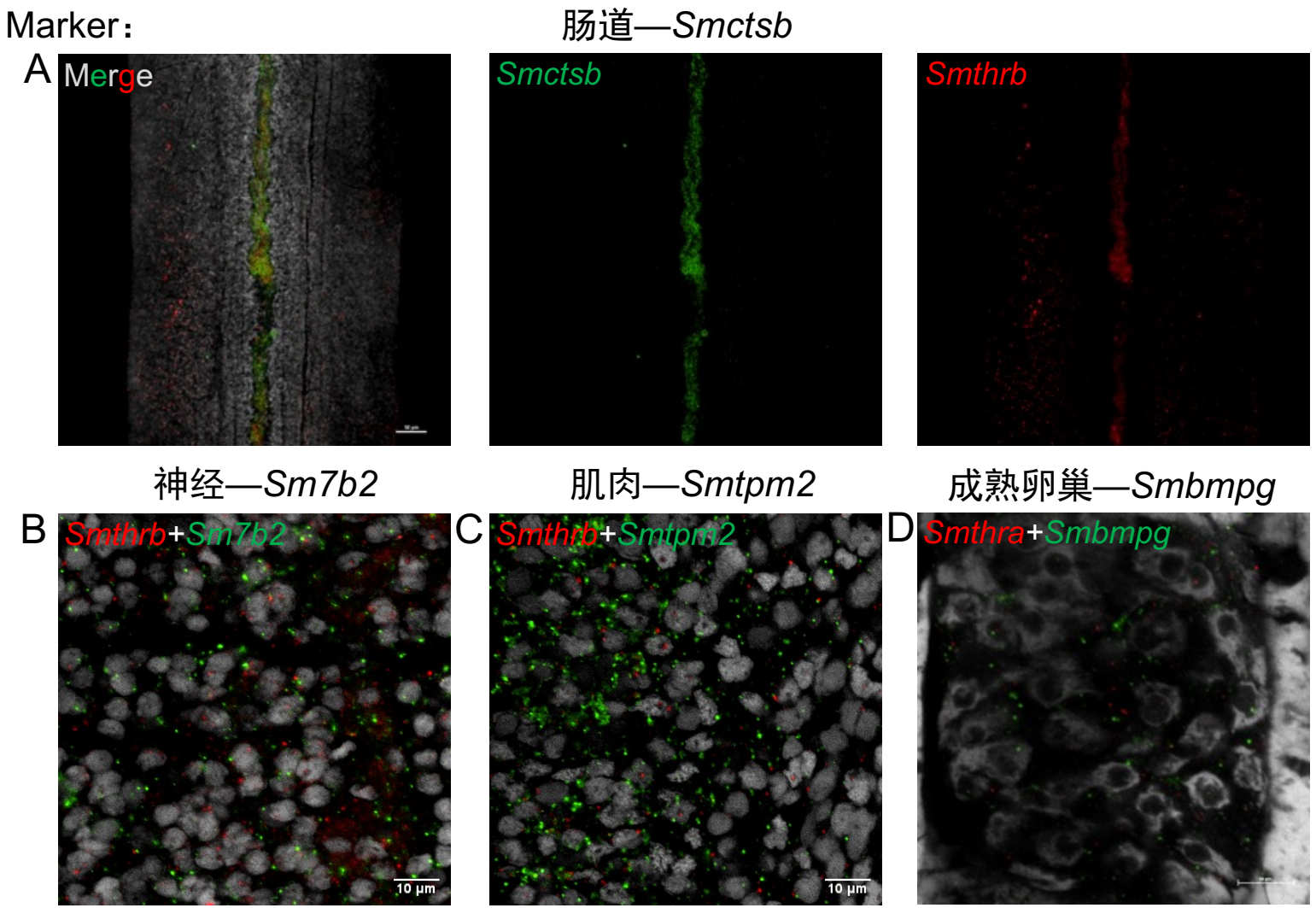






***Smthra*在雌虫卵巢的部分区域表达**

研究结果：*Smthr*的细胞定位—FISH



*Smthrb*在肠道和部分神经、肌肉细胞中有表达

*Smthra*在成熟卵巢区域有表达

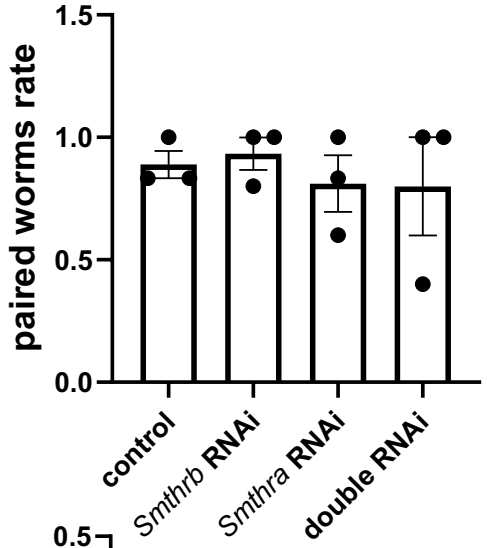
研究结果：*Smthr*的功能研究—体外RNA干扰

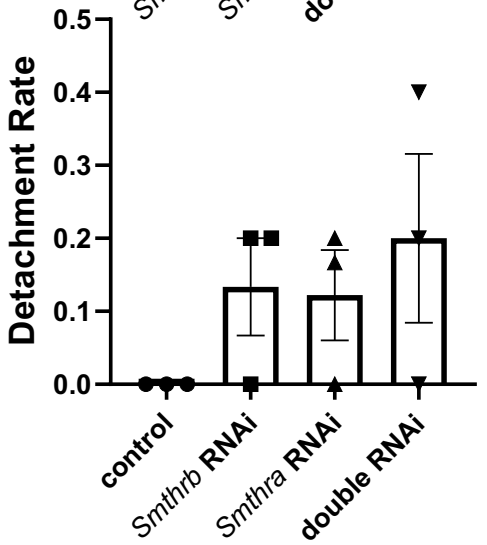
control

Smthrb RNAi

double RNAi

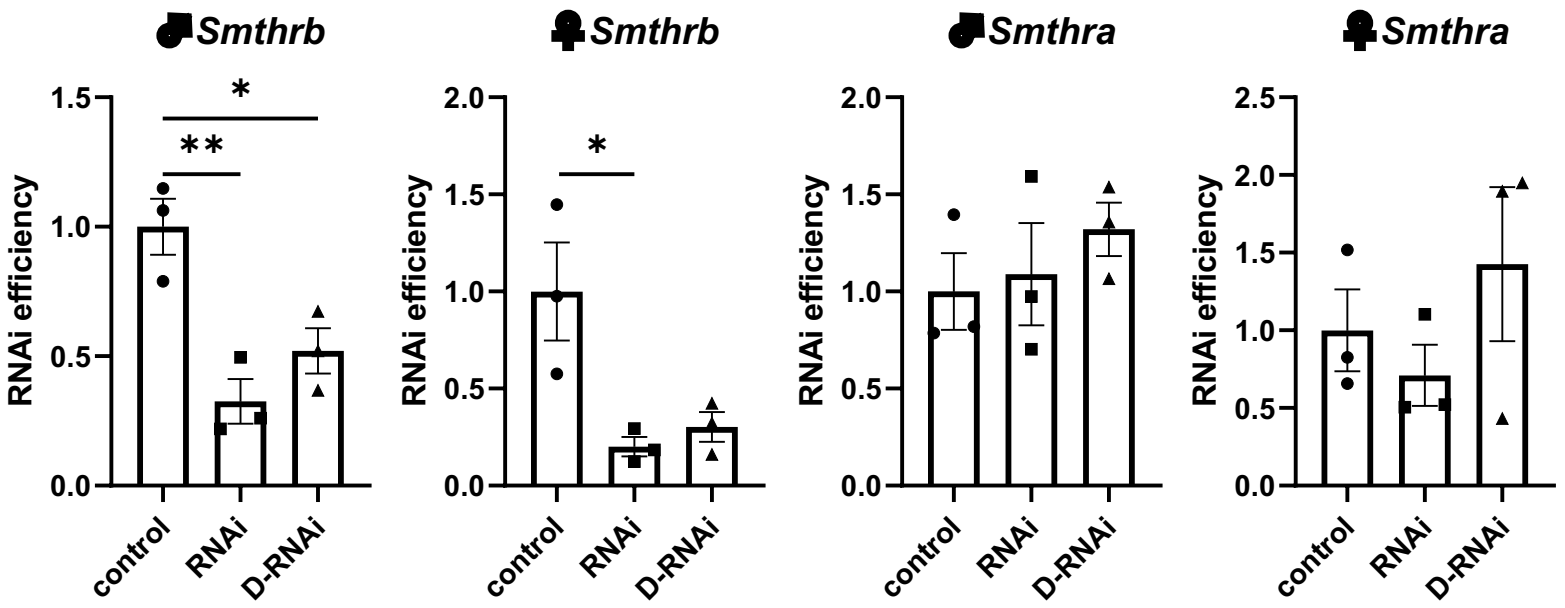
Smthra RNAi





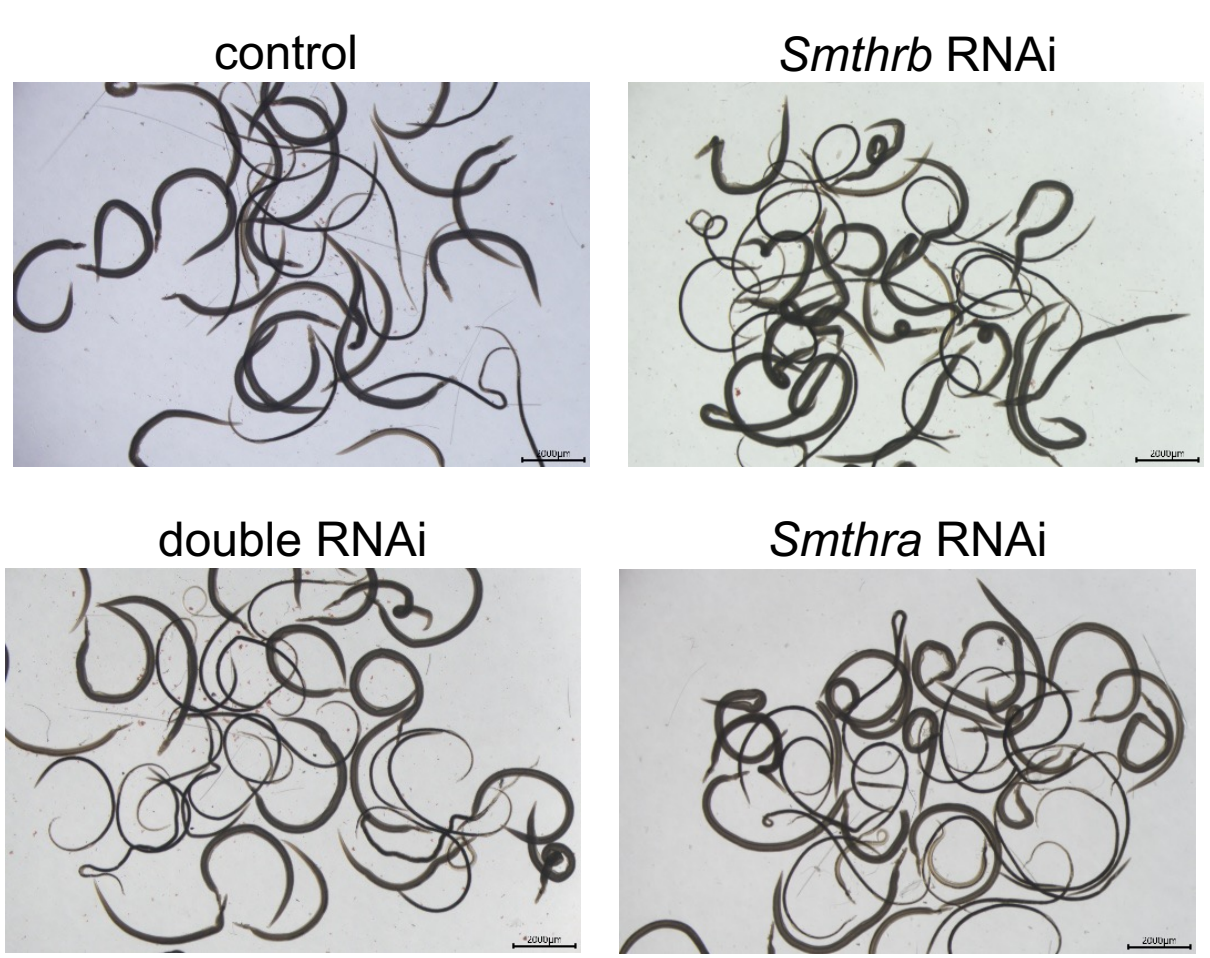
体外干扰26d未影响虫体形态及活力

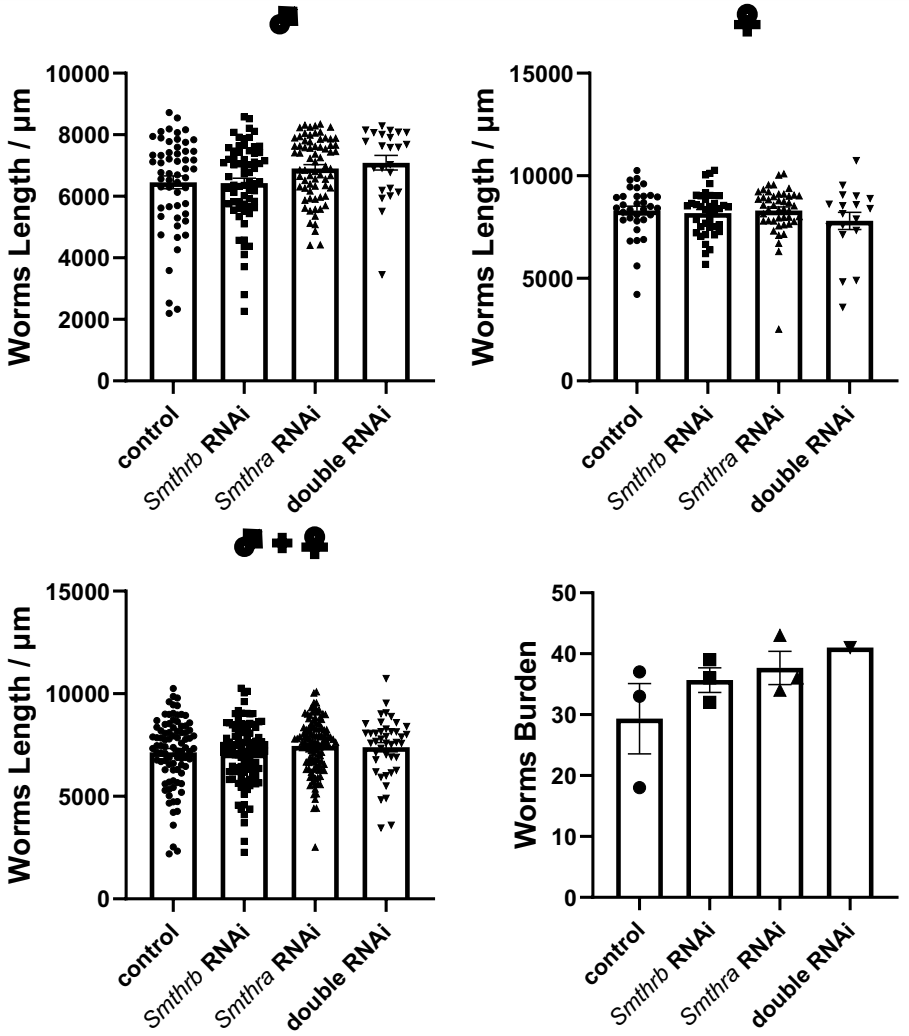
研究结果：*Smthr*的功能研究—体外RNA干扰



仅*Smthrb*被显著敲低

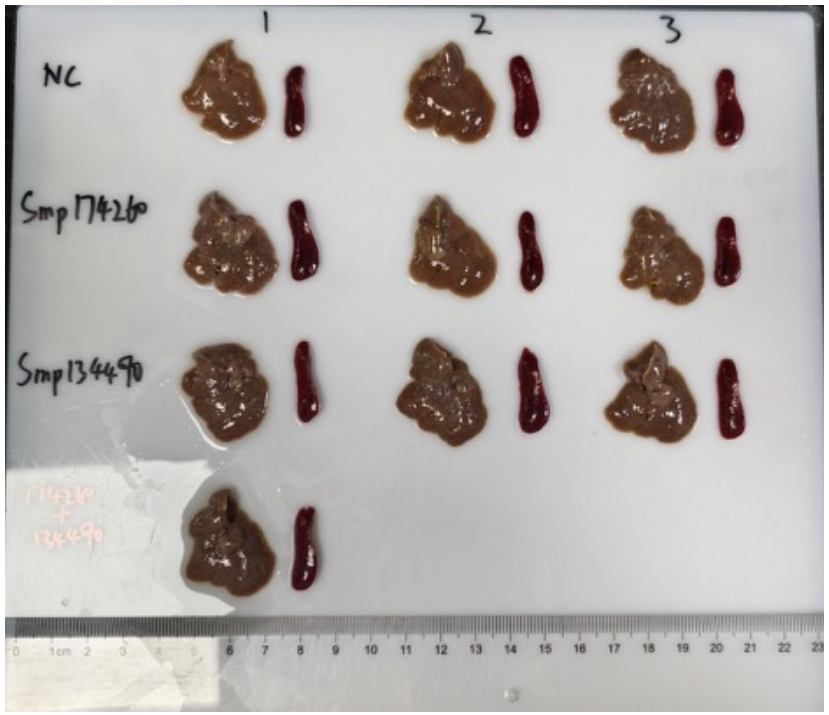
研究结果：*Smthr*的功能研究—体内RNA干扰

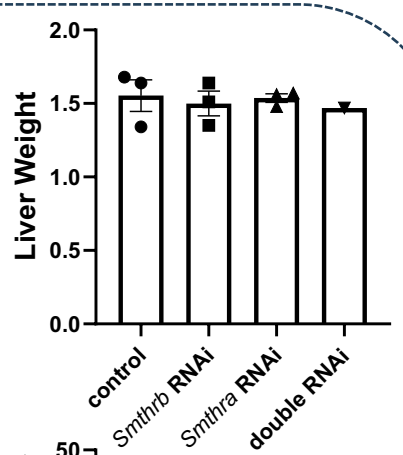


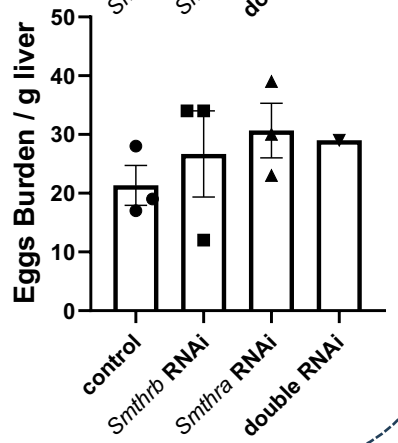


体内干扰49d未影响虫体形态、虫长和虫数

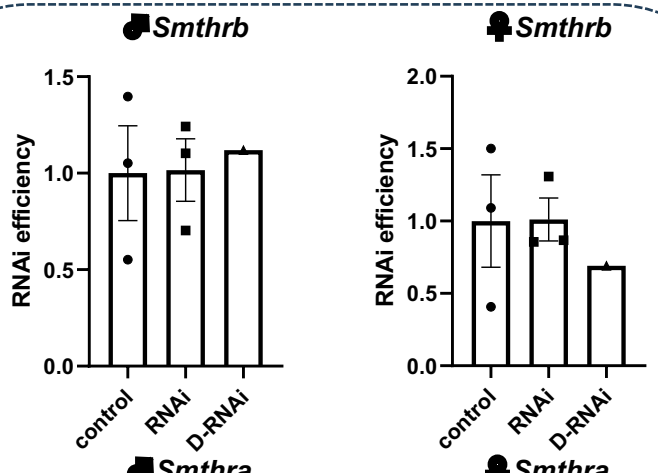
研究结果：*Smthr*的功能研究—体内RNA干扰

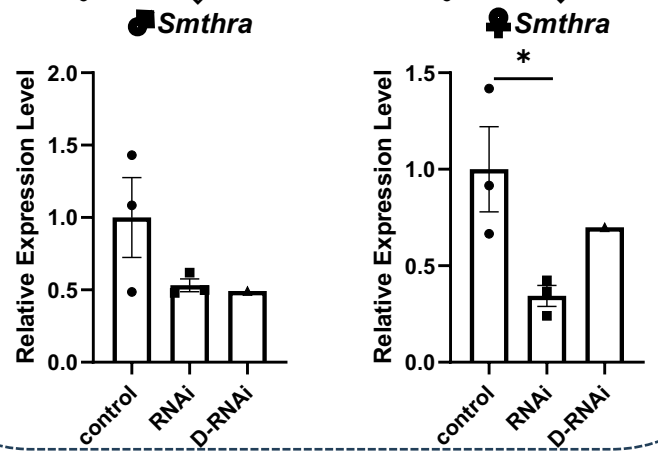






肝脏病理和虫卵数无显著差别





***Smthrb*未被敲低**
***Smthra*存在敲低趋势**

总结展望

总结

- *Sm*THR具有典型的ZnF_C4结构域和HOLI结构域，且与宿主同源性较低
- *Smthrb*在肠道和部分神经、肌肉细胞中有表达，*Smthra*在成熟卵巢区域有表达
- 对*Smthrb*和*Smthra*的部分敲低不影响血吸虫的正常生理活动

展望

- 目前干扰效率低，需要对RNA干扰进一步优化
- 可在培养基中加入甲状腺素，初步分析宿主激素对血吸虫生理活动的影响

致谢

- 感谢王吉鹏老师对本课题的悉心指导
- 感谢实验室师兄师姐们对本课题的支持帮助
- 感谢专家老师们对论文及答辩的评审
- 感谢家人朋友的关心陪伴

恳请批评指正！

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时间：2025.5.28