

曼氏血吸虫甲状腺激素 受体的分子表征

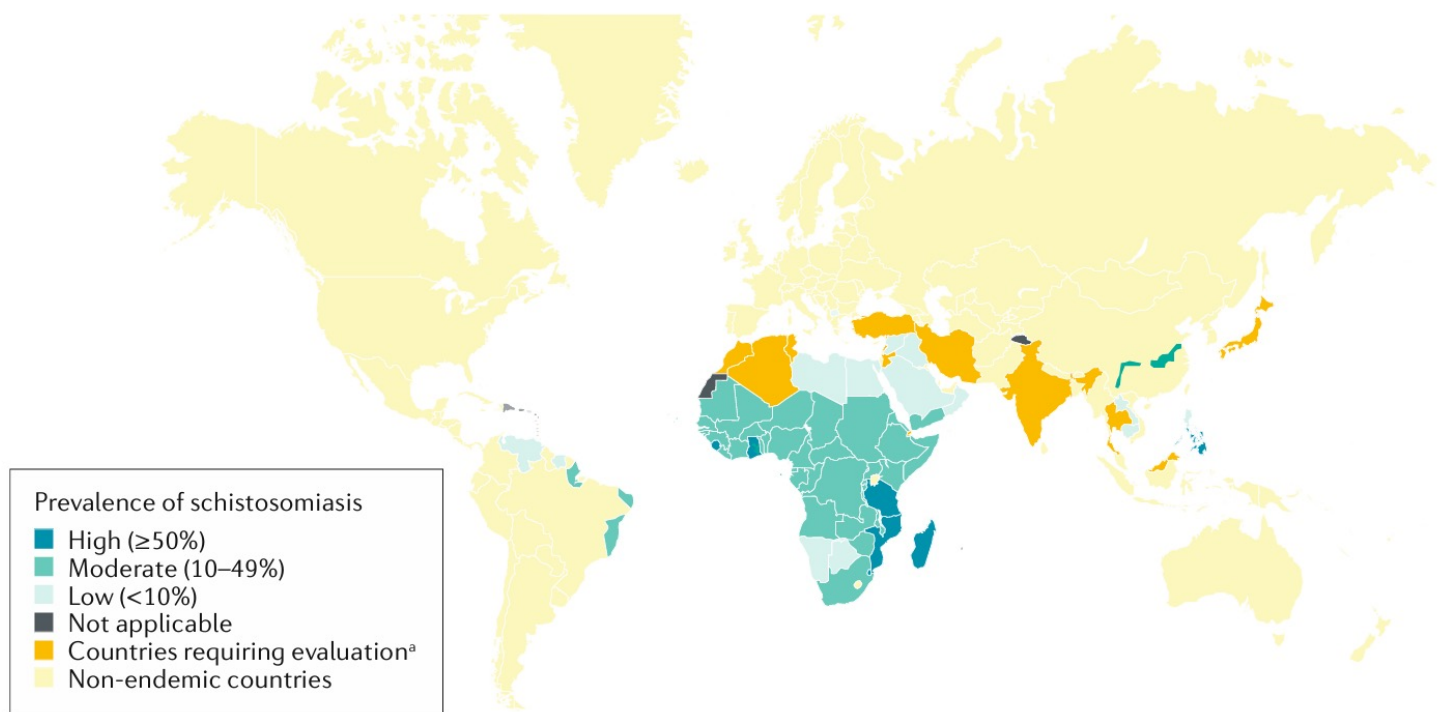
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时间：2025.5.28

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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：

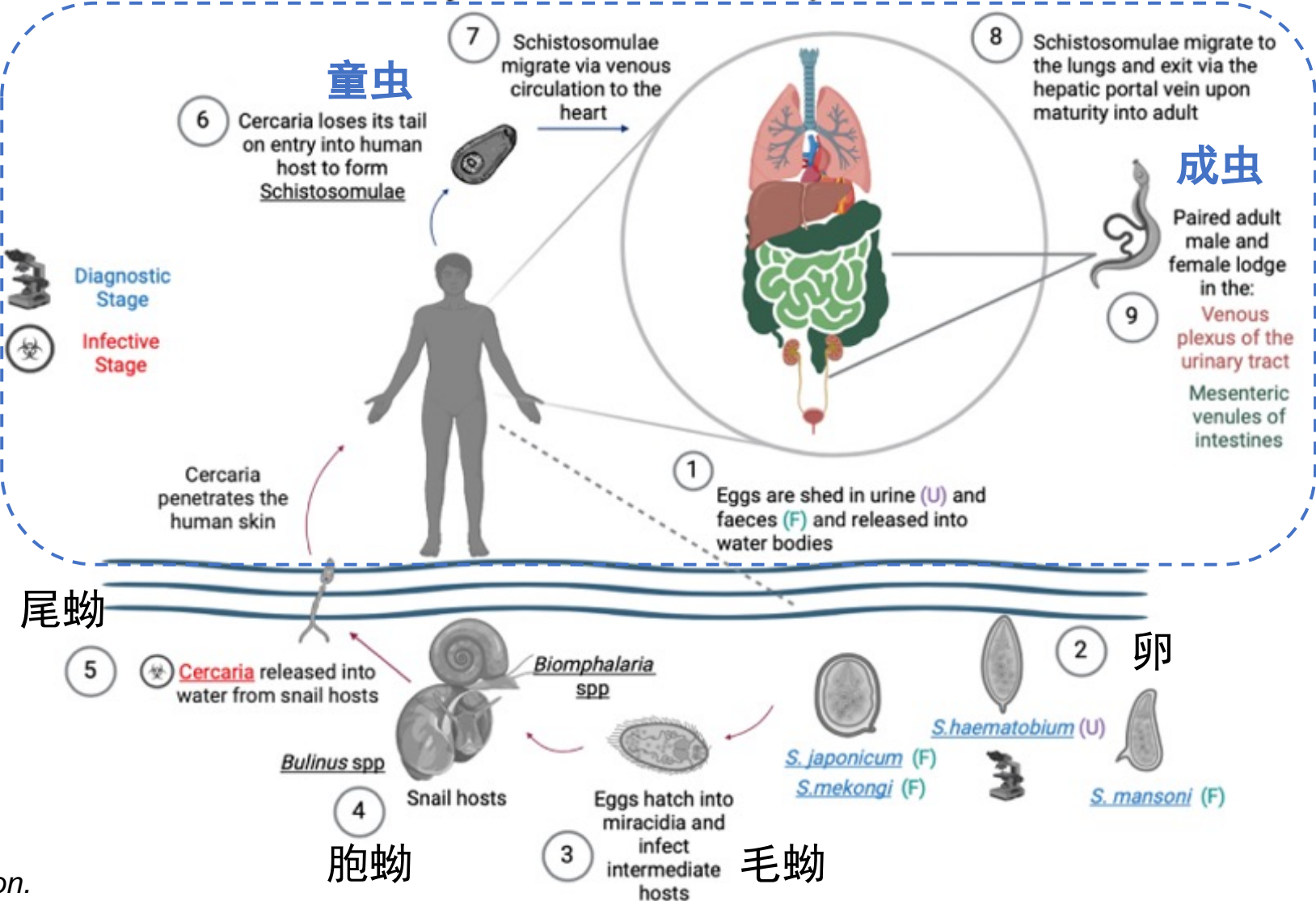
曼氏血吸虫、日本血吸虫、埃及血吸虫

药物治疗：

吡喹酮（耐药性）

研究背景：血吸虫的生活史

Life Cycle of Schistosoma parasites



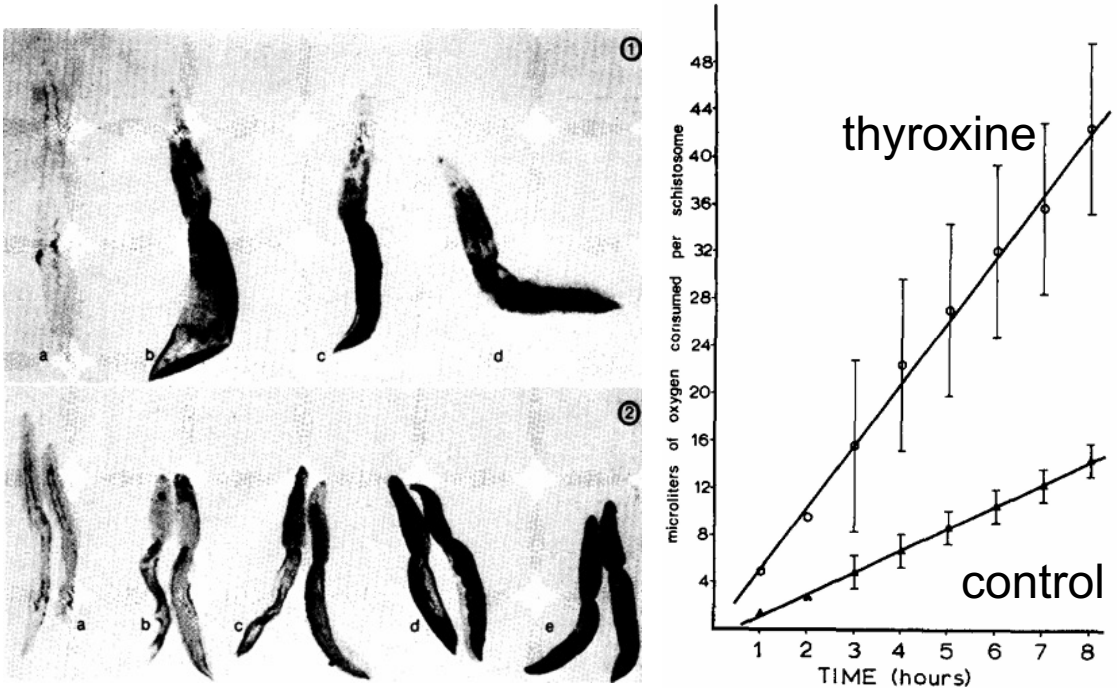
血吸虫成虫可在人体内存活数十年

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：

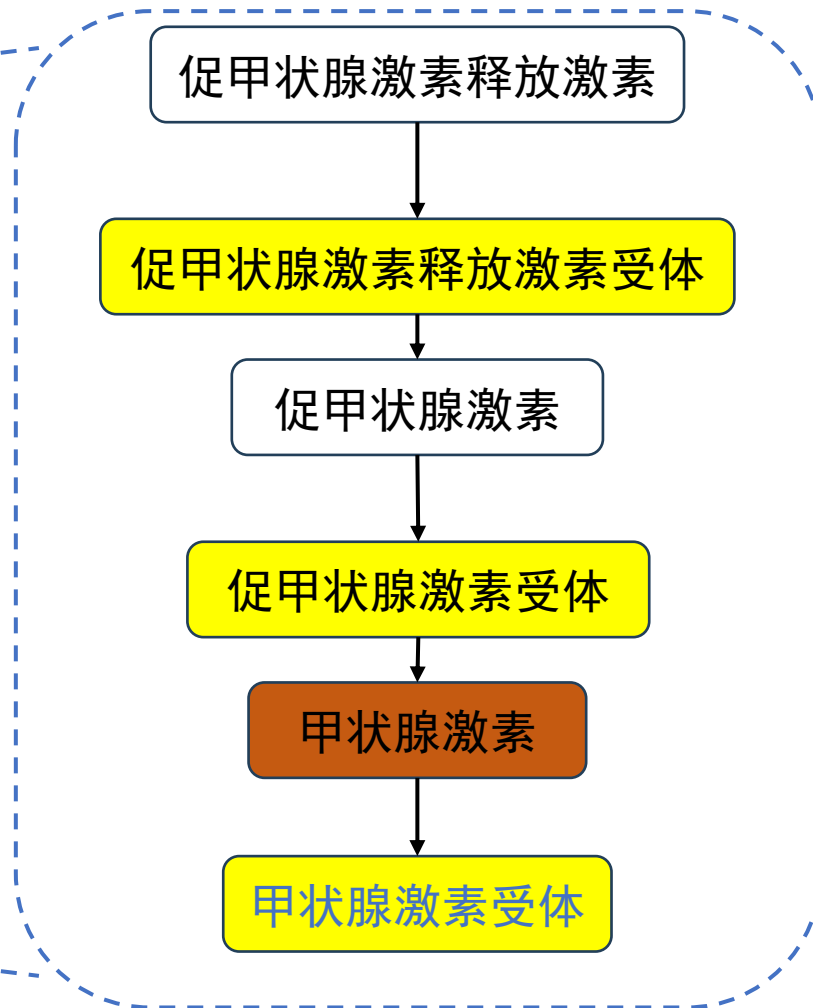
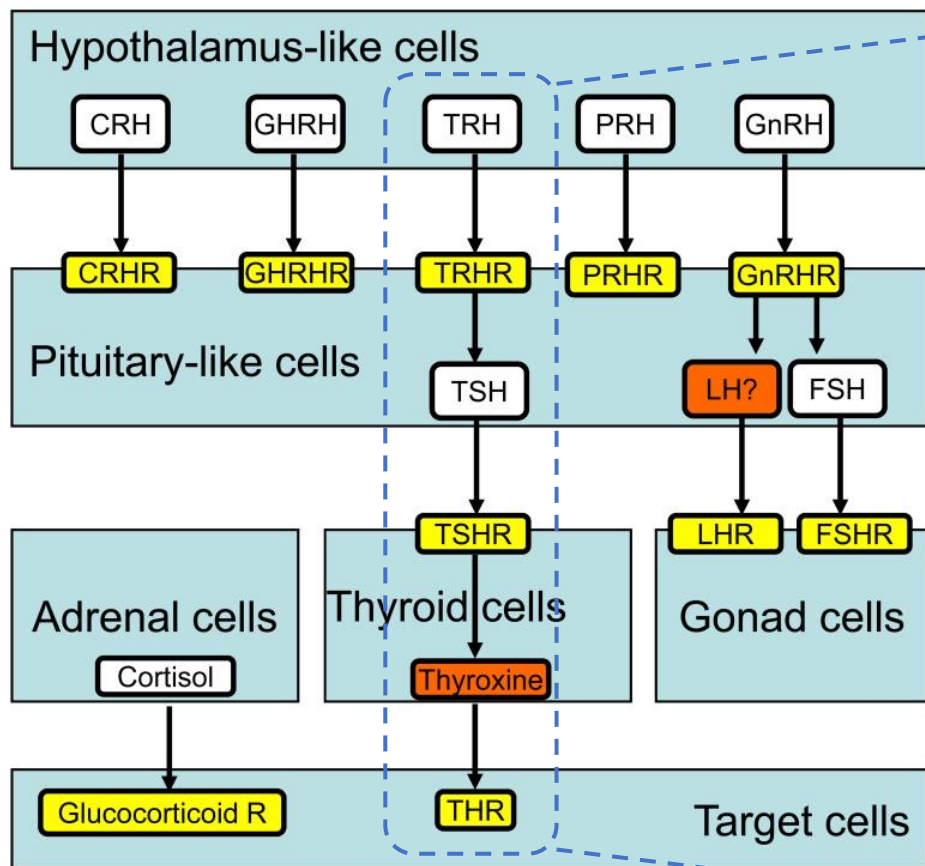


体外的甲状腺素（T4）处理引起虫体代谢变化

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：

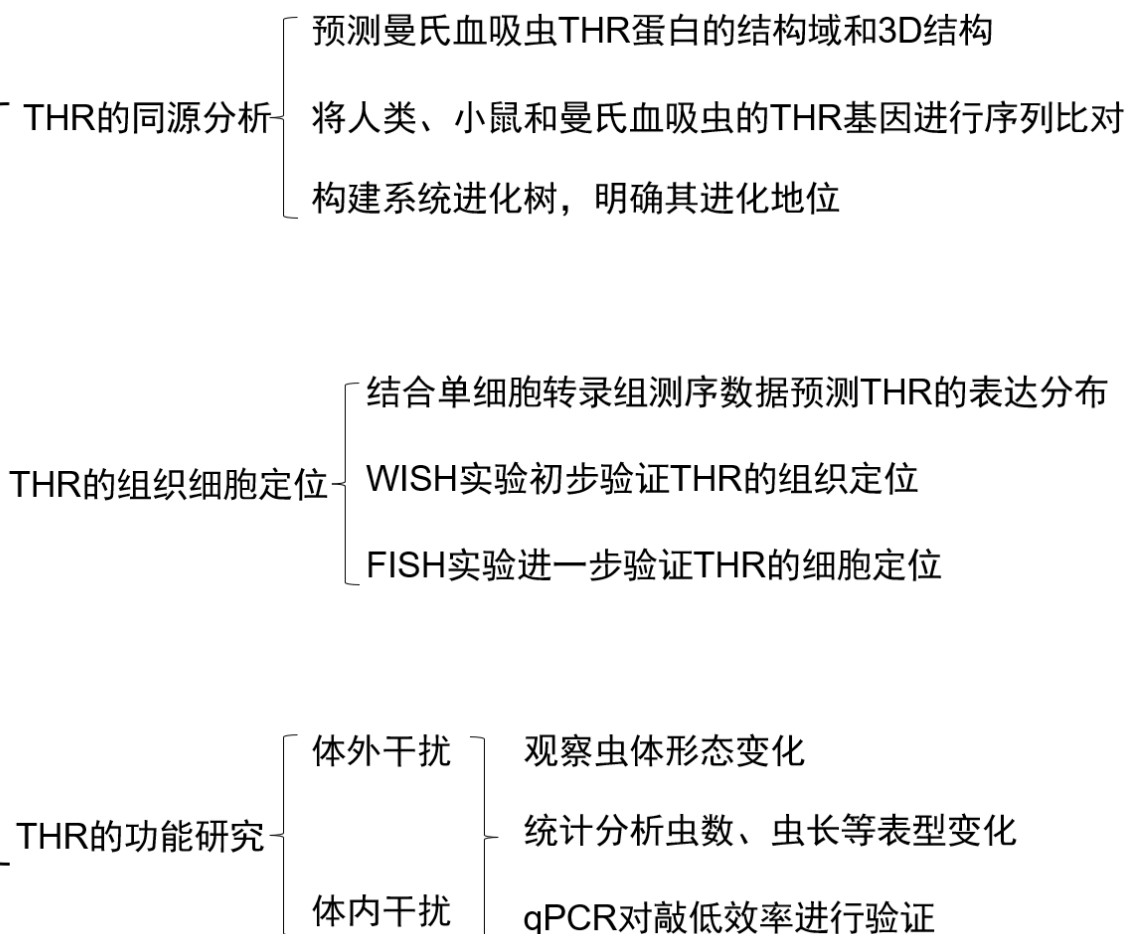


合成甲状腺素、活性三碘甲状腺原氨酸以及脱碘的完整系统

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：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

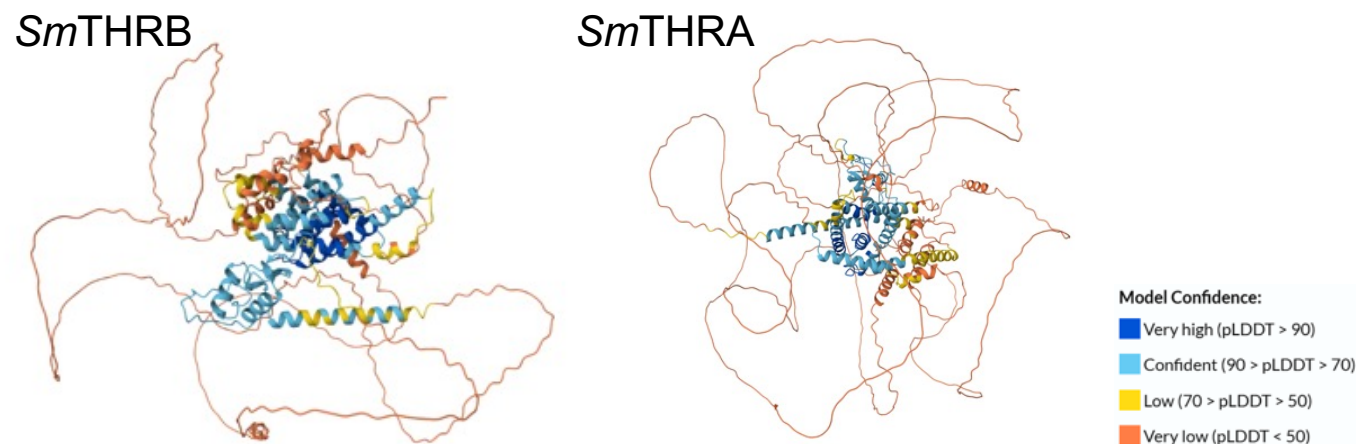
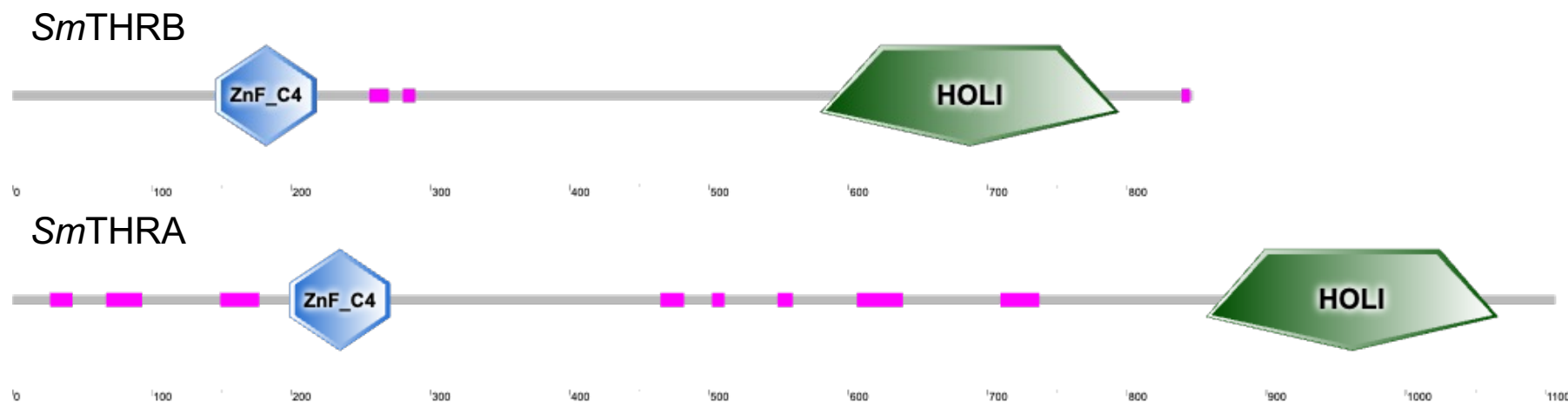
技术路线：曼氏血吸虫甲状腺激素受体分子表征



研究结果：SmTHR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 → SmTHRB
Smp_134490 / Smthra → SmTHRA



研究结果：SmTHRB的保守性分析



THRB的序列比对：
SmTHRB具备典型
的功能结构域序列
保守性，且与宿主
同源性较低

SmTHRB
1 10 20 30 40 50
SmTHRB KYKQLLSKHIN.....ESSQHGNLVGLNHTTNDIQSVQLEYHTNSPLNPTESQ
Mus_musculus_THRB TPNMTENGLPADWKQKPRPDGQDWMVGLMSACLRKSHVERRGALKNEQTSPLHIQ
Homo_sapiens_THRB TPNMTENGLPADWKPKHCPDREHDWMLVGLMSACLRKSHSERRSTLRNEQSSPHLIQ

SmTHRB
60 70 80 90 100 110
SmTHRB TSYPLPPPIHVTESLVFVTENKLEDTIRAFNTENTTSFQVNTASQLLSSPSRNSNI
Mus_musculus_THRB ATW.....SSIFHLDPDNDQSSISAC..TFQTEE.....
Homo_sapiens_THRB TW.....SIFHLDPDNDQSSVSAC..TFQTEE.....

SmTHRB
120 130 140 150 160 170
SmTHRB TNKQIKLSTLSNPPKIKKREYIPSYNDPLAGPEPQVVCGRNATCFHYRAATCEGCKGF
Mus_musculus_THRBKKCKGYIPSYNDK...DELVCVVCGRKATGHHYRCITCEGCKGF
Homo_sapiens_THRBKKCKGYIPSYNDK...DELVCVVCGRKATGHHYRCITCEGCKGF

SmTHRB
180 190 200 210 220 230
SmTHRB FRRSVQKKLI..YICKFGRCGSVSDKNRNSCQKCRFRCISGGMADLVLDDEKRLAKR
Mus_musculus_THRB FRRTIQKSLHPSYSCKYEGKCIIDKVTNRNQCQBCRFKKCIYVGMAIDLVLDDSKRLAKR
Homo_sapiens_THRB FRRTIQKSLHPSYSCKYEGKCIIDKVTNRNQCQBCRFKKCIYVGMAIDLVLDDSKRLAKR

SmTHRB
240 250 260 270 280 290
SmTHRB FLIEANRARKAAAEATASAVYVTDPSINIPNITNPNVSVSKYHITHNQPISTNTISSTP
Mus_musculus_THRB FLIEENRKRREELQKS...TAVYVTDPSINIPNITNPNVSVSKYHITGHPEPTDEEWE...
Homo_sapiens_THRB FLIEENRKRREELQKS...TAVYVTDPSINIPNITNPNVSVSKYHITGHPEPTDEEWE...

SmTHRB
300 310 320 330 340 350
SmTHRB VIMSTIPYHSTIHSNIHFTNQFANSTIRSQFNCPNITRYLEVTNNDIHSFVNPKTPDA
Mus_musculus_THRBLTKITVEAHVATNAQGSNW.....
Homo_sapiens_THRBLTKITVEAHVATNAQGSNW.....

SmTHRB
360 370 380 390 400 410
SmTHRB TYSANEAKLIVQPIQITIDKLOPTTMMNMCWNPTCGAFYTQCFMNDASNDHNHNSKITPL
Mus_musculus_THRBKQKRRFLPEDIGQAPTIVNAP.....
Homo_sapiens_THRBKQKRRFLPEDIGQAPTIVNAP.....

SmTHRB
420 430 440 450 460 470
SmTHRB SFKESINRIQLSSVSMQINKNPLFPSEDGYCNLLSKYSNFNSQQSVYTKAVDNNRINHSN
Mus_musculus_THRB
Homo_sapiens_THRB
TT α6 η4

SmTHRB
420 430 440 450 460 470
SmTHRB SFKESINRIQLSSVSMQINKNPLFPSEDGYCNLLSKYSNFNSQQSVYTKAVDNNRINHSN
Mus_musculus_THRB
Homo_sapiens_THRB
TT α6 η4

SmTHRB
480 490 500 510 520 530
SmTHRB ANNQINTHYEPQQYSPVTPPEKQTLSCDQPAITDNLFSYPKHVSIMDSNDTVHNDPCW
Mus_musculus_THRB
Homo_sapiens_THRB
TT α6 η4

SmTHRB
540 550 560 570 580 590
SmTHRB TTEDQNMVDSIVQAYSNNMLNPSFKRKMNDGVDKPEKAFYSSTDRIKSLIPMTASIV
Mus_musculus_THRBEGGKVDLE...AF...SHFKIITPAITRVV
Homo_sapiens_THRBEGGKVDLE...AF...SHFKIITPAITRVV
α7 η5 α8

SmTHRB
600 610 620 630 640 650
SmTHRB AFARLVPGFELLDANQOTRLLRGCCLDITLRLAAYLLSRIAVSLGIVDSNGHNKPOFTIS
Mus_musculus_THRB DPAKKLPMPCELPCEDQIILLKGCCEIMSLRAAVRYDPDSEITLNGEMAVTRGOLKNG
Homo_sapiens_THRB DPAKKLPMPCELPCEDQIILLKGCCEIMSLRAAVRYDPDSEITLNGEMAVTRGOLKNG
η6 α9

SmTHRB
660 670 680 690 700 710
SmTHRB FLDSADIFVQNVPSHQHNVASVTPNNIPQLGTSYVKCAQMIRAVALKARLEIDQTEVA
Mus_musculus_THRB GL...GVVSDAIF...DGLMSGSFNLDDTEVA
Homo_sapiens_THRB GL...GVVSDAIF...DGLMSGSFNLDDTEVA
η7 η8 TT η9 α10

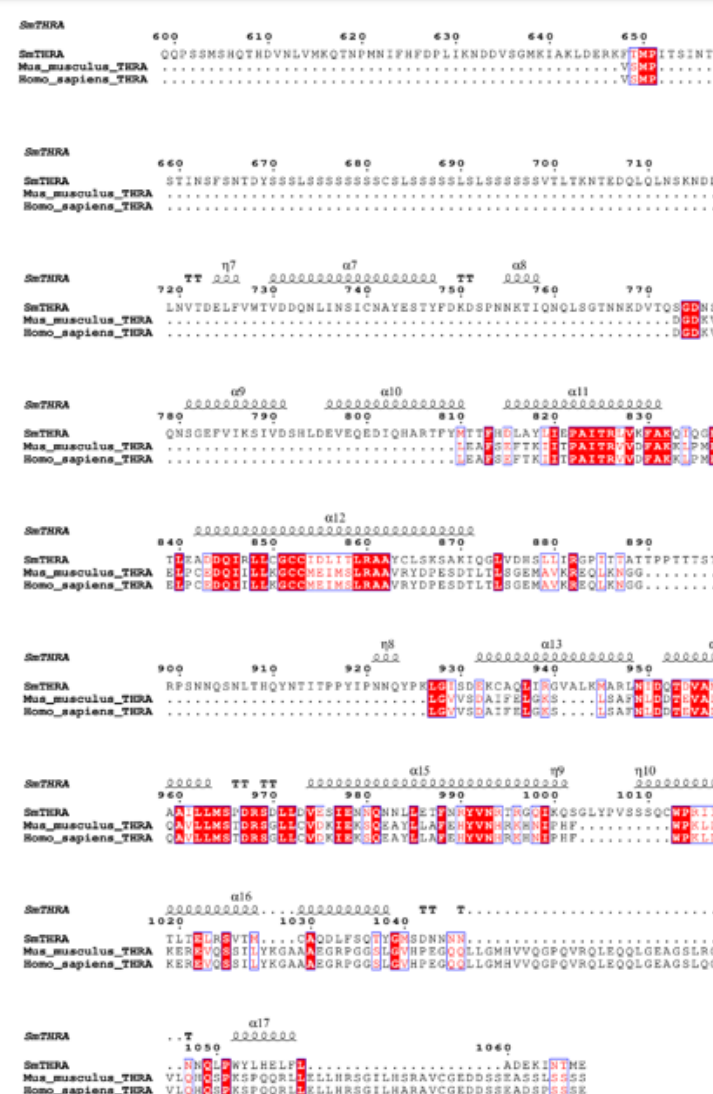
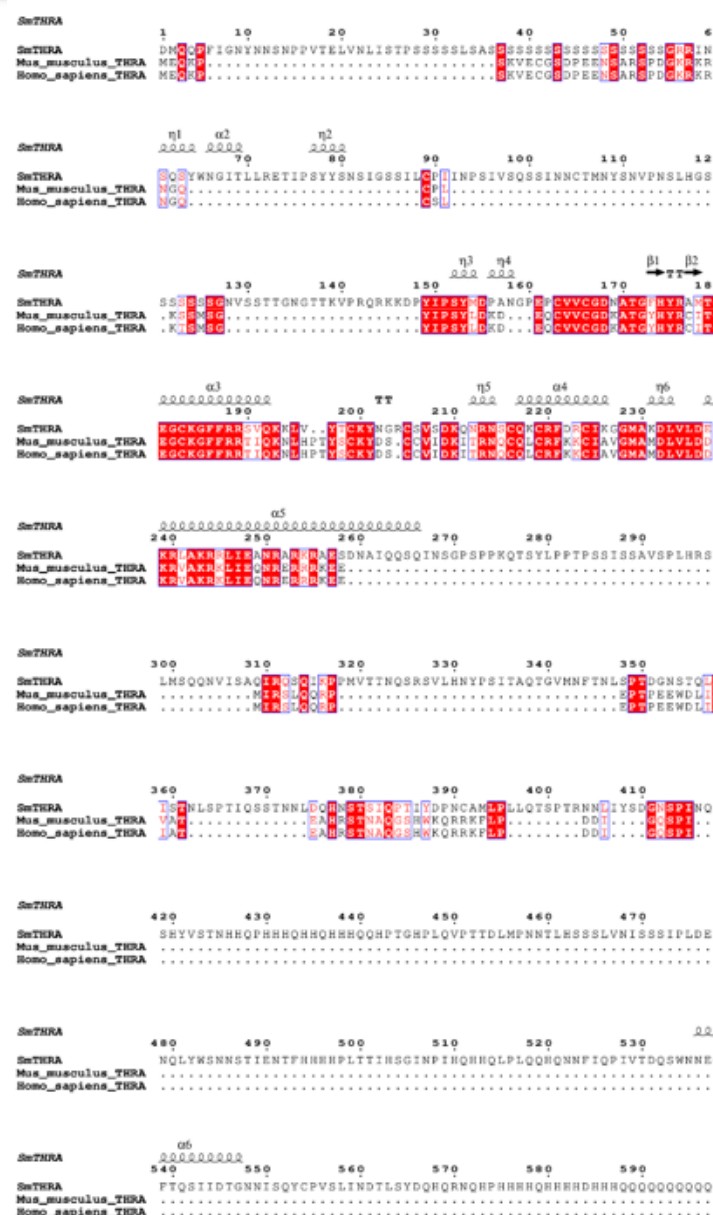
SmTHRB
720 730 740 750 760 770
SmTHRB LMTSHLLMSPDRGLTDCETVEITQDILETFNRYANRIRKIRFNRMNNHNSRSININ
Mus_musculus_THRB LLQAVLLMSSDRGLACVRIEYQDSFLAFEHYENYRK...
Homo_sapiens_THRB LLQAVLLMSSDRGLACVRIEYQDSFLAFEHYENYRK...
α11 α12

SmTHRB
780 790 800 810 820
SmTHRB GISQQQQTWPRLIMATLRLSITCNOGLFVEKAYGNTTEQIPWYFHEFTG
Mus_musculus_THRB ...HVVTHWPRLIMATLRLSITCNOGLFVEKAYGNTTEQIPWYFHEFTG
Homo_sapiens_THRB ...HVVTHWPRLIMATLRLSITCNOGLFVEKAYGNTTEQIPWYFHEFTG
α13 α14 η10 α15

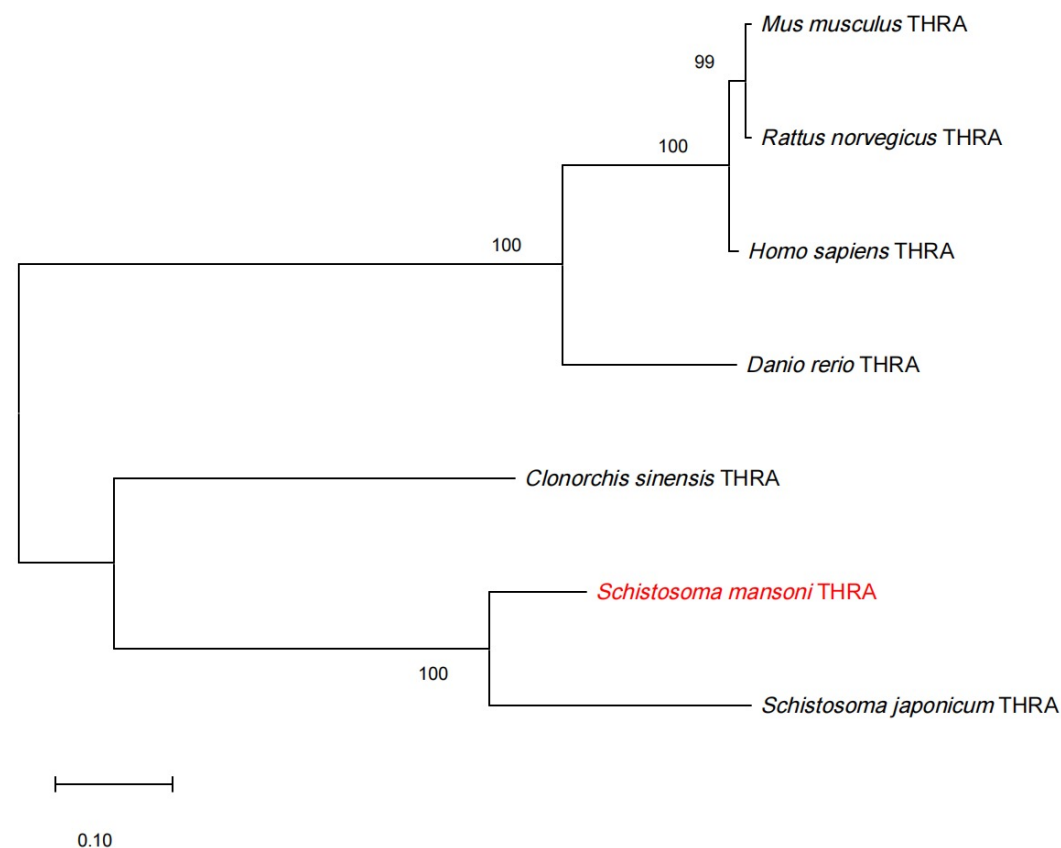
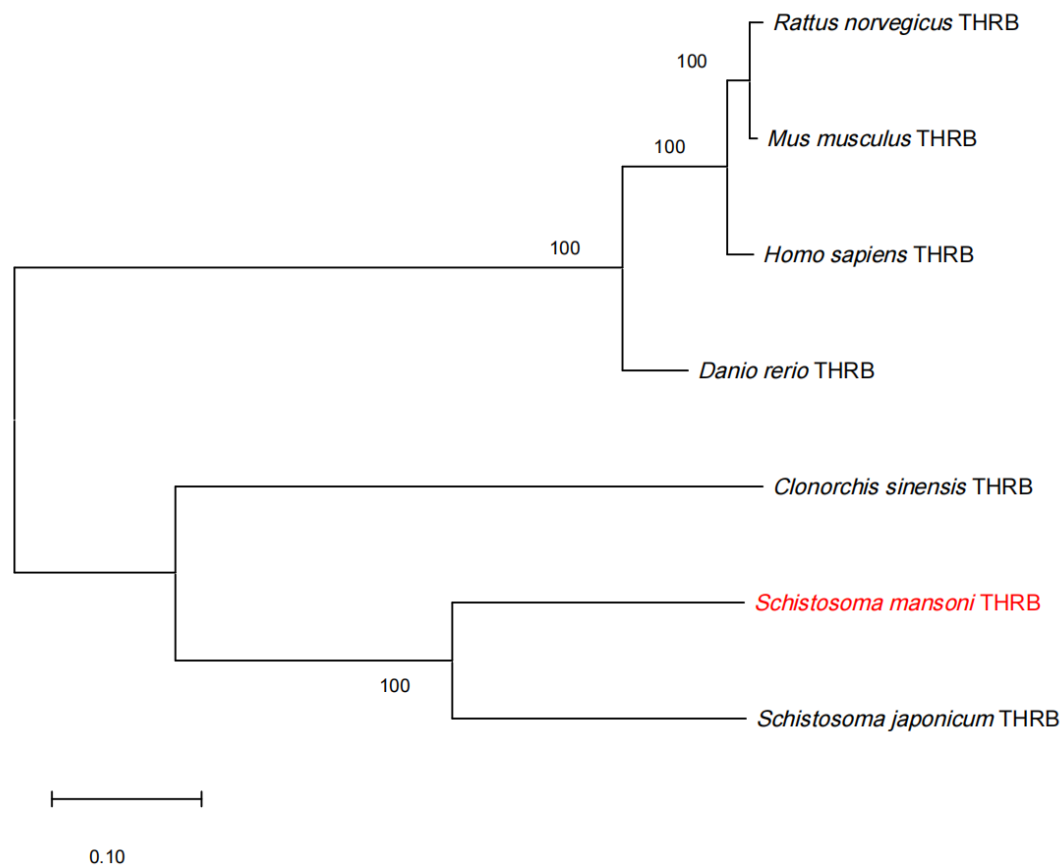
研究结果：SmTHRA的保守性分析



THRA的序列比对：
SmTHRA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

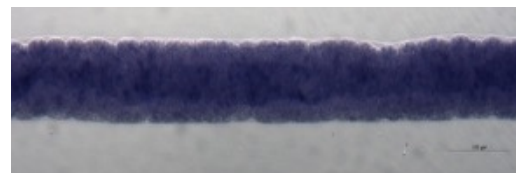
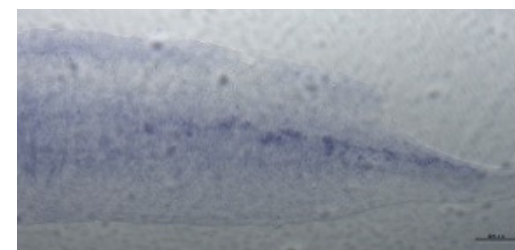
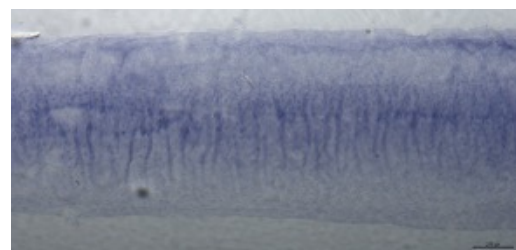
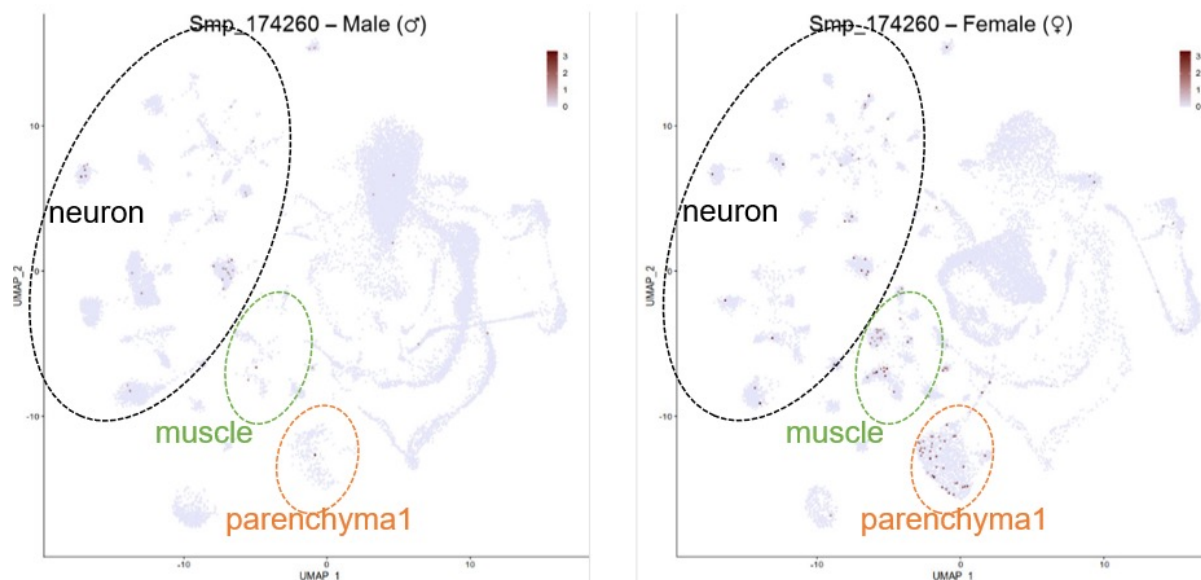


***Sm*THR在吸虫中具备一定保守性**

研究结果: *Smthrb*的组织定位—WISH



Smthrb

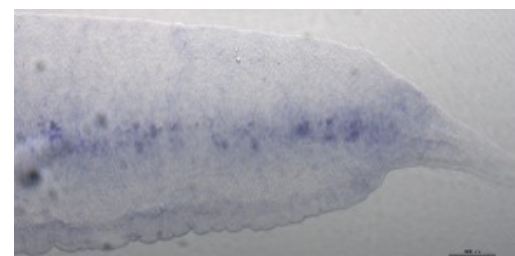
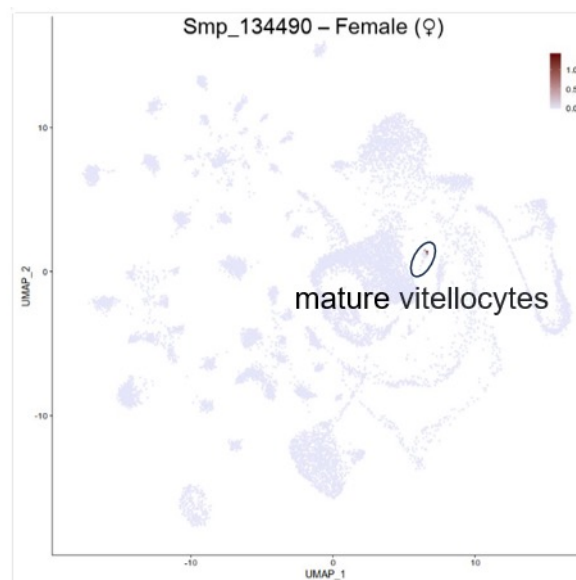
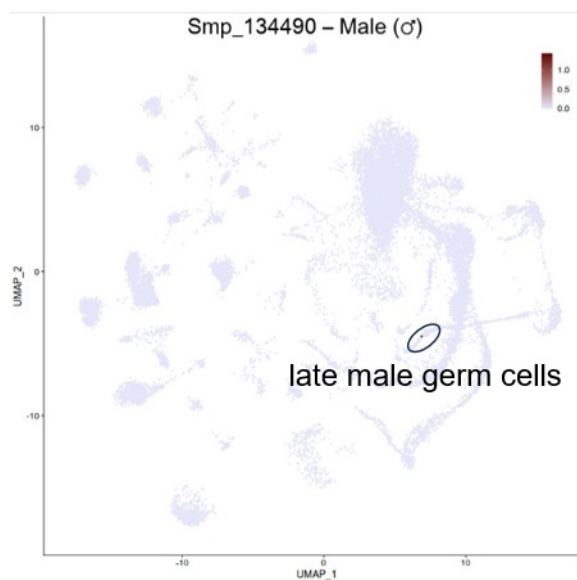


*Smthrb*在单细胞图谱所示细胞类型和肠道富集表达

研究结果: *Smthra*的组织定位—WISH



Smthra



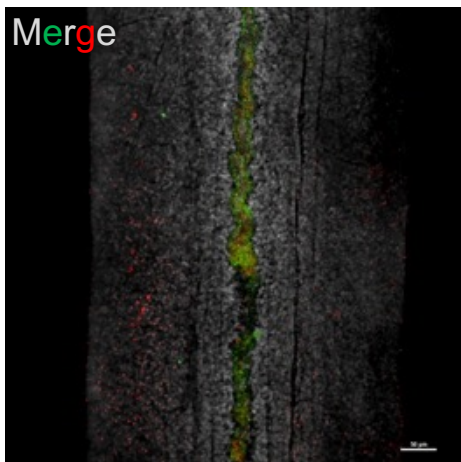
*Smthra*在雌虫卵巢的部分区域表达

研究结果: *Smthrb*的细胞定位—FISH

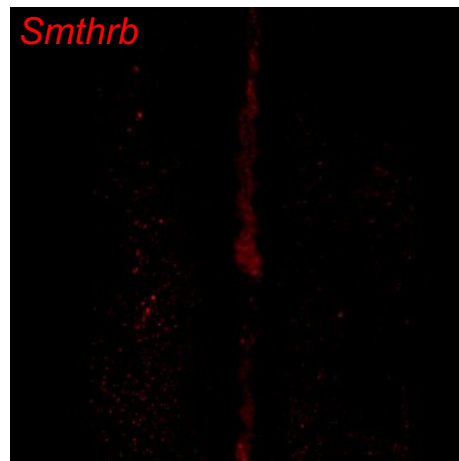
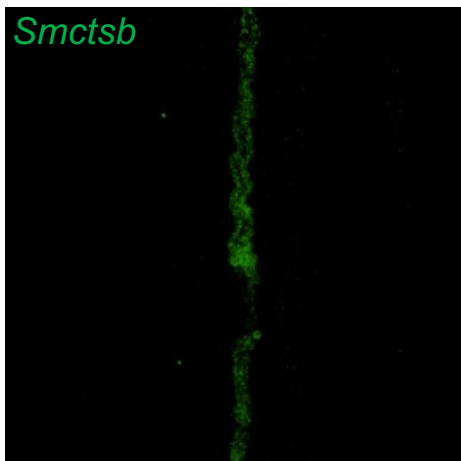


Marker:

A Merge



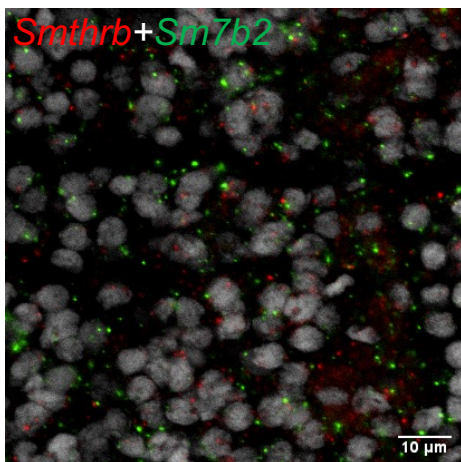
肠道—*Smctsrb*



*Smthrb*在肠道和部分神经、肌肉细胞中有表达

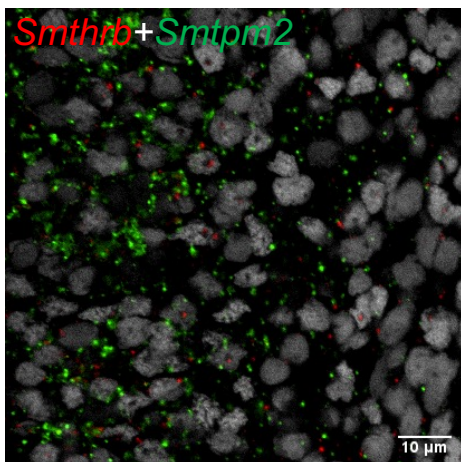
神经—*Sm7b2*

B



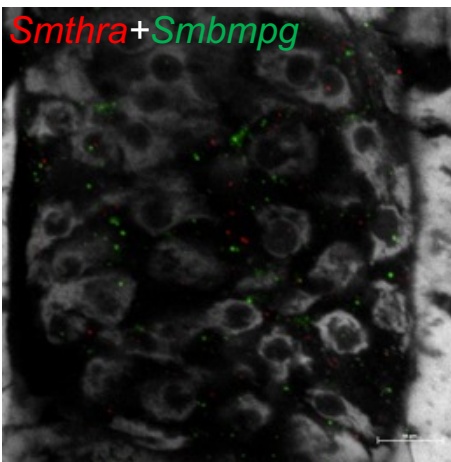
肌肉—*Smtpm2*

C



成熟卵巢—*Smbmpg*

D

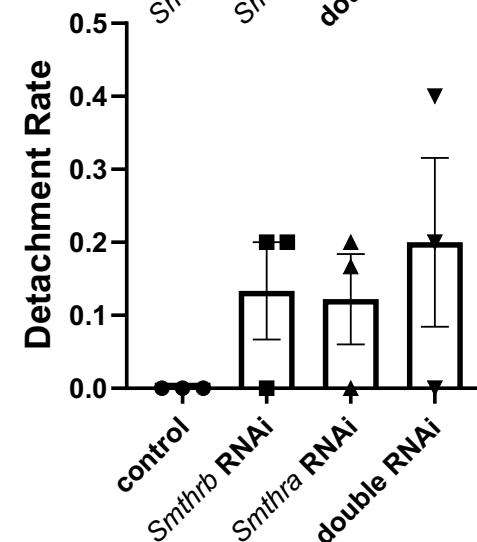
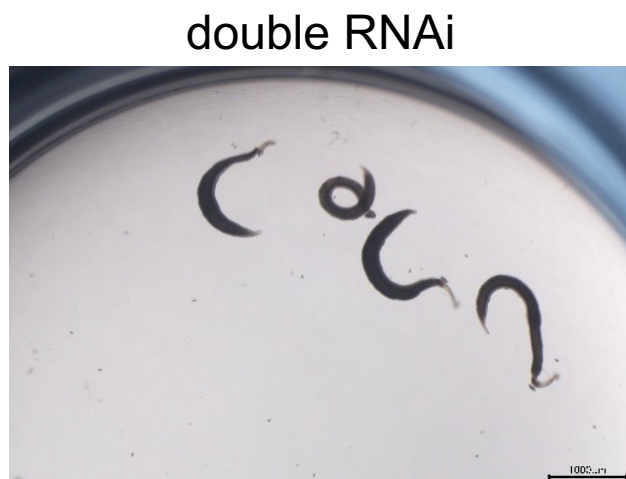
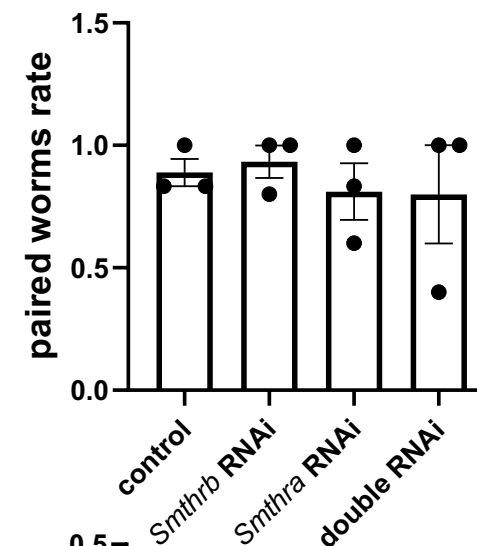


*Smthra*在成熟卵巢区域有表达

研究结果: *Smthrb*的功能研究—体外RNA干扰

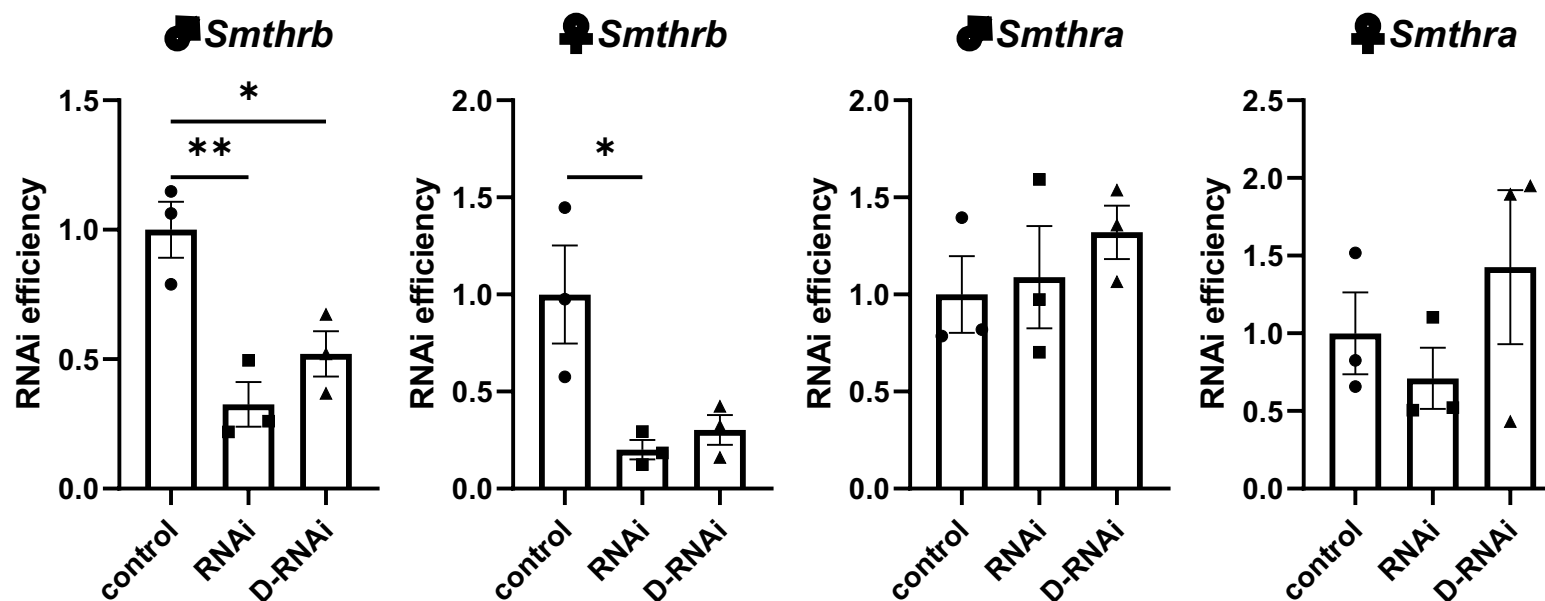


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体外干扰26d未影响虫体形态及活力

研究结果: *Smthrb*的功能研究—体外RNA干扰



仅*Smthrb*被显著敲低

研究结果: *Smthrb*的功能研究—体内RNA干扰



control



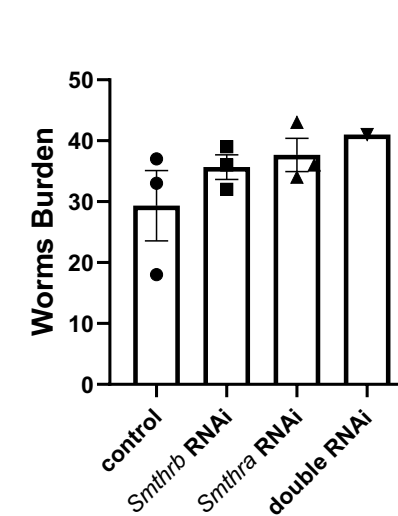
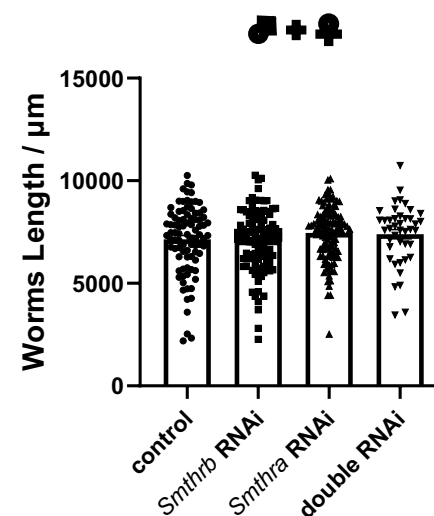
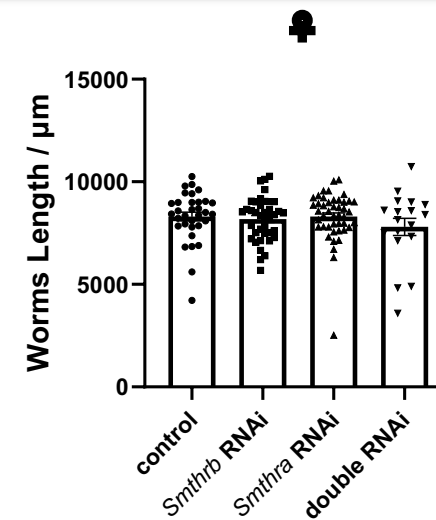
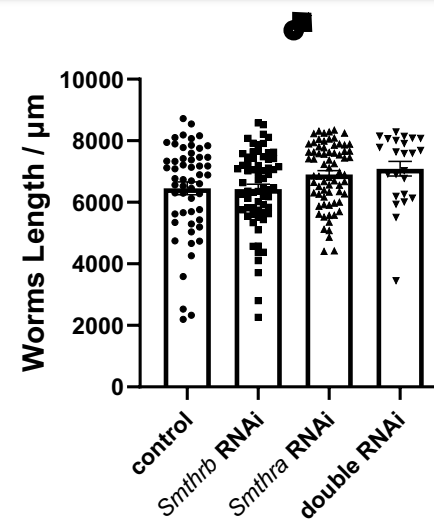
Smthrb RNAi



double RNAi



Smthra RNAi

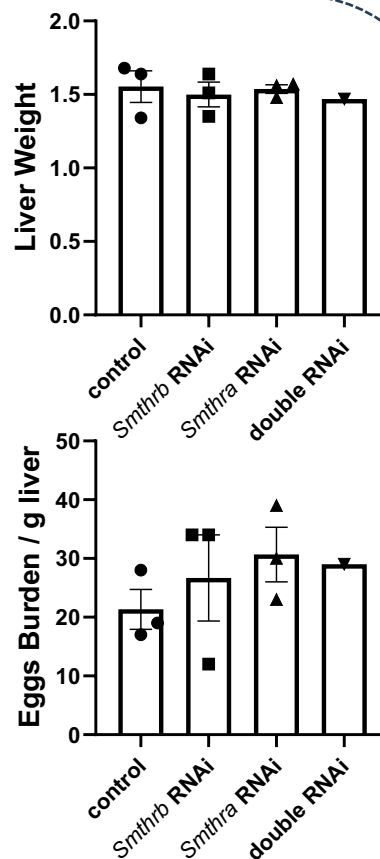
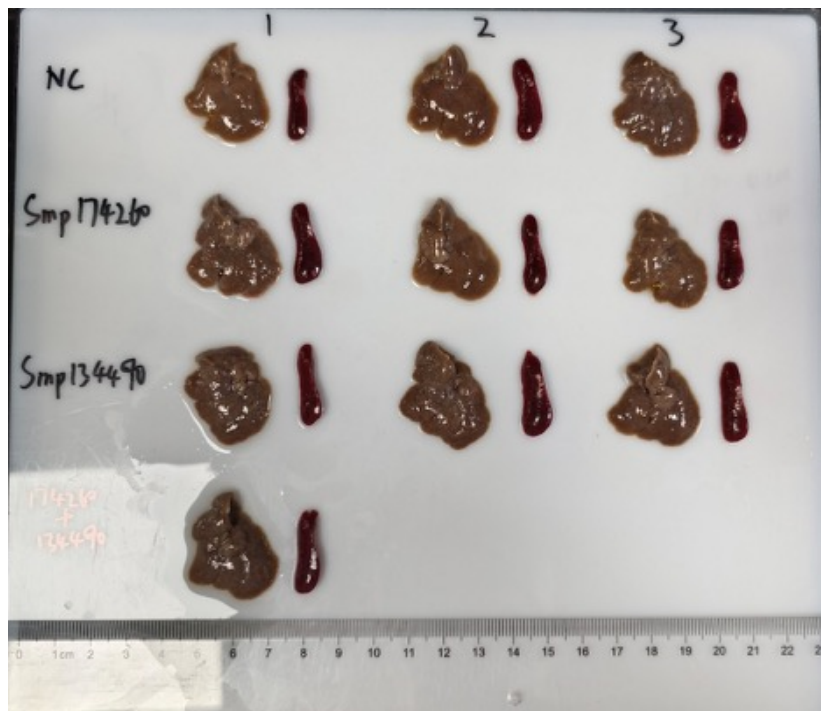


体内干扰49d未影响虫体形态、虫长和虫数

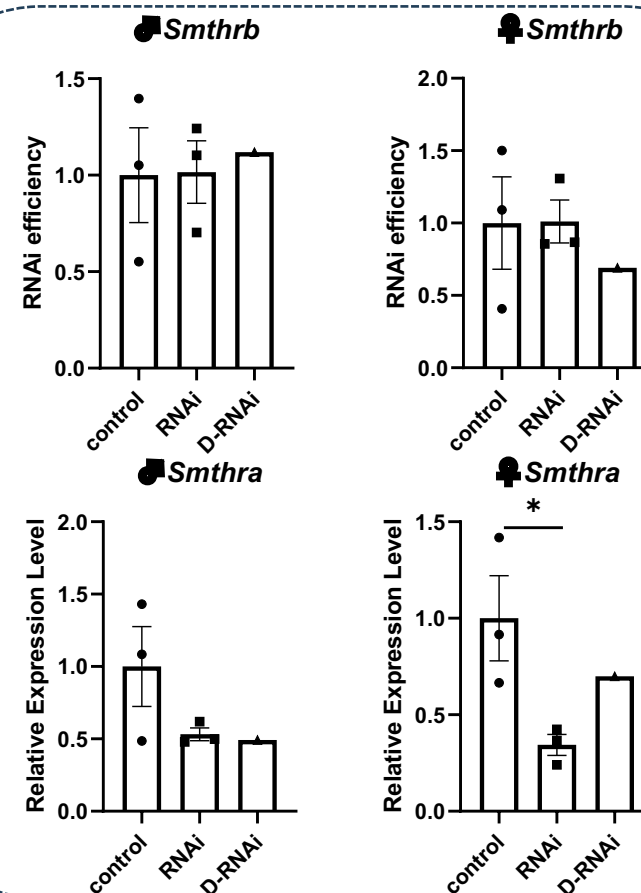
研究结果: *Smthr*的功能研究—体内RNA干扰



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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

- *SmTHR*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



- 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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指导老师：王吉鹏

时间：2025.5.28