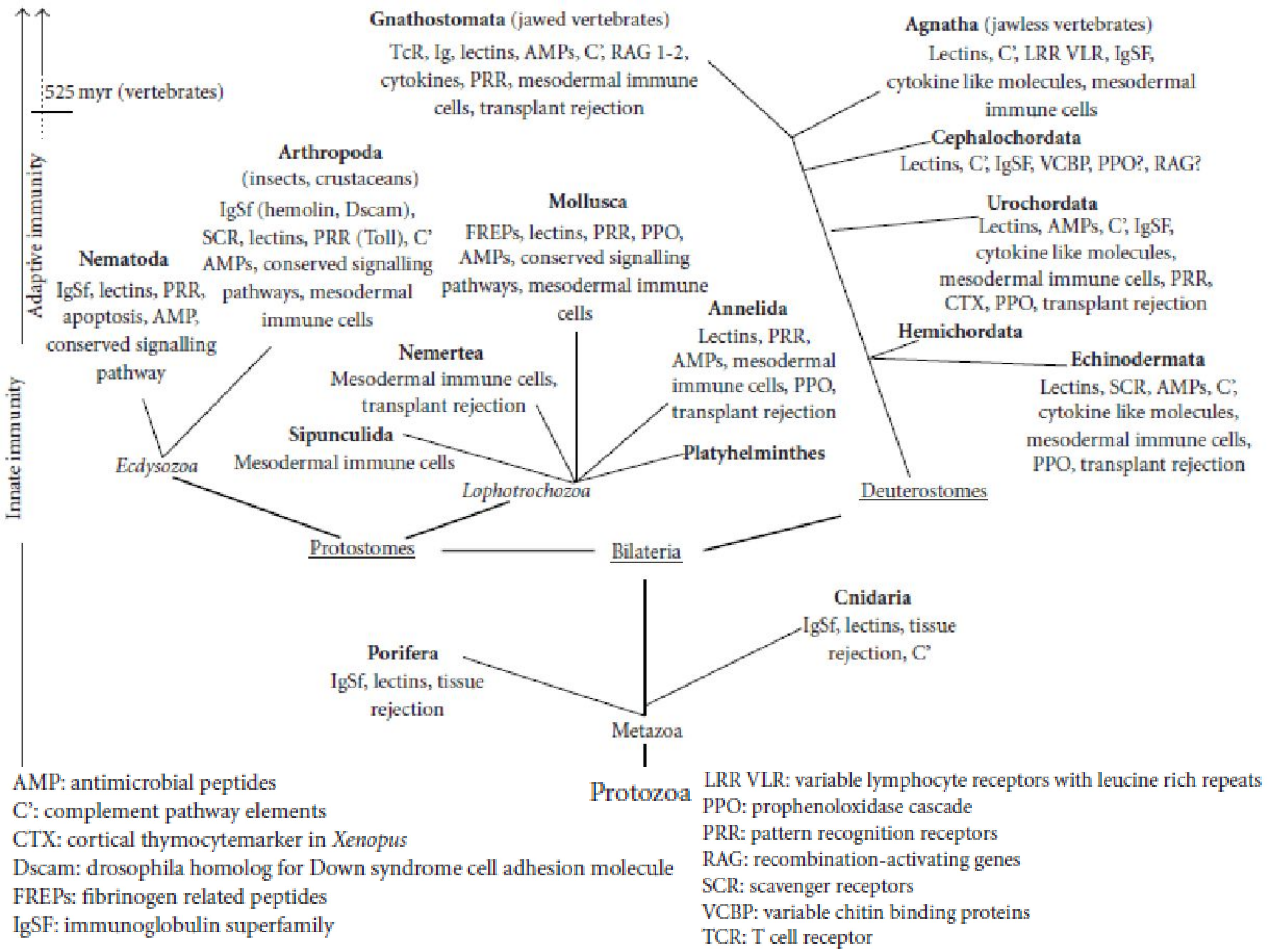
Эволюционная иммунология
Лекция 6 «Разнообразие иммунных реакций беспозвоночных»

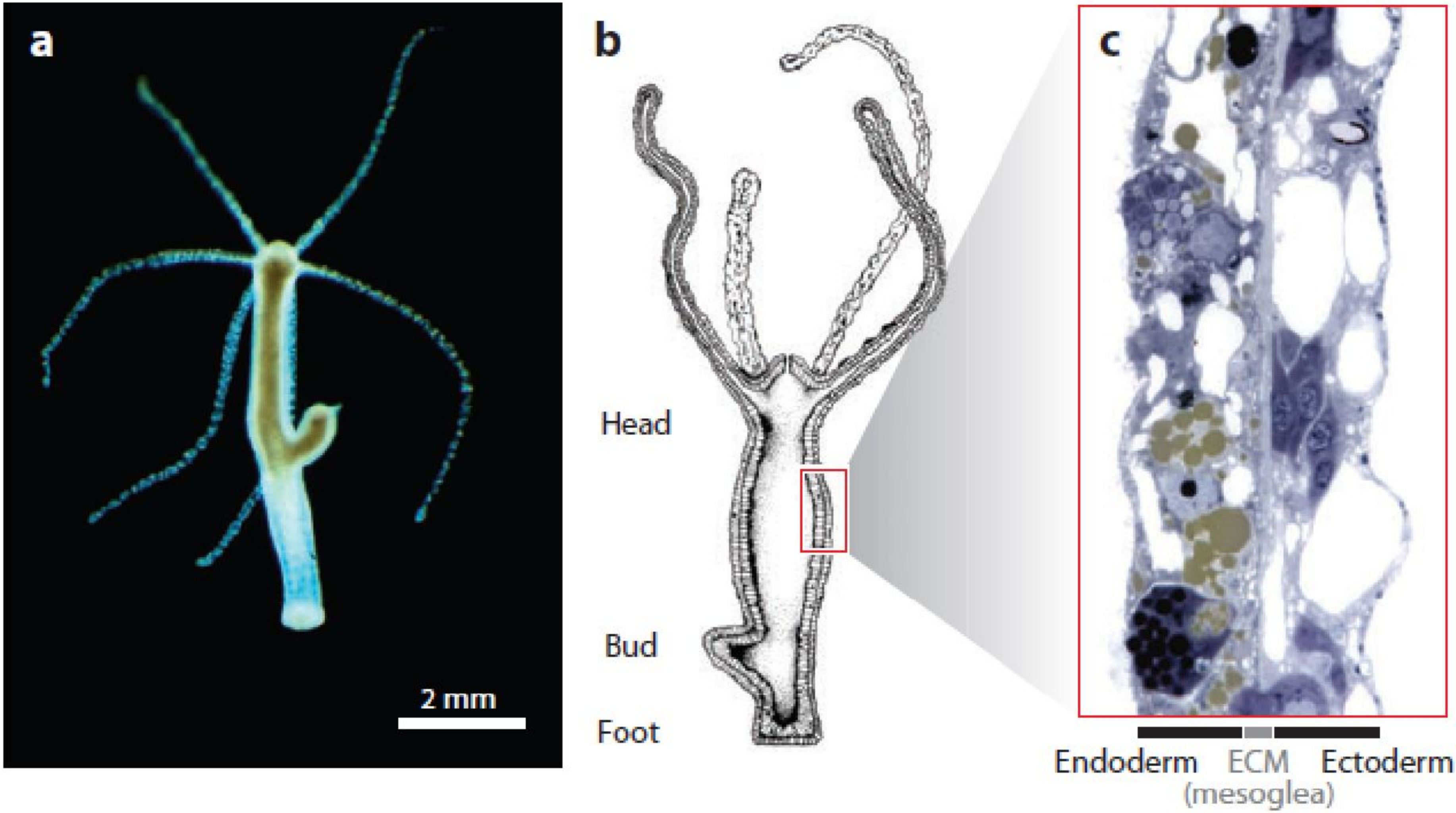
Шилов Е.С.
19 марта 2018

Иммуноциты беспозвоночных

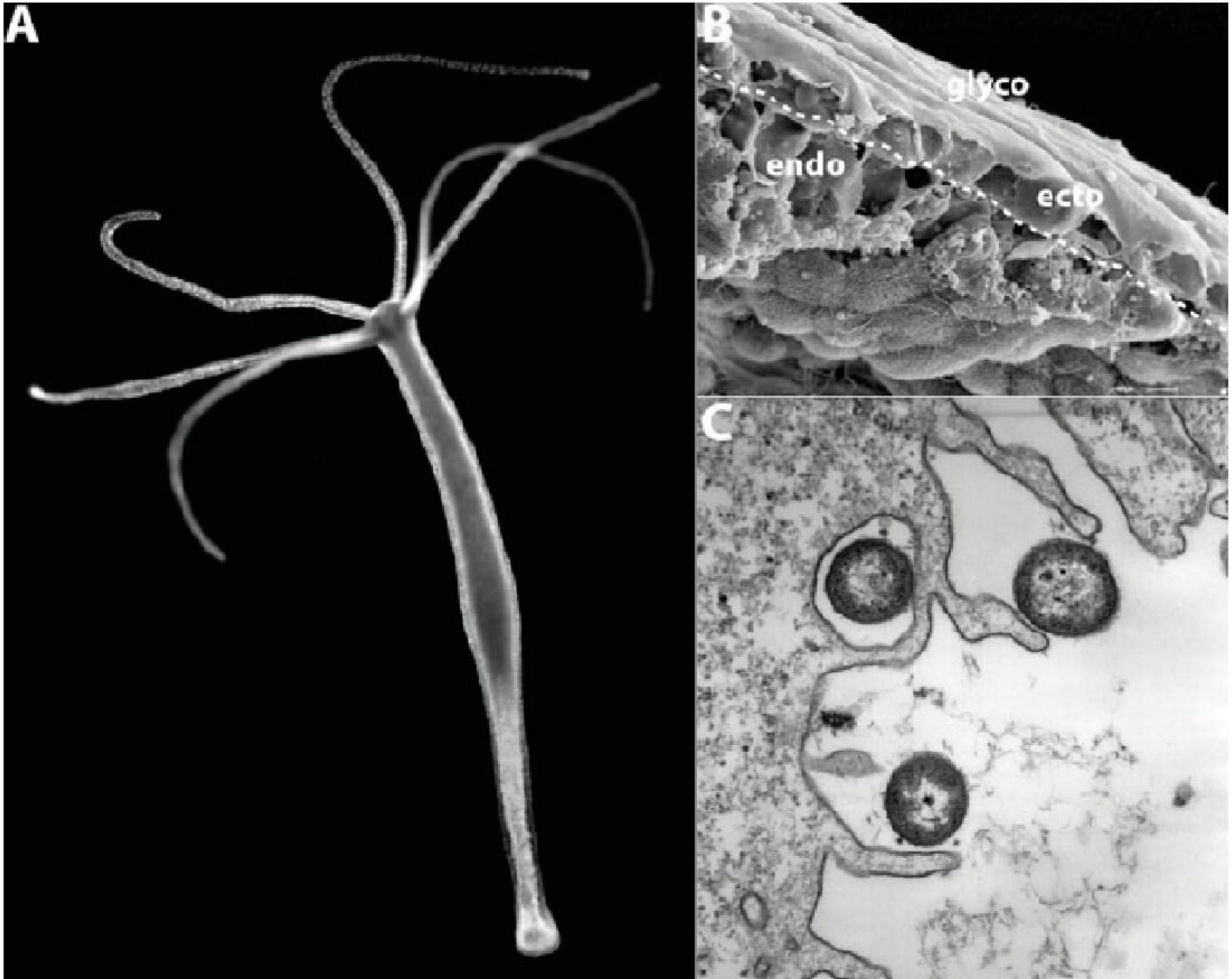
Таксон	Макрофагоподобные клетки	Лимфоциты и лимфоцитоподобные клетки	Очаги гемопоэза
Губки	Блуждающие амебоциты (археоциты)	–	–
Кишечнополостные	Блуждающие амебоциты	–	–
Немертины	Гиалиновые амебоциты	Лимфоцитоподобные амебоциты	–
Кольчатые черви	Гиалиновые амебоциты (нейтрофилы)	Лимфоцитоподобные клетки двух типов (базофилы)	Парные узелки в целоме, гемопоэтическая ткань в алиментарном кровяном синусе
Моллюски	Гиалиновые амебоциты	Лимфоцитоподобные клетки	Гемопоэтическая ткань целома. «Белое тело» головоногих моллюсков
Членистоногие	Плазматоциты	Прогемоциты	Гемопоэтические участки в различных частях тела
Иглокожие	Фагоцитирующие амебоциты	Лимфоциты	Аксиальный орган
Оболочники	Макрофаги	Лимфоциты	Лимфатические узелки в глоточной стенке, вокруг пищеварительного тракта, в стенках тела


Adaptive immunity
Innate immunity
525 myr (vertebrates)
Gnathostomata (jawed vertebrates)
TcR, Ig, lectins, AMPs, C', RAG 1-2, cytokines, PRR, mesodermal immune cells, transplant rejection
Agnatha (jawless vertebrates)
Lectins, C', LRR VLR, IgSF, cytokine like molecules, mesodermal immune cells
Cephalochordata
Lectins, C', IgSF, VCBP, PPO?, RAG?
Urochordata
Lectins, AMPs, C', IgSF, cytokine like molecules, mesodermal immune cells, PRR, CTX, PPO, transplant rejection
Hemichordata
Echinodermata
Lectins, SCR, AMPs, C', cytokine like molecules, mesodermal immune cells, PPO, transplant rejection
Deuterostomes
Arthropoda
(insects, crustaceans)
IgSf (hemolin, Dscam), SCR, lectins, PRR (Toll), C' AMPs, conserved signalling pathways, mesodermal immune cells
Nematoda
IgSf, lectins, PRR, apoptosis, AMP, conserved signalling pathway
Ecdysozoa
Mollusca
FREPs, lectins, PRR, PPO, AMPs, conserved signalling pathways, mesodermal immune cells
Annelida
Lectins, PRR, AMPs, mesodermal immune cells, PPO, transplant rejection
Nemertea
Mesodermal immune cells, transplant rejection
Sipunculida
Mesodermal immune cells
Platyhelminthes
Lophotrochozoa
Protostomes
Bilateria
Cnidaria
IgSf, lectins, tissue rejection, C'
Porifera
IgSf, lectins, tissue rejection
Metazoa
Protozoa
AMP: antimicrobial peptides
C': complement pathway elements
CTX: cortical thymocytemarker in Xenopus
Dscam: drosophila homolog for Down syndrome cell adhesion molecule
FREPs: fibrinogen related peptides
IgSF: immunoglobulin superfamily
LRR VLR: variable lymphocyte receptors with leucine rich repeats
PPO: prophenoloxidase cascade
PRR: pattern recognition receptors
RAG: recombination-activating genes
SCR: scavenger receptors
VCBP: variable chitin binding proteins
TCR: T cell receptor

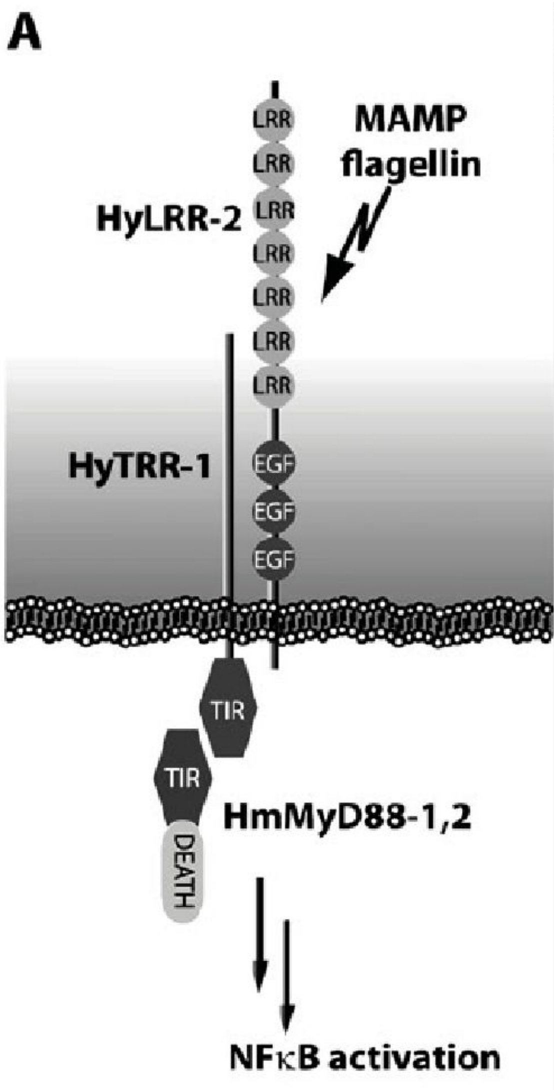
Строение гидры

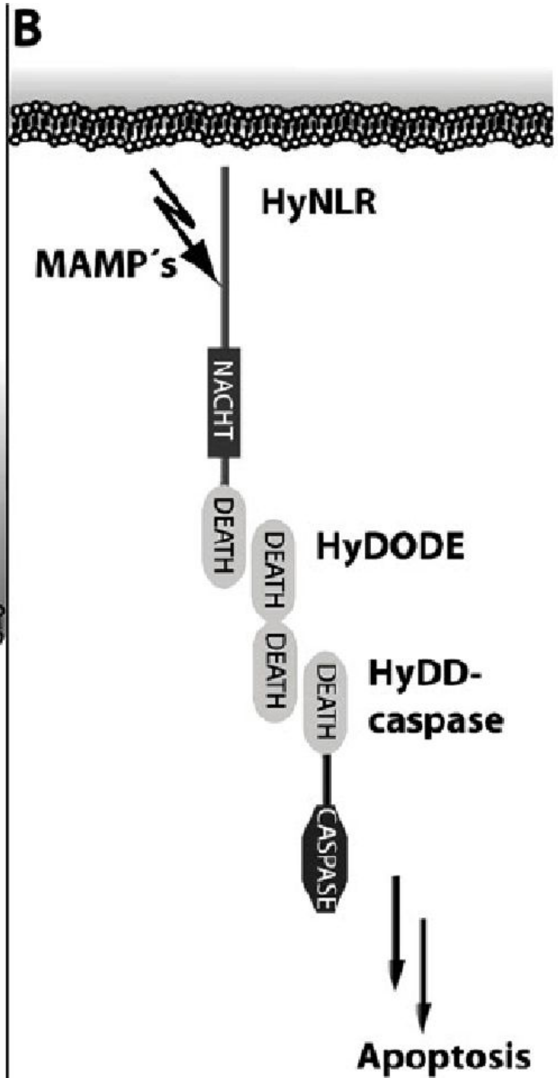


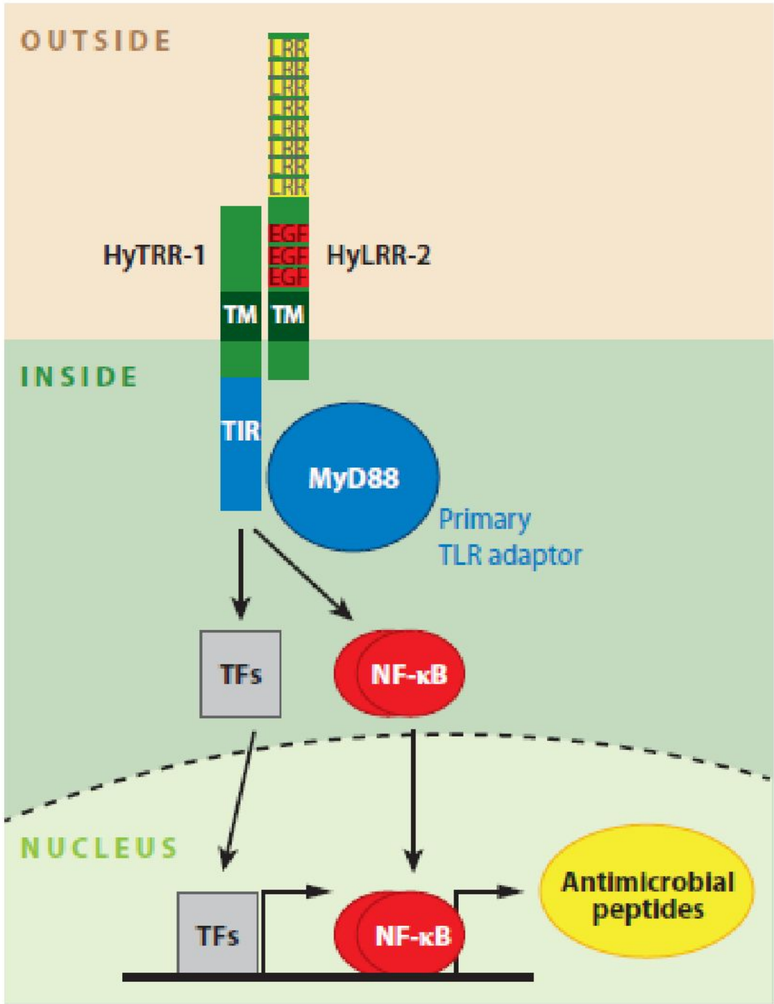
Эпителиальные клетки гидроидных способны к фагоцитозу



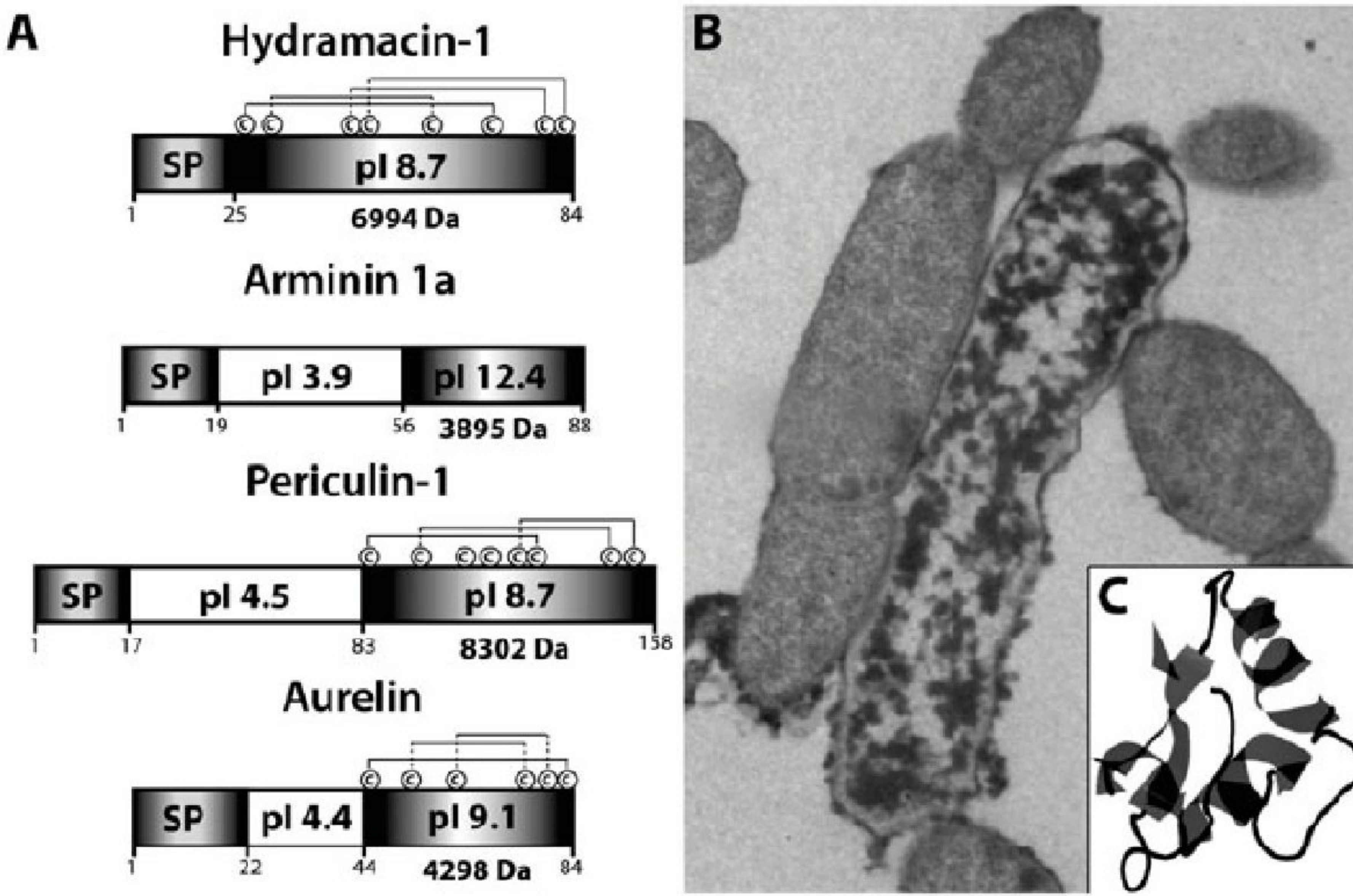
У книдарий есть собственные TLR- и NLR - рецепторы







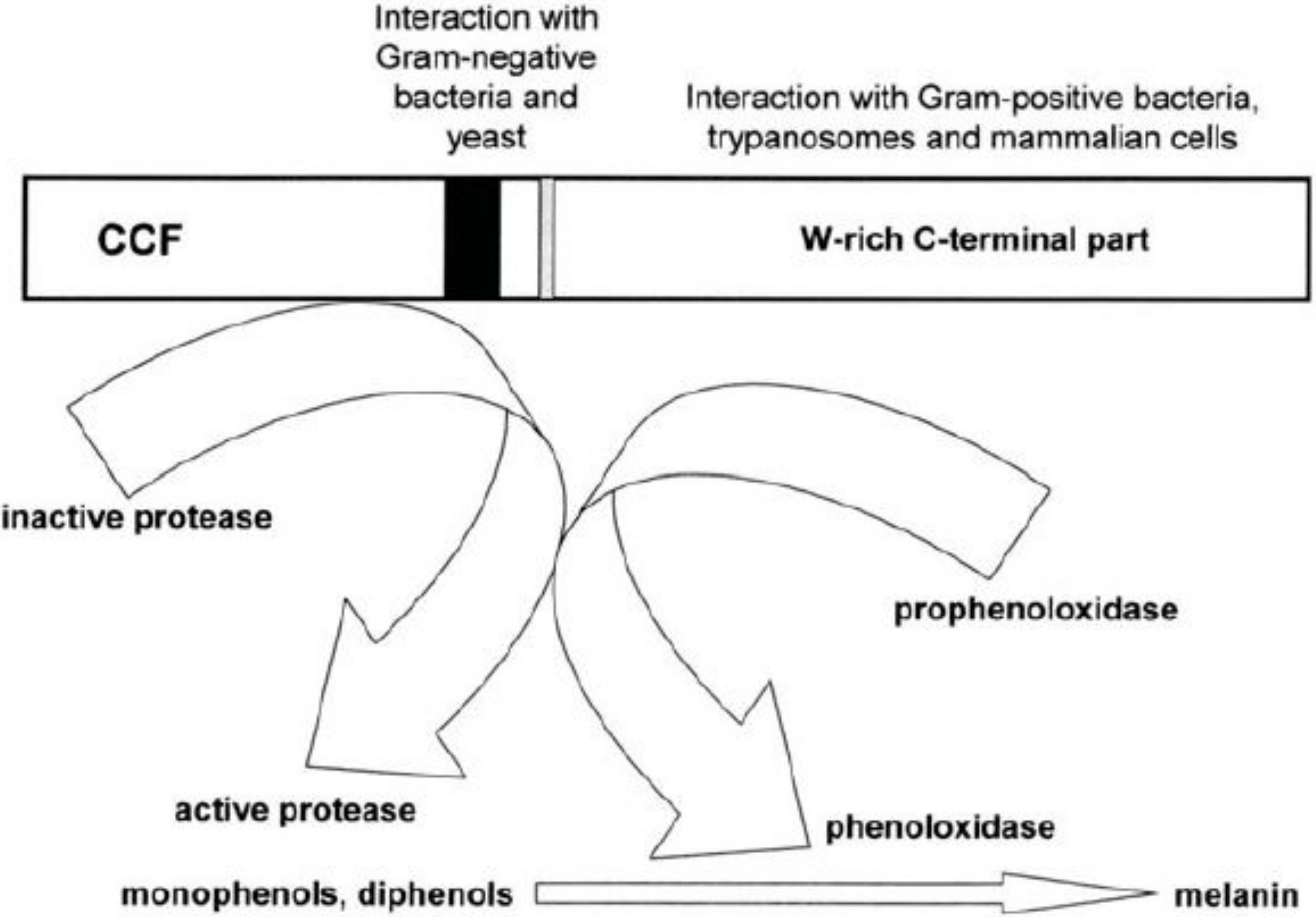
Антимикробные пептиды книдарий

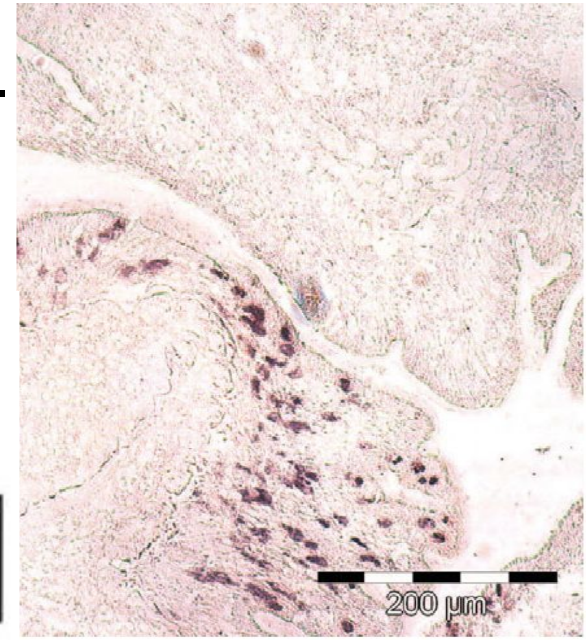


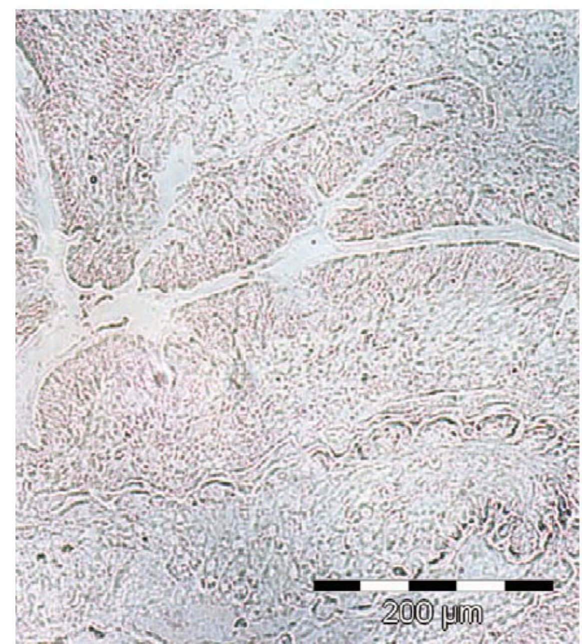
Странный белок дождевого червя CCF

Белок жидкости целомической полости массой 42 кДа, распознаёт (?) О-антиген ЛПС, мурамилдипептиды, мурамовую кислоту, бета-люканы, диацетилхитобиозу.

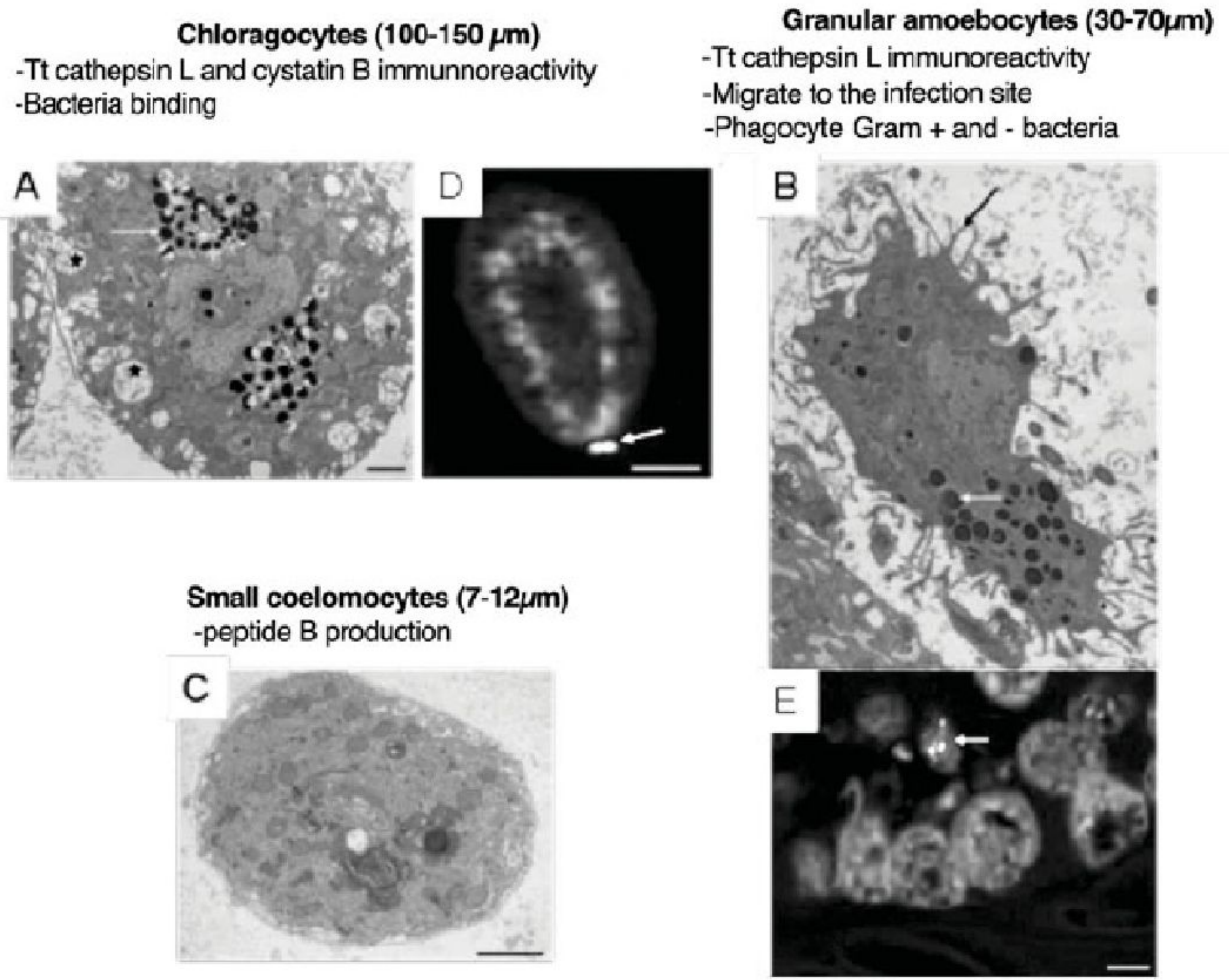
Активирует профенолоксидазу, опсонизирует клетки патогенов, его синтез индуцируется ЛПСом, а сам он лизирует клетки L929 (и другие тоже). Так ли это?



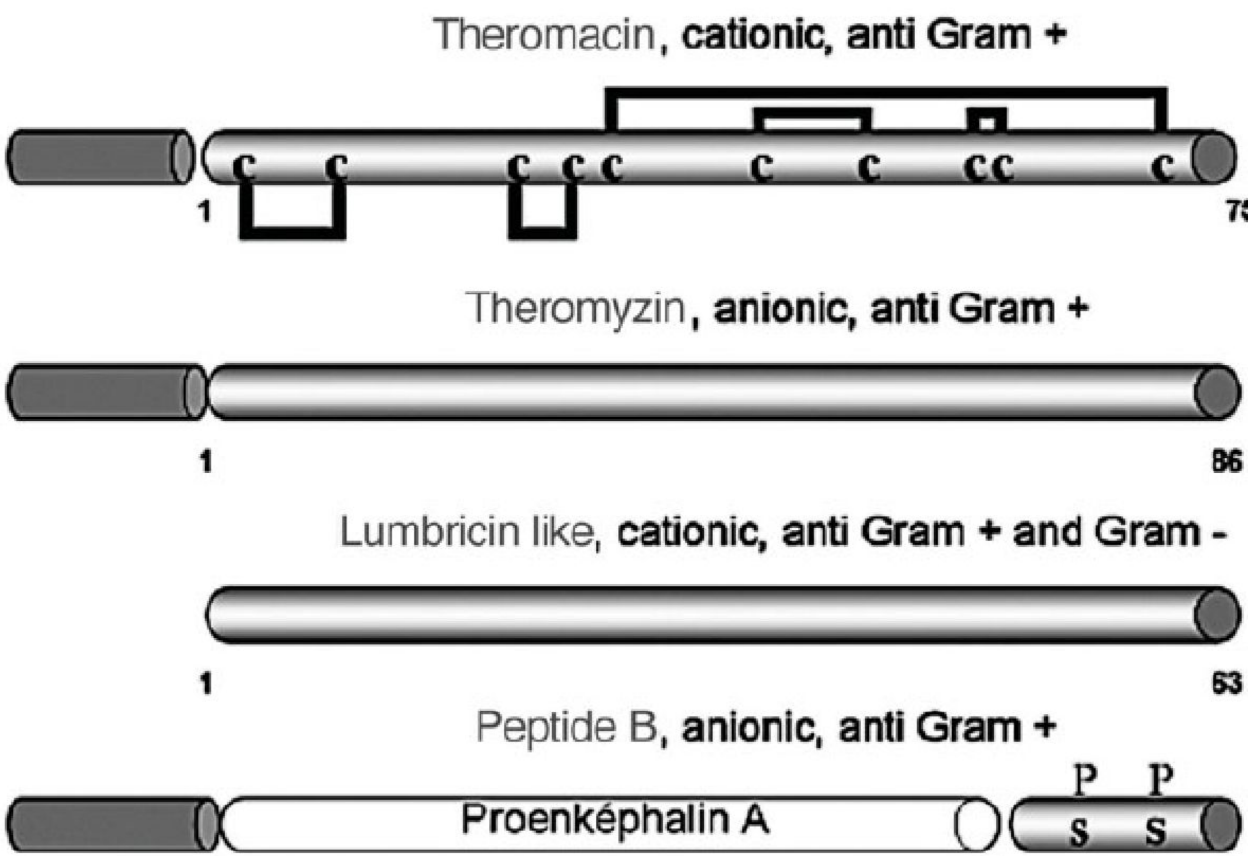




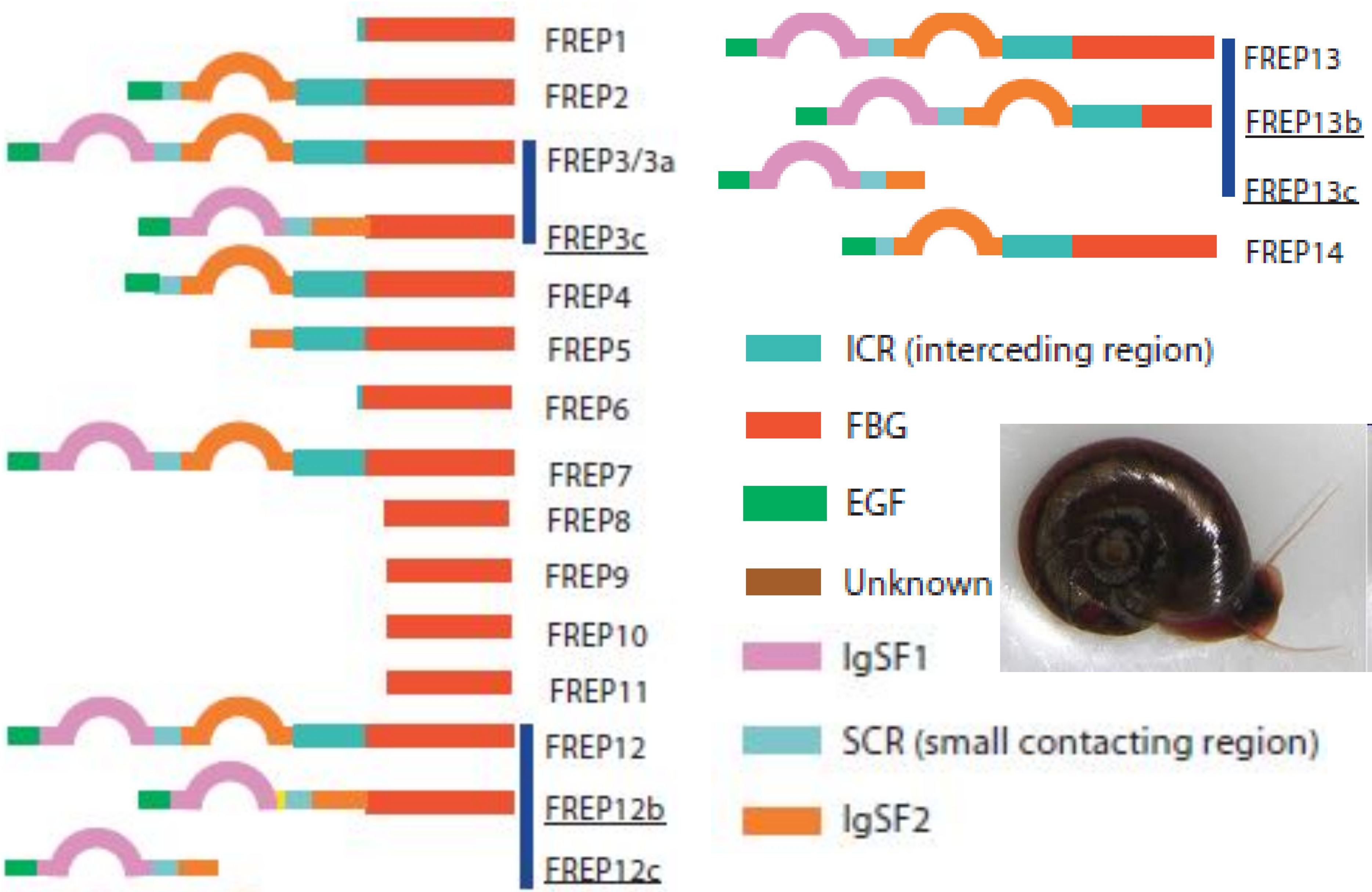
Хлорагогенные клетки, малые целомоциты и амёбоциты кольчатых червей



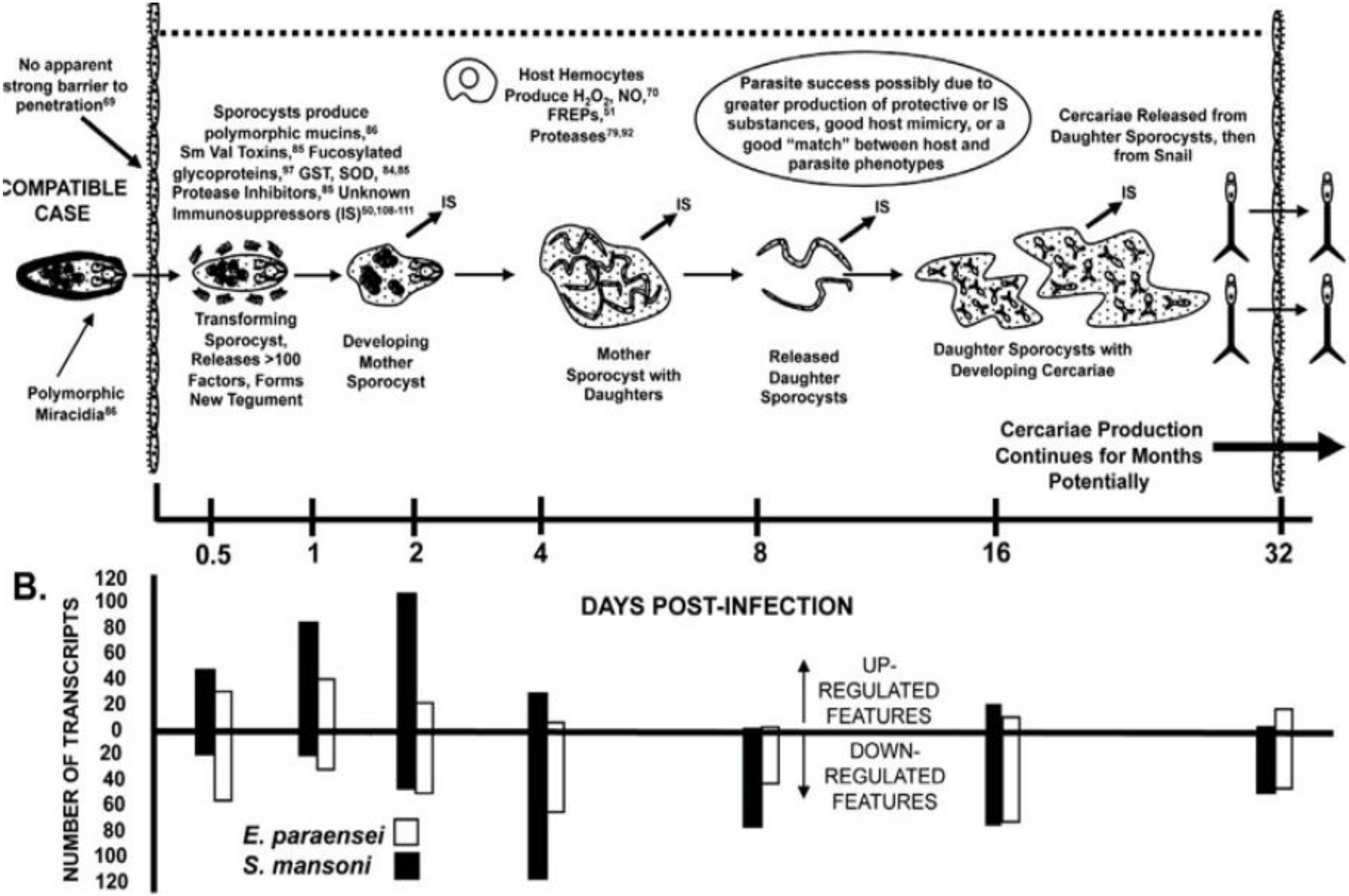
Антимикробные пептиды пиявки



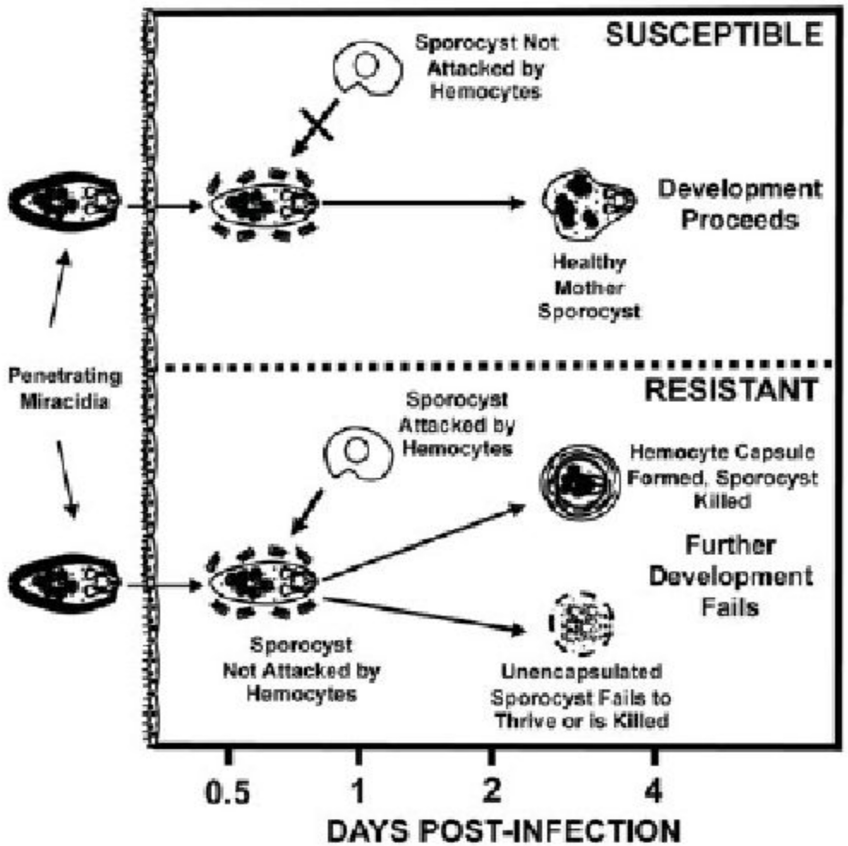
Строение FREP белков улитки *Biomphalaria glabrata*



Улитки против трематод



Различия между чувствительными и устойчивыми улитками



CONSTITUTIVE DIFFERENCES BETWEEN SUSCEPTIBLE AND RESISTANT SNAILS

Resistant Snails have more hemocytes than susceptible snails
Bg-Sm: [179]

Resistant hemocytes have different behavior or properties
Bg-Sm: [177]
Bt-Sm: [178]

Resistant Snails produce more parasite-toxic reactive oxygen species (ROS)
Bg-Sm: [70,101,179-182]

Resistant Snails have novel recognition/killing capacity in their plasma
Bt-Sm: [183,184]
Bg-Sm: [44]

Innate differences in the levels of potentially immune relevant factors
Bg-Sm: [185]
Bg-Ec: [73,78,94,186,187]
Bt-Sm: [188]

Resistant snails have greater ability to resist parasite offensive strategies, including signaling pathway targets
Bg-Sm: [48,110]
Bg-Ec: [110]

Resistant and susceptible snails may differ in the ease with which they are mimicked by parasites
Bg-Sm: [97]

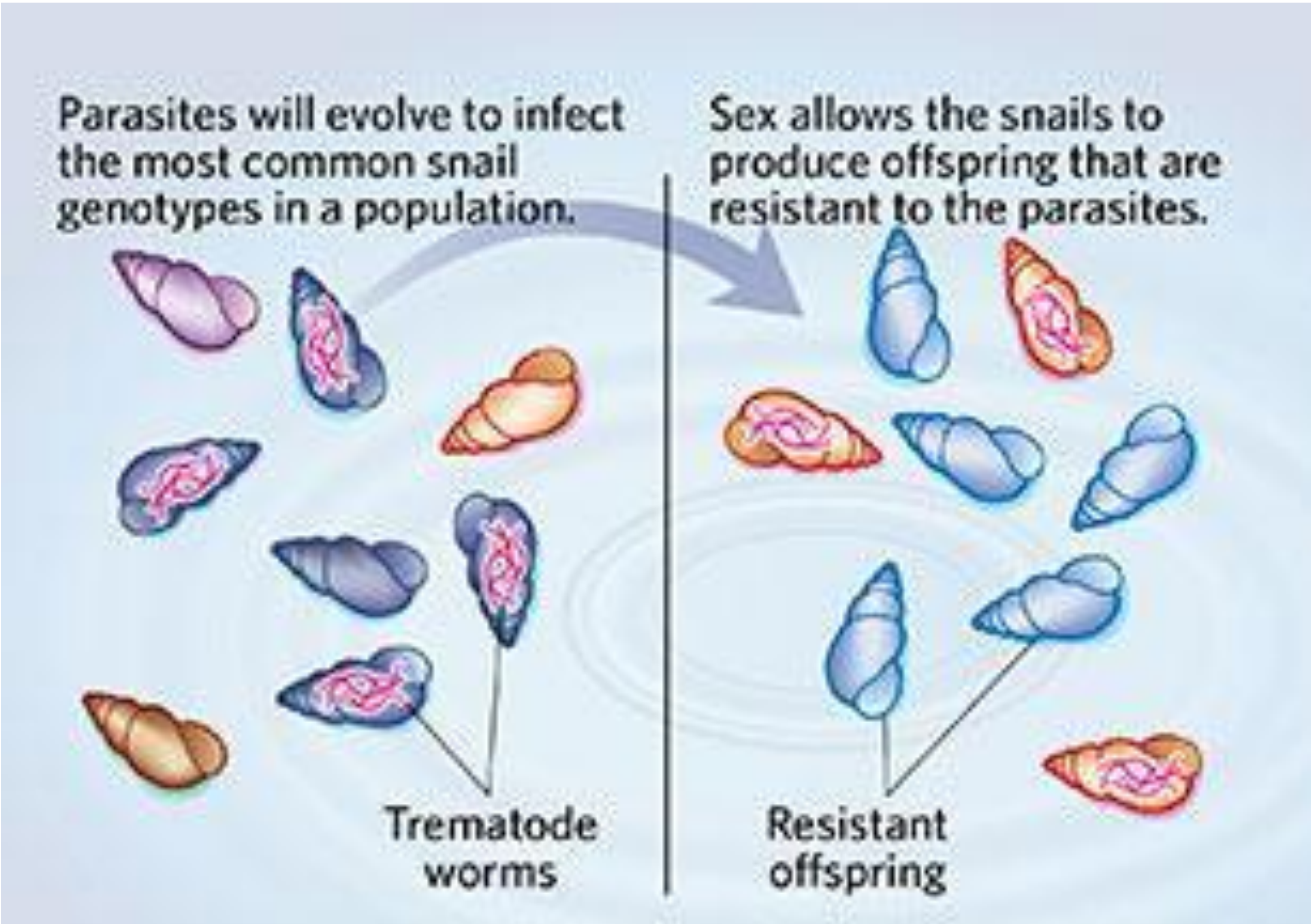
RESPONSE CAPACITIES FOLLOWING EXPOSURE TO INFECTION

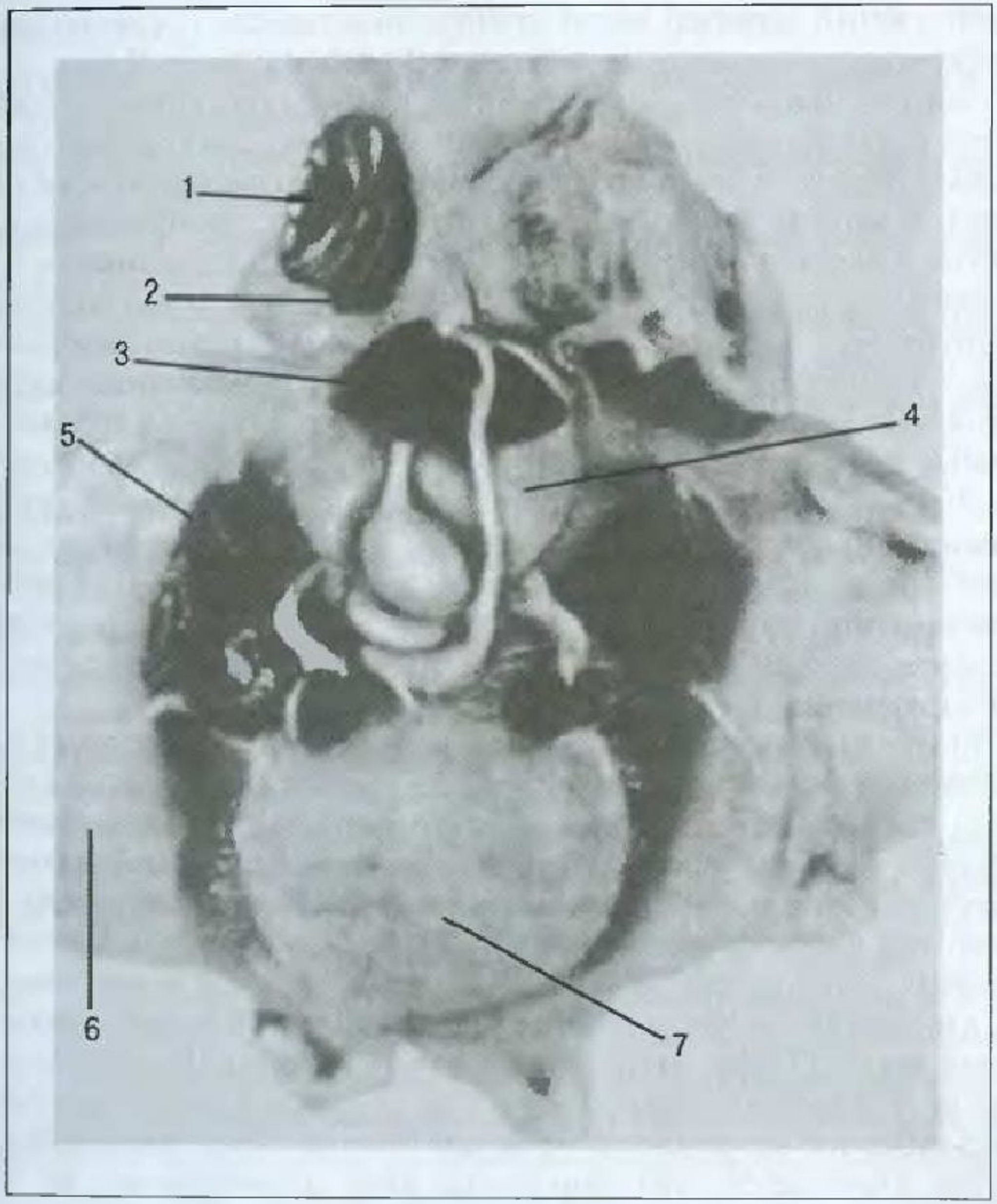
Resistant Snails are more stimulated to make hemocytes following exposure
Bg-Sm: [189]

Resistant snails respond more prominently or differently to infection than susceptible snails
Bg-Sm: [92,100,102,103,185,189-191]
Bg-Ec: [73,76,77,94,187]
Bt-Sm: [188]

Гипотеза черной королевы

Половое размножение помогает устойчивости к паразитам на популяционном уровне





Euprymna scolopes

Рис. 7.7. Диссекция осьминога Eledone cerrosa через 2 дня после внутривенной инъекции большой дозы туши

Лимфоидный орган — белое тело (2) — расположен непосредственно за глазом (1); 3 — задняя слюнная железа; 4 — печень; 5 — жабры; 6 — мантия; 7 — гонады

Строение светового органа эупримны

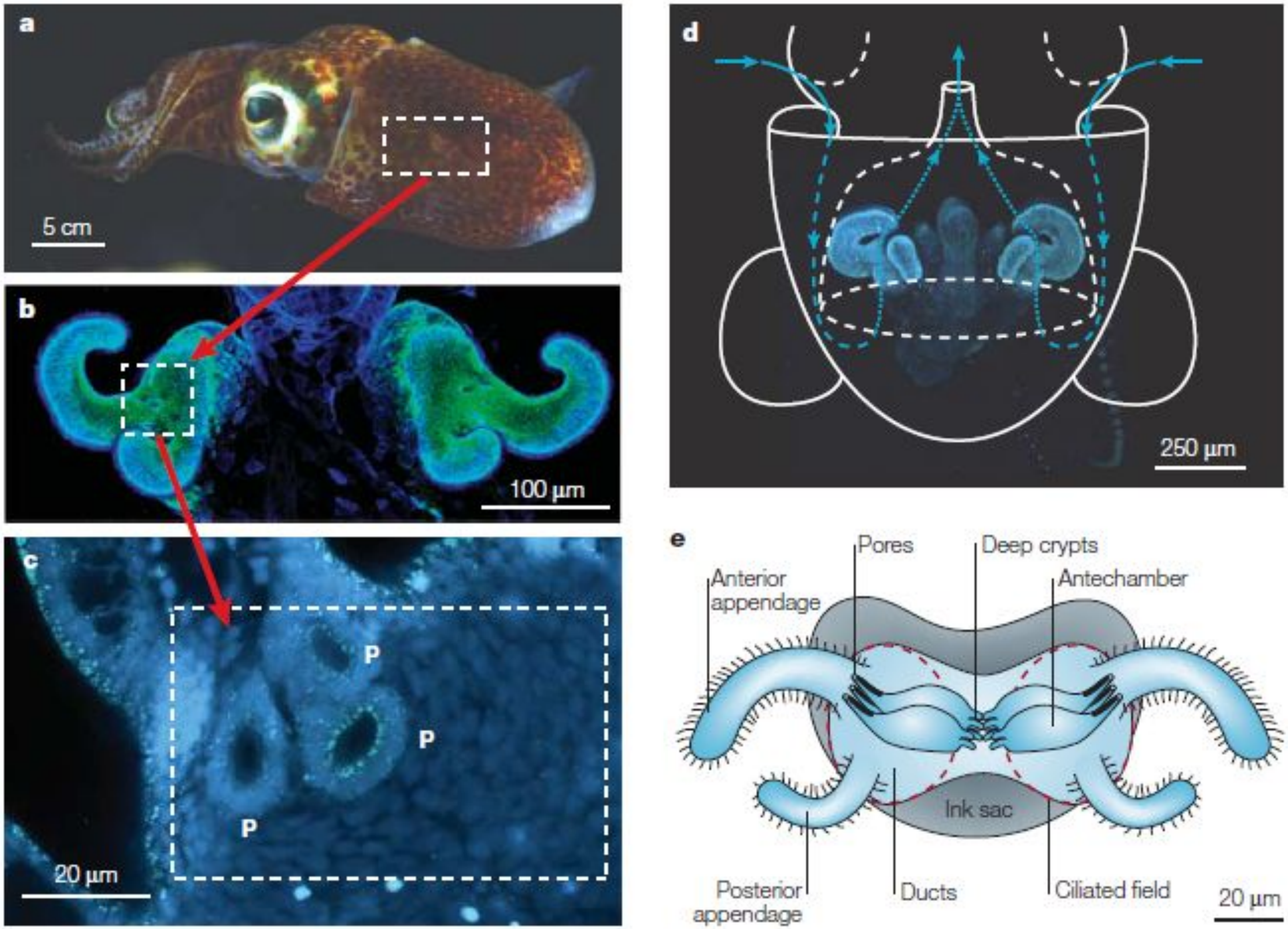
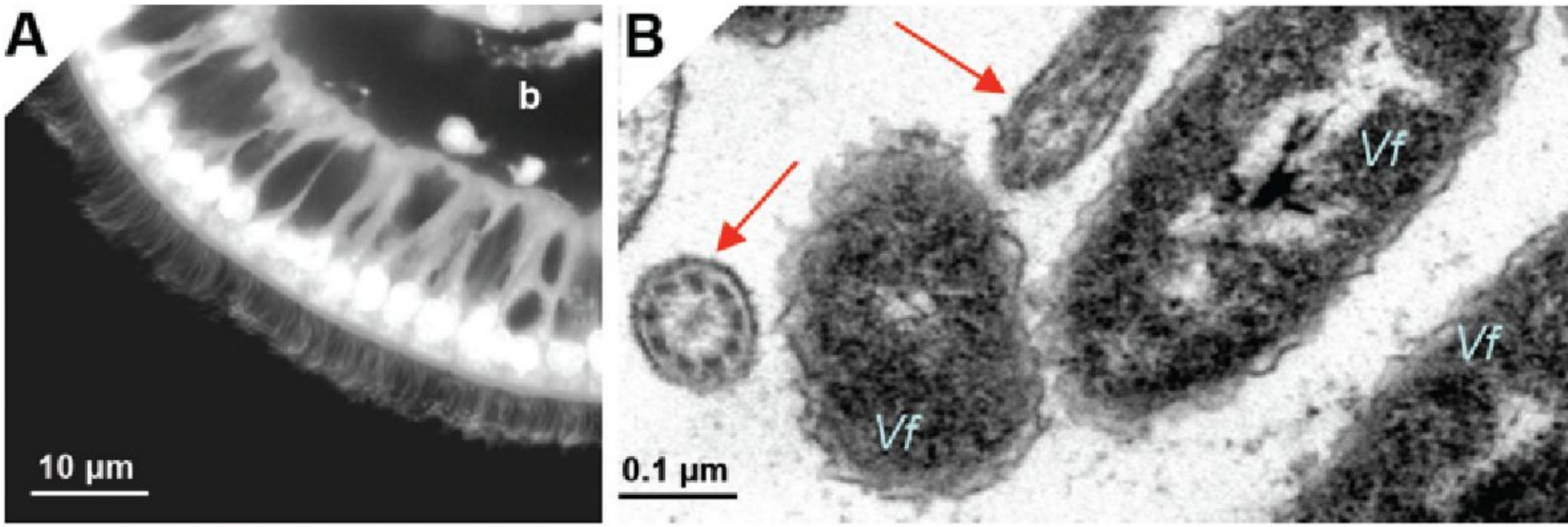
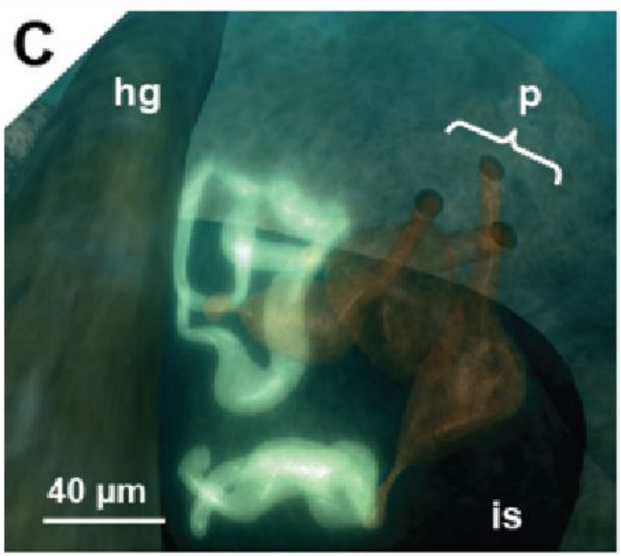
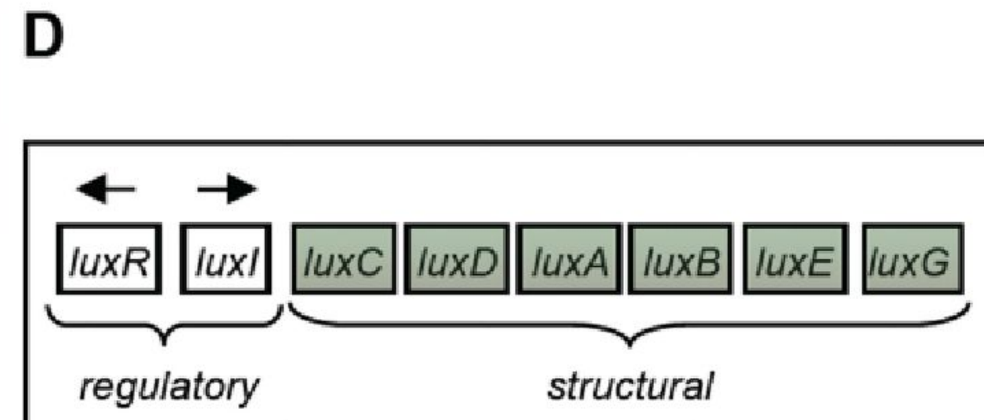


Figure 2 | **The juvenile light-organ system. a** | A host squid swimming in the water column. **b** | A confocal micrograph showing the complex ciliated epithelium on the surface of the juvenile light organ. **c** | A confocal micrograph showing the pores (P) on the surface of the organ through which the symbionts enter host tissues. **d** | The pattern of water flow through the mantle cavity. **e** | The internal components of the squid light organ at hatching. Part **d** is reproduced with permission from REF. 18 © (2000) National Academy of Sciences.

Vibrio fischeri прикрепляются к ресничному эпителию светового органа каракатицы

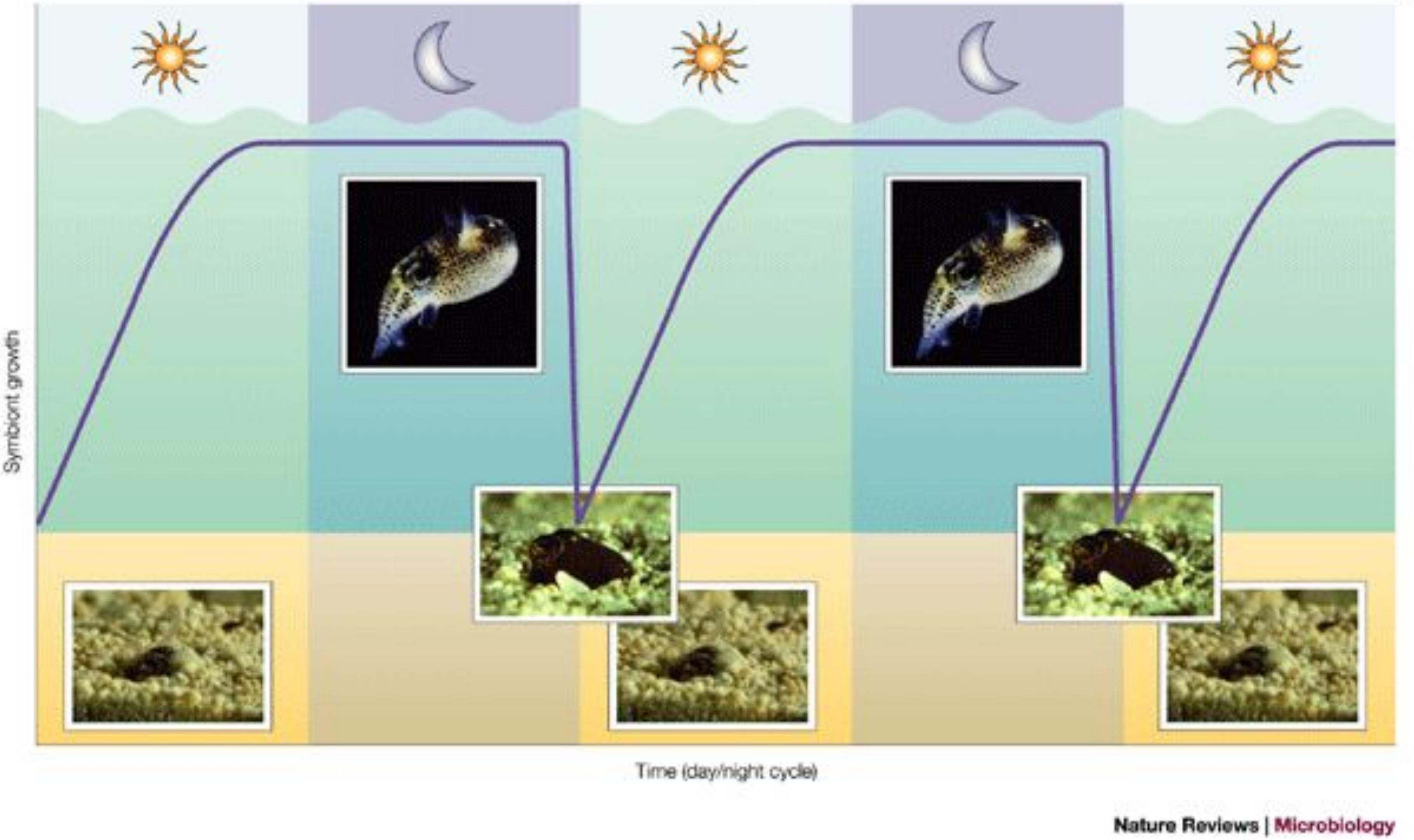




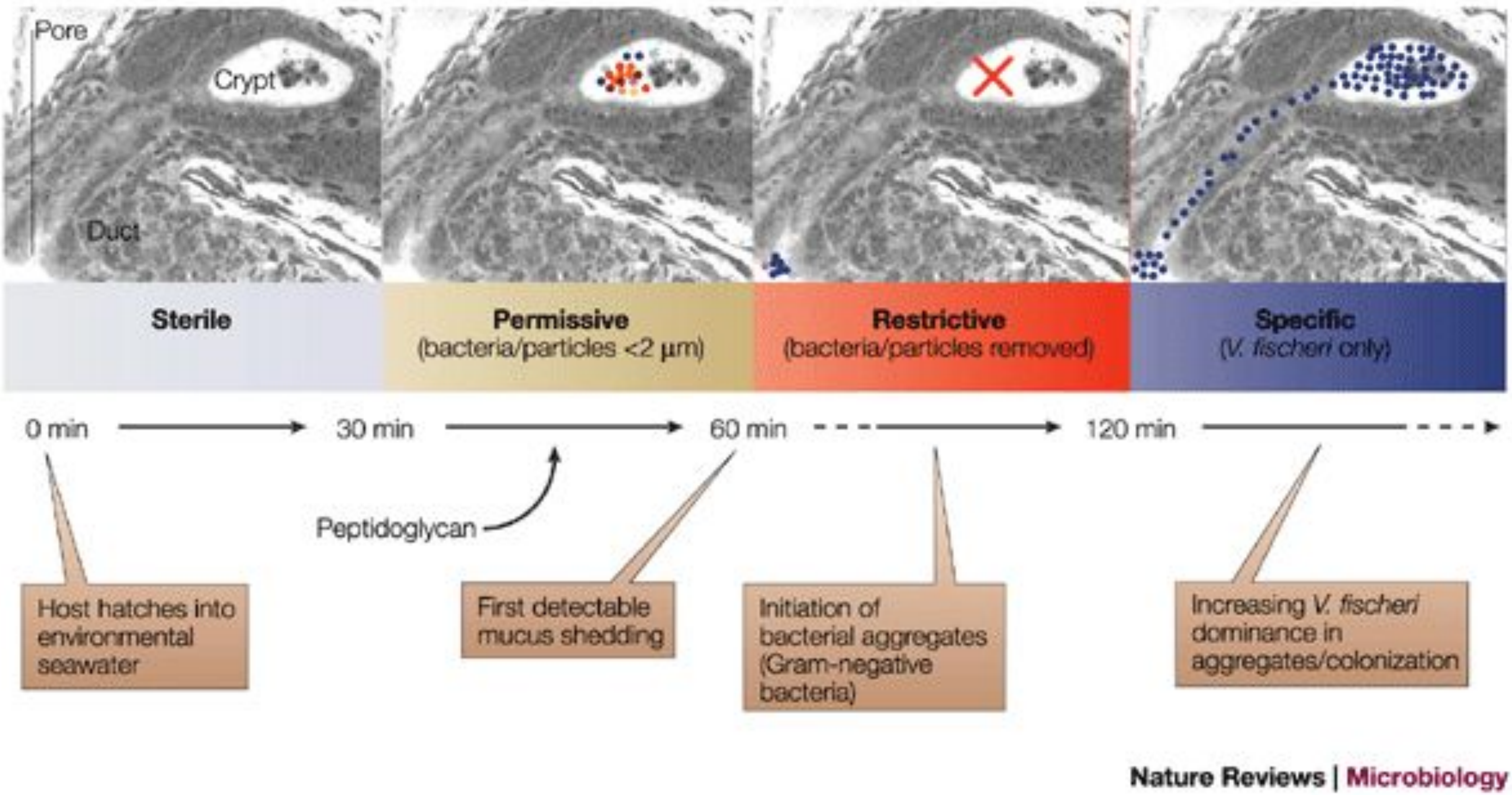


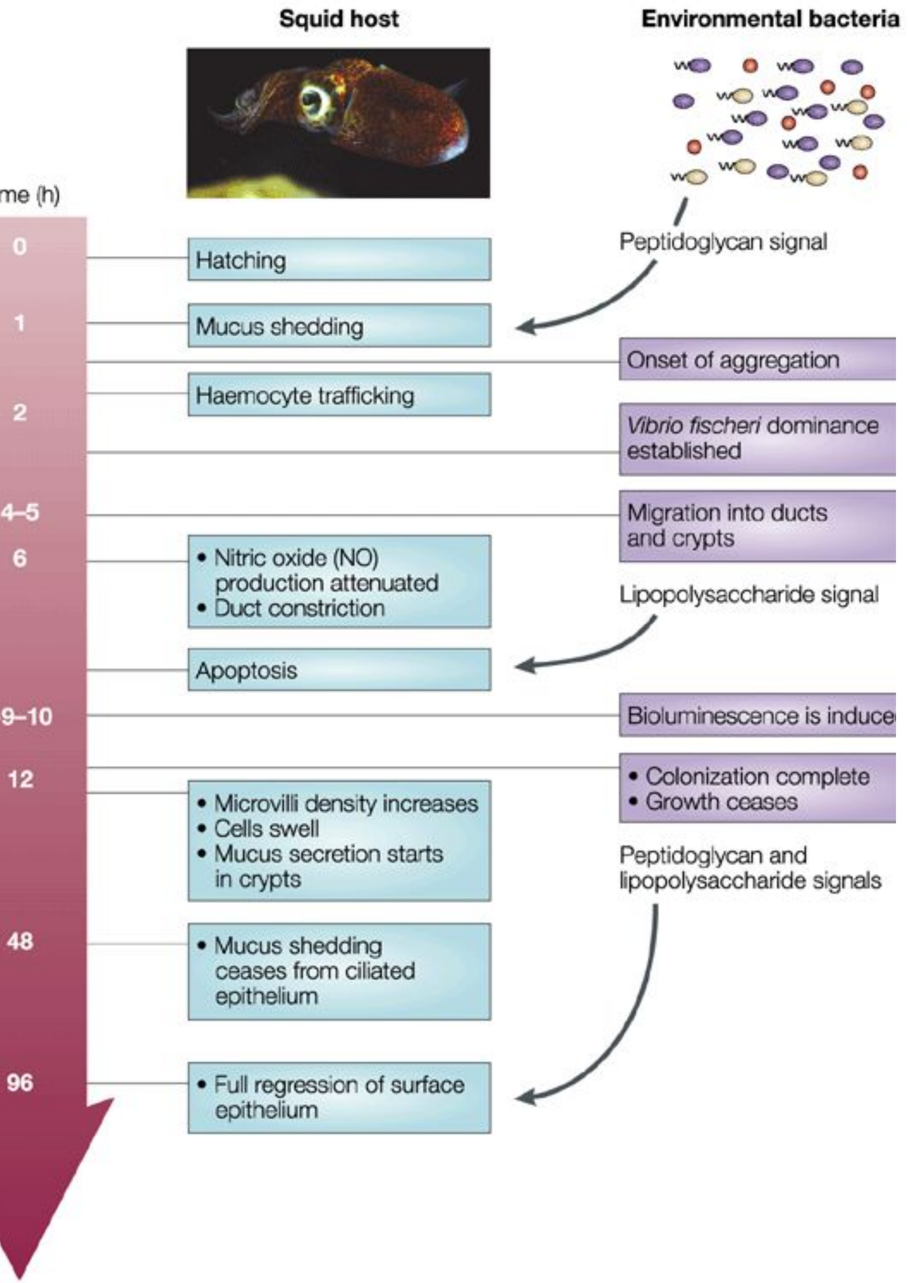
Интенсивность свечения зависит от чувства кворума

Каракатица регулирует количество симбионтов в световом органе



Заселение светового органа каракатицы после рождения





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Модель колонизации

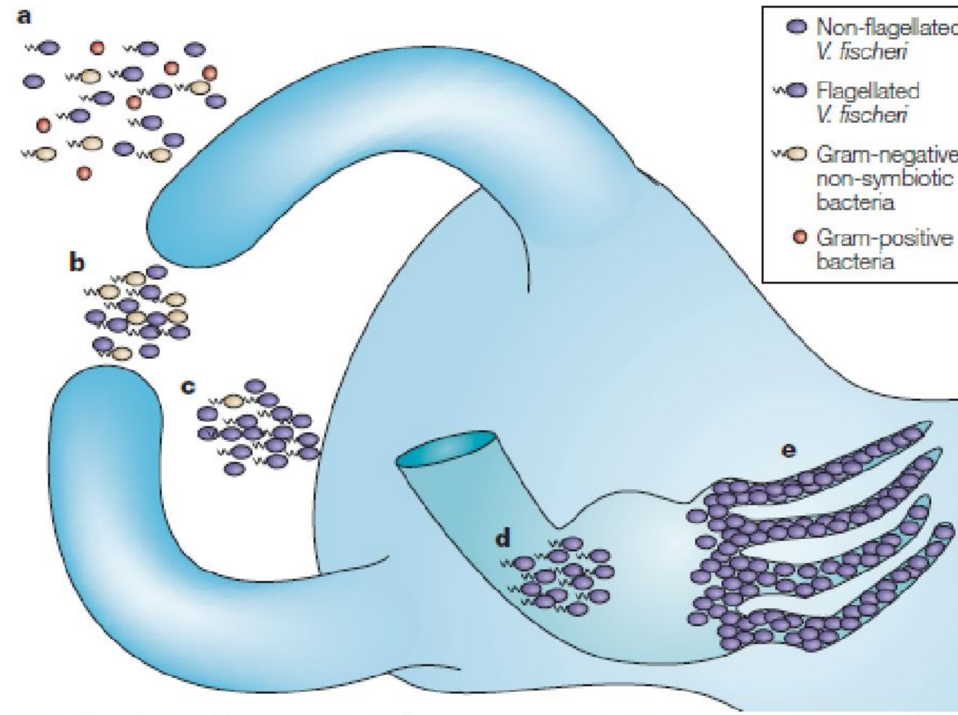


Figure 8 | **The winnowing.** This model depicts the progression of light-organ colonization as a series of steps, each more specific for symbiosis-competent *Vibrio fischeri*. **a** | In response to Gram-positive and Gram-negative bacteria (alive or dead) the bacterial peptidoglycan signal causes the cells of the ciliated surface epithelium to secrete mucus. **b** | Only viable Gram-negative bacteria form dense aggregations. **c** | Motile or non-motile *V. fischeri* out-compete other Gram-negative bacteria for space and become dominant in the aggregations. **d** | Viable and motile *V. fischeri* are the only bacteria that are able to migrate through the pores and into the ducts to colonize host tissue. **e** | Following successful colonization, symbiotic bacterial cells become non-motile and induce host-epithelial cell swelling. Only bioluminescent *V. fischeri* will sustain long-term colonization of the crypt epithelium.

Деградация ресничного эпителия светового органа идет в ответ на MAMP *Vibrio fischeri*

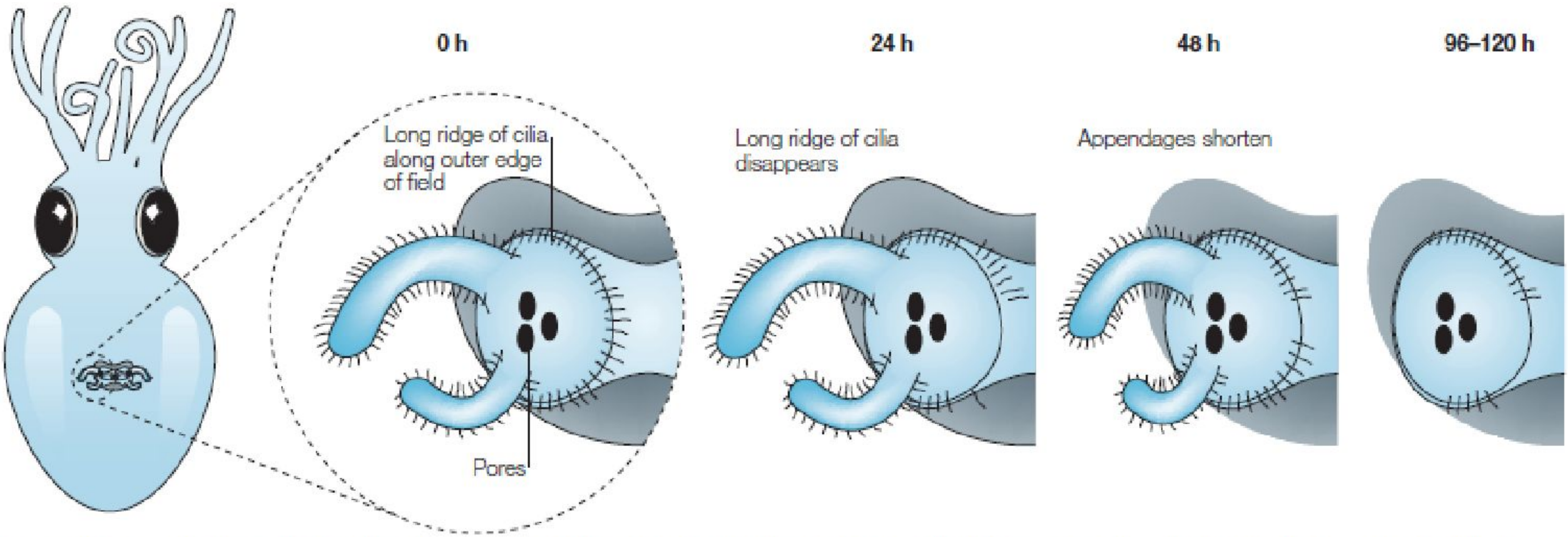
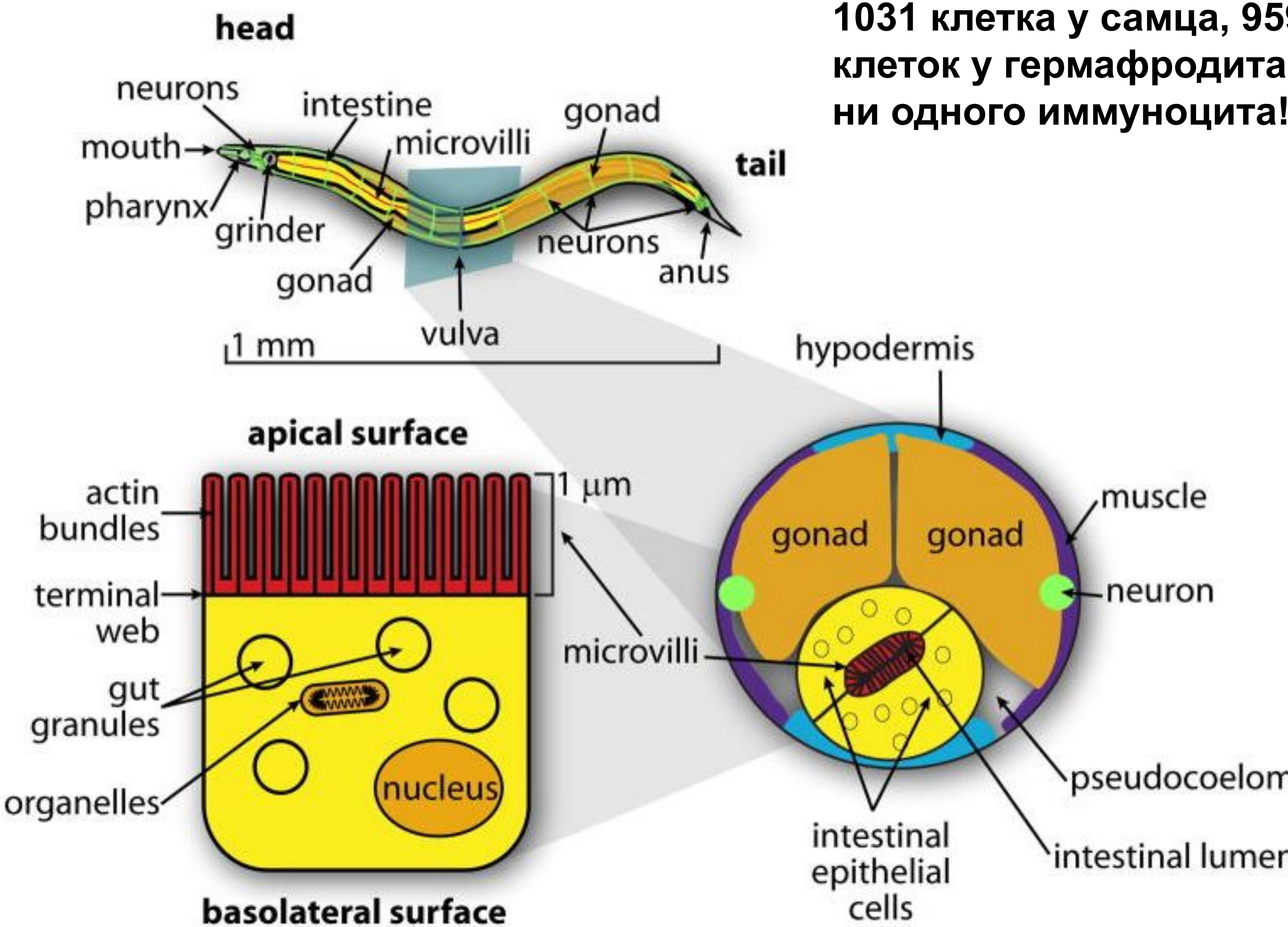


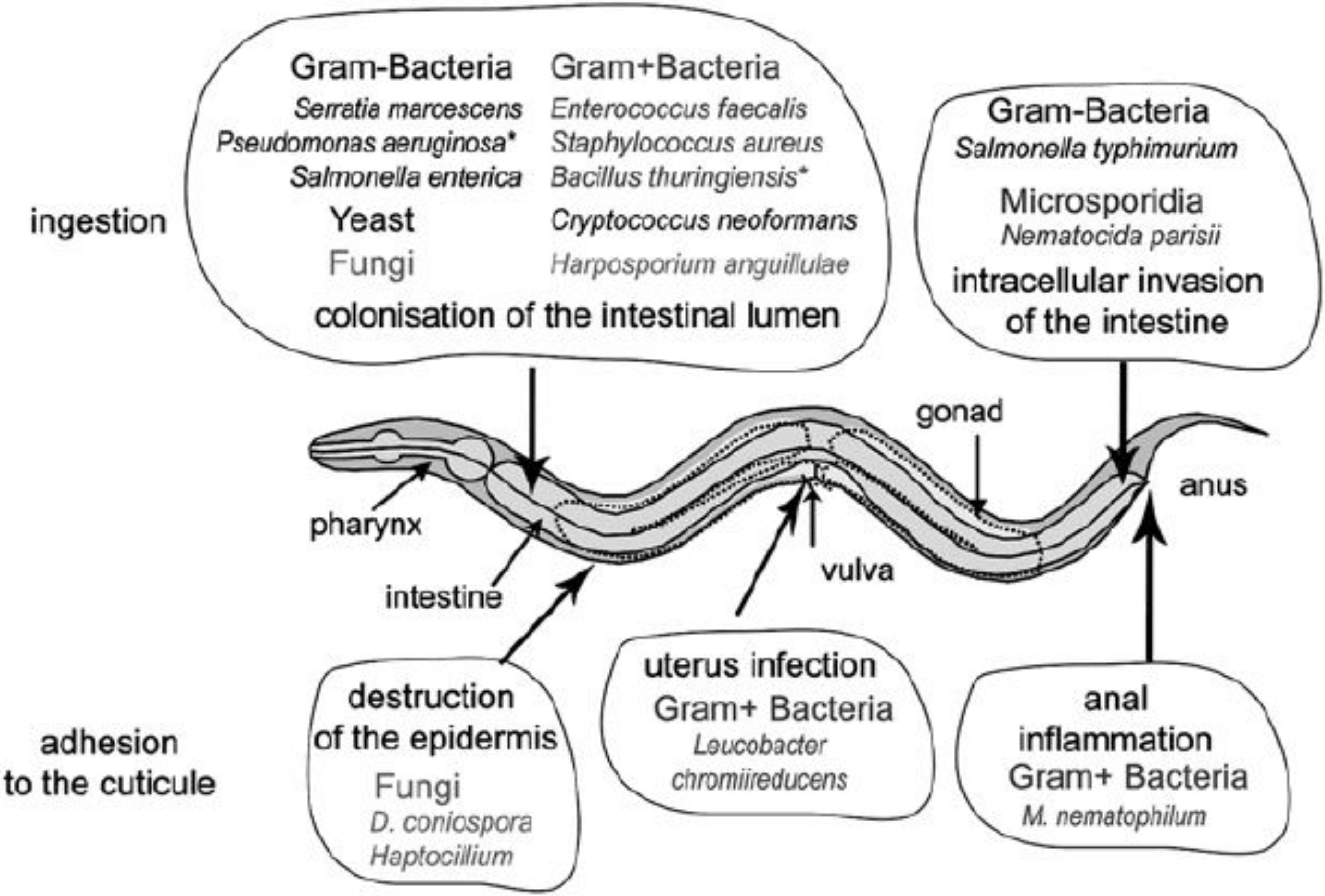
Figure 5 | **The gradual, symbiont-induced regression of the ciliated epithelium of the juvenile light organ.** Schematic depicting the loss of host ciliated epithelial fields after successful colonization by *Vibrio fischeri*.

Общее строении нематоды

1031 клетка у самца, 959 клеток у гермафродита и ни одного иммуноцита!



Патогены нематод и пути их проникновения



Грибковые инфекции нематод

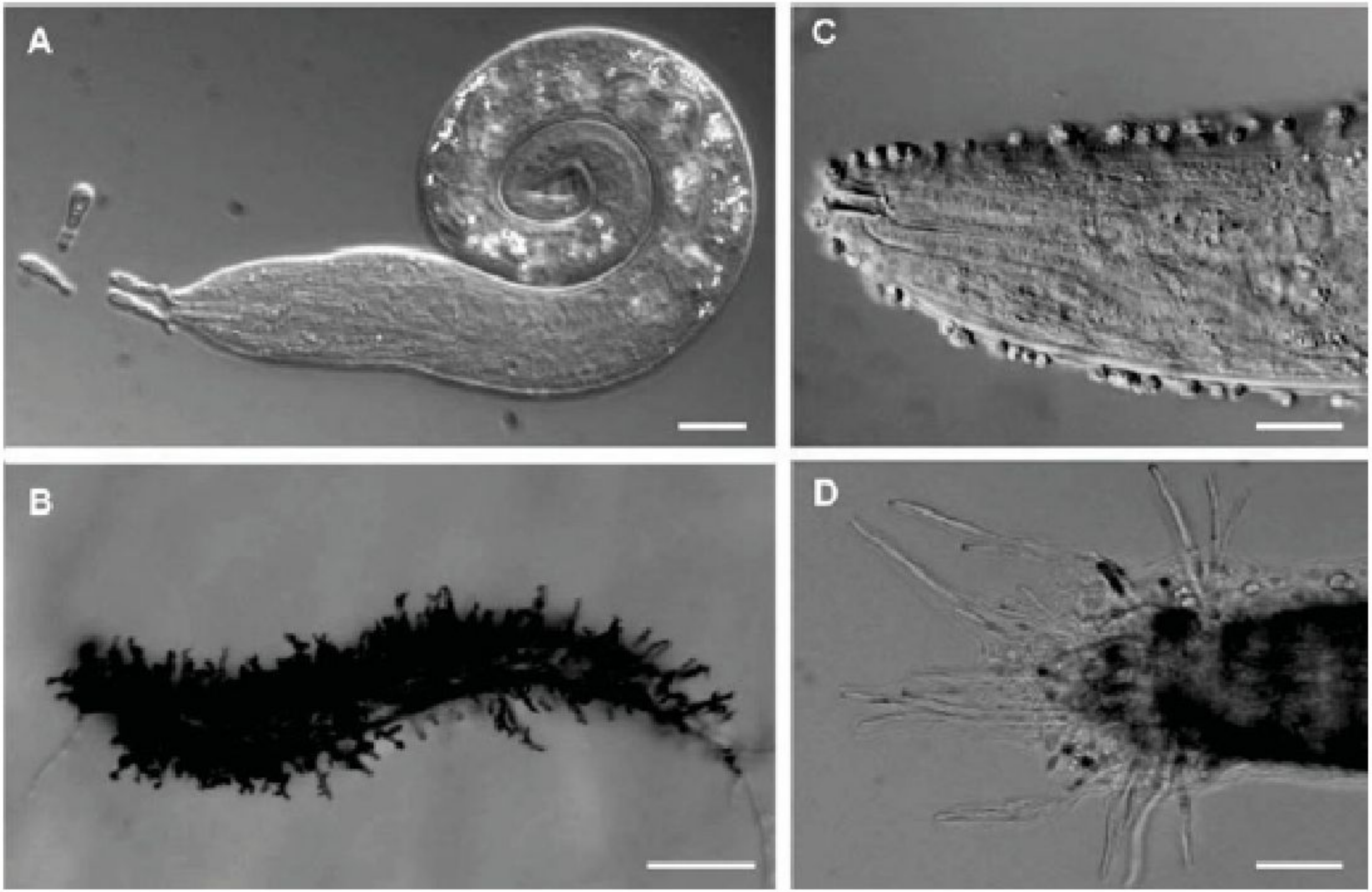
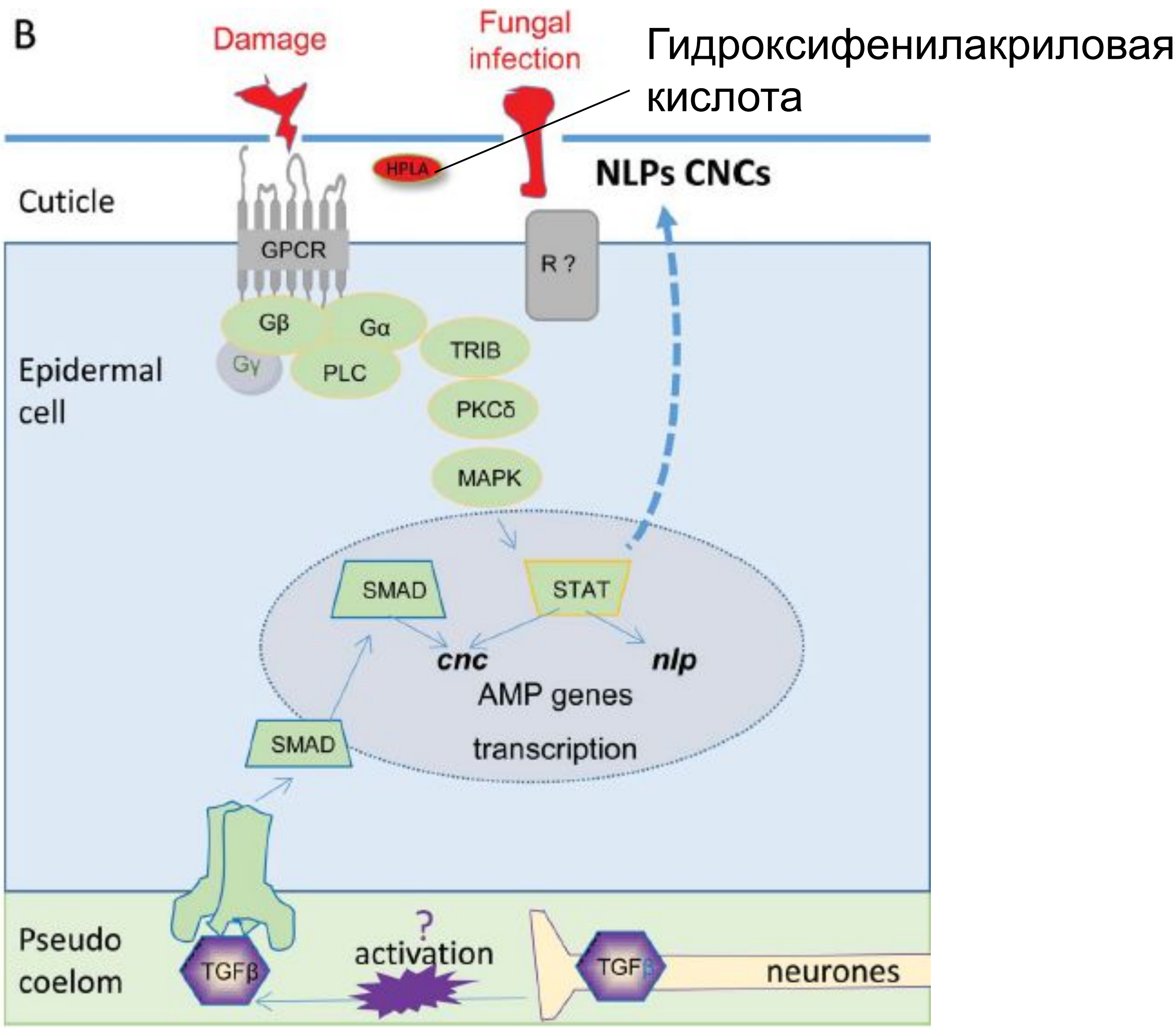
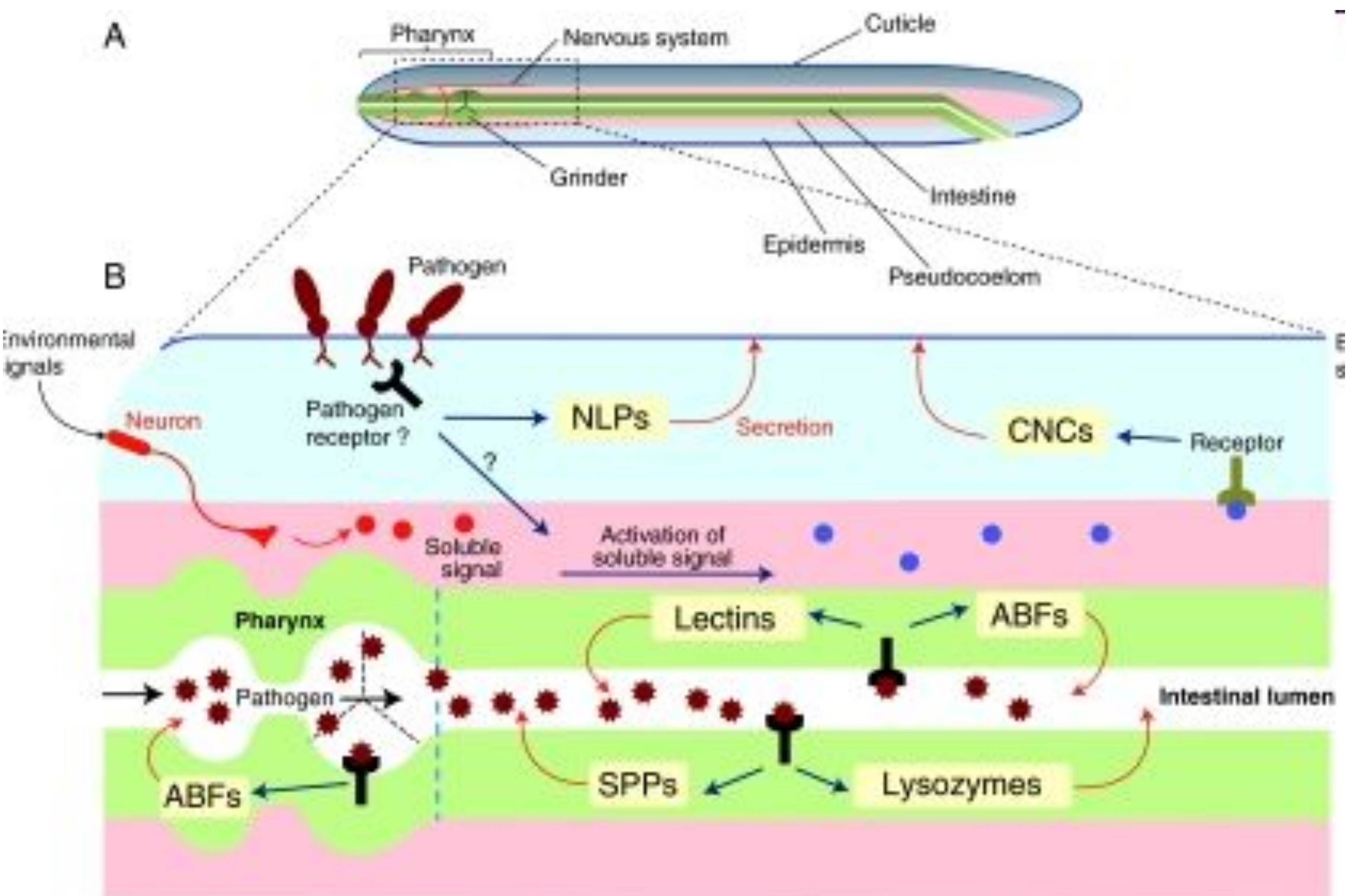


Figure 2. Fungal infection of *C. elegans*. (A and B) *D. coniospora*, (C and D) *Haptocillium*. (A and C) adhesion of the spores to the cuticle after few hours, (B and D) after 2 days fungal hyphae grow out of the worm. Scale bars are 10 µm (A), 100 µm (B) and 50 µm (C and D).

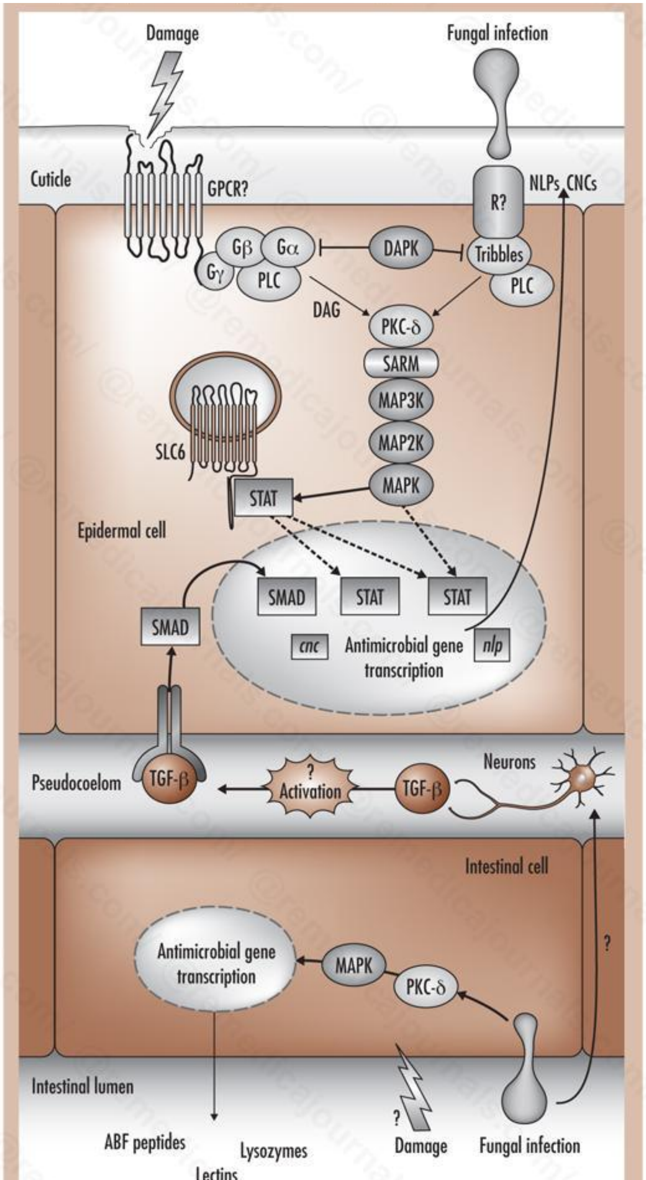
MAP-киназный каскад как сигнал о повреждении покровов

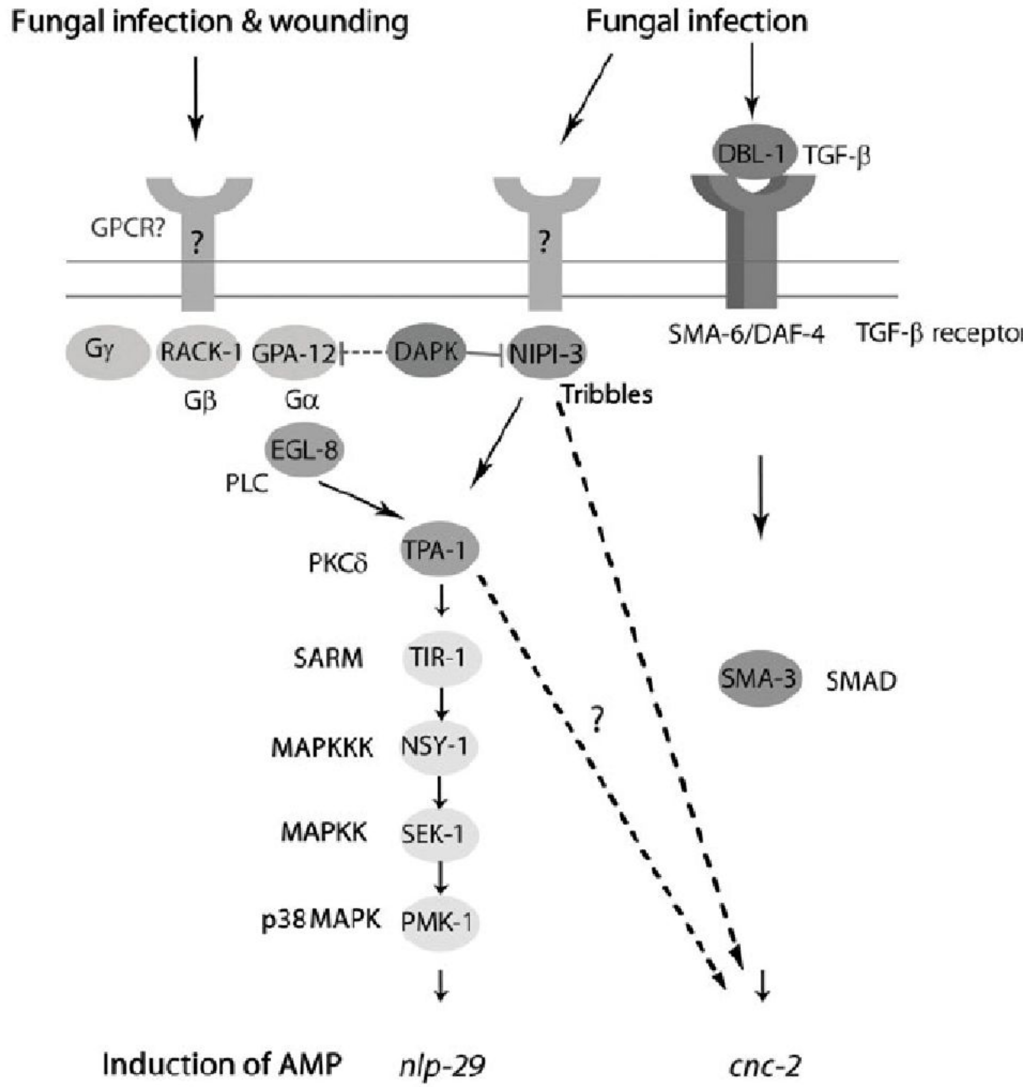


Иммунная система нематод



Сигнальные пути, вовлеченные в иммунный ответ нематоды, еще не известны полностью





Различие сигнальных путей

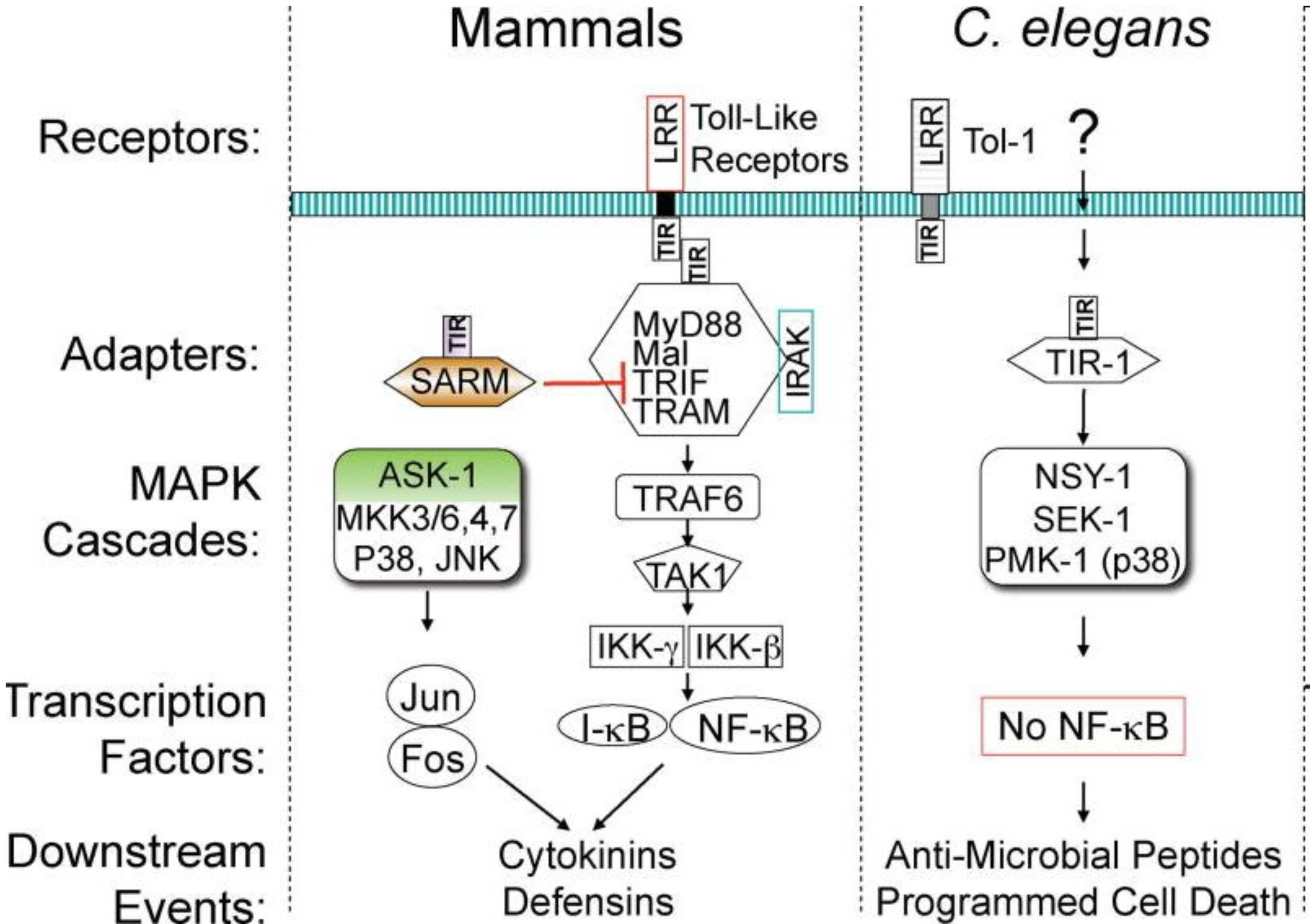
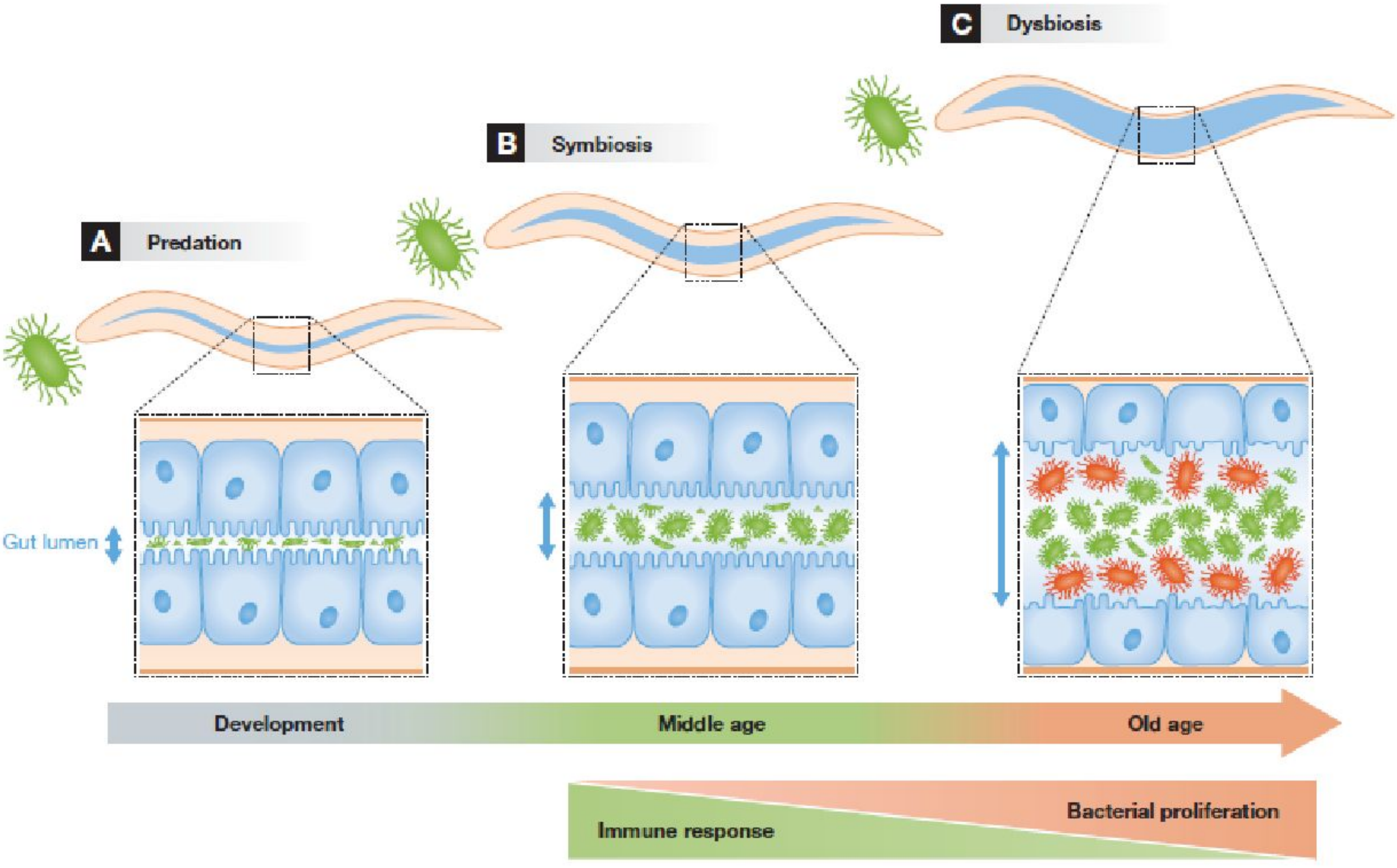


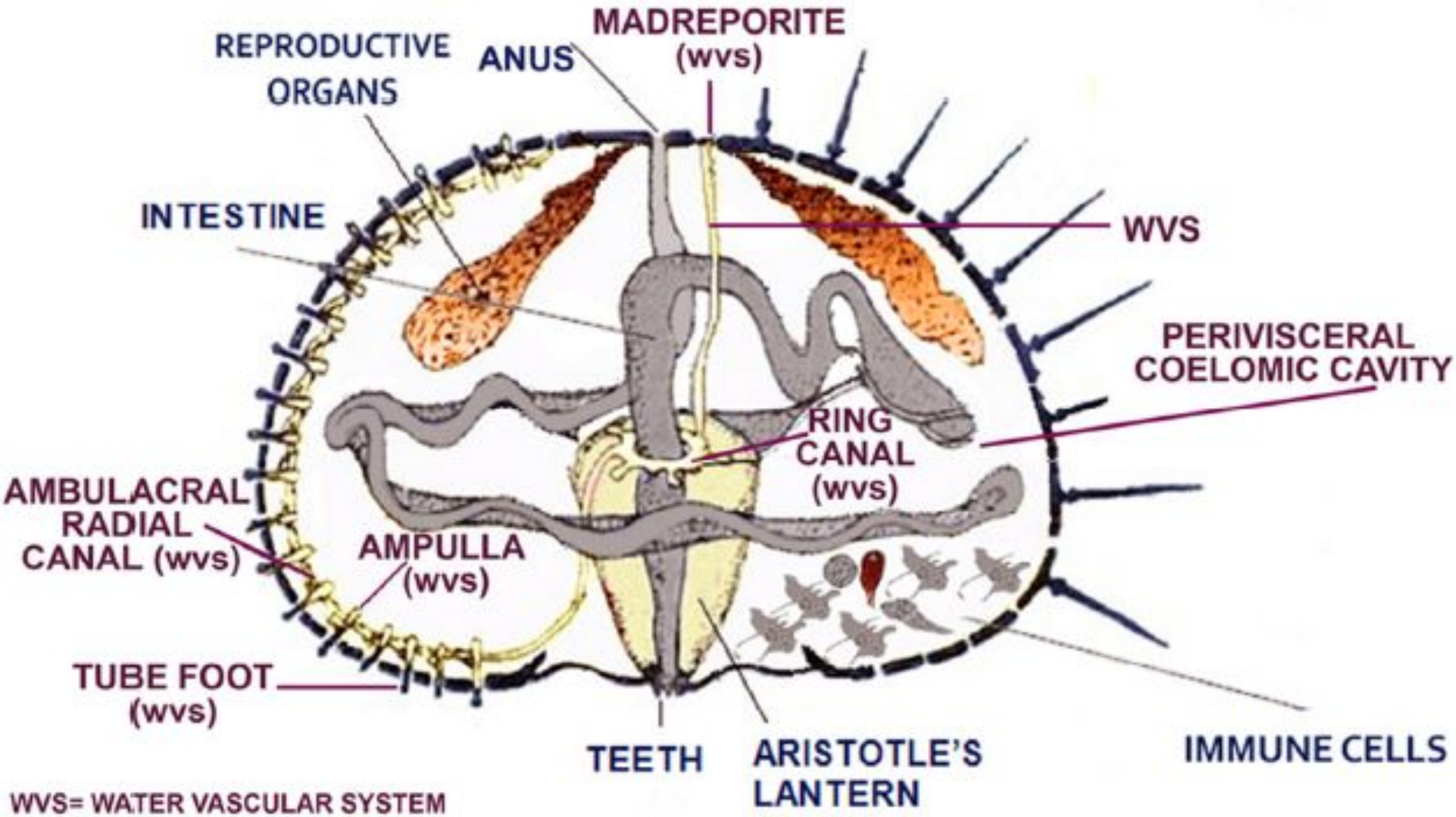
Table 1. Summary of the major signalling pathways in the *C. elegans* Immune System (updated from ref. 86)

Pathway	Tissue	Components	Homologues	References
p38 MAPK	Epidermis	GPA-12, RACK-1	G protein subunits	82
		EGL-8, PLC-3	Phospholipase C	82
		NIPI-3	Tribbles kinase	35
	Epidermis and intestine	TPA-1	Protein kinase C	82,87
		TIR-1	SARM	24,34,88
		NSY-1, SEK-1, PMK-1	MAP kinases	12,35
FSHR-1	Intestine	FSHR-1	G protein coupled receptor	26
ZIP-2	Intestine	ZIP-2	b-zip transcription factor	65
Insulin signalling	Nervous system	INS-7	Insulin-like peptide	76
	Intestine	DAF-2	Insulin receptor	42
		AGE-1	PI3 kinase	42
		AKT-1, AKT-2	Akt kinase	43
		DAF-16	FOXO transcription factor	42
TGF-β	Nervous system	DBL-1	TGF-β	54,55
	epidermis	SMA-6	TGF-βreceptor	55
		SMA-3	SMAD protein	55
Wnt/Hox	Intestine/ Hindgut	BAR-1	β-catenin	61
		EGL-5	Hox transcription factor	61,64
ERK MAPK	Hindgut	LIN-45, MEK-2, MPK-1	ERK MAP kinase	39
		EGL-8	Phospholipase C	89
		SUR-2	Mediator component	39
UPR[1]	Intestine	XBP-1	X box protein	50,52
		HSP-4	Heat shock protein	
	Pharynx	CED-1, C03F11.3	Scavenger receptor	51
Autophagy	Intestine	BEC-1, LGG-1	ATG proteins	16

Микробиота нематоды и старение



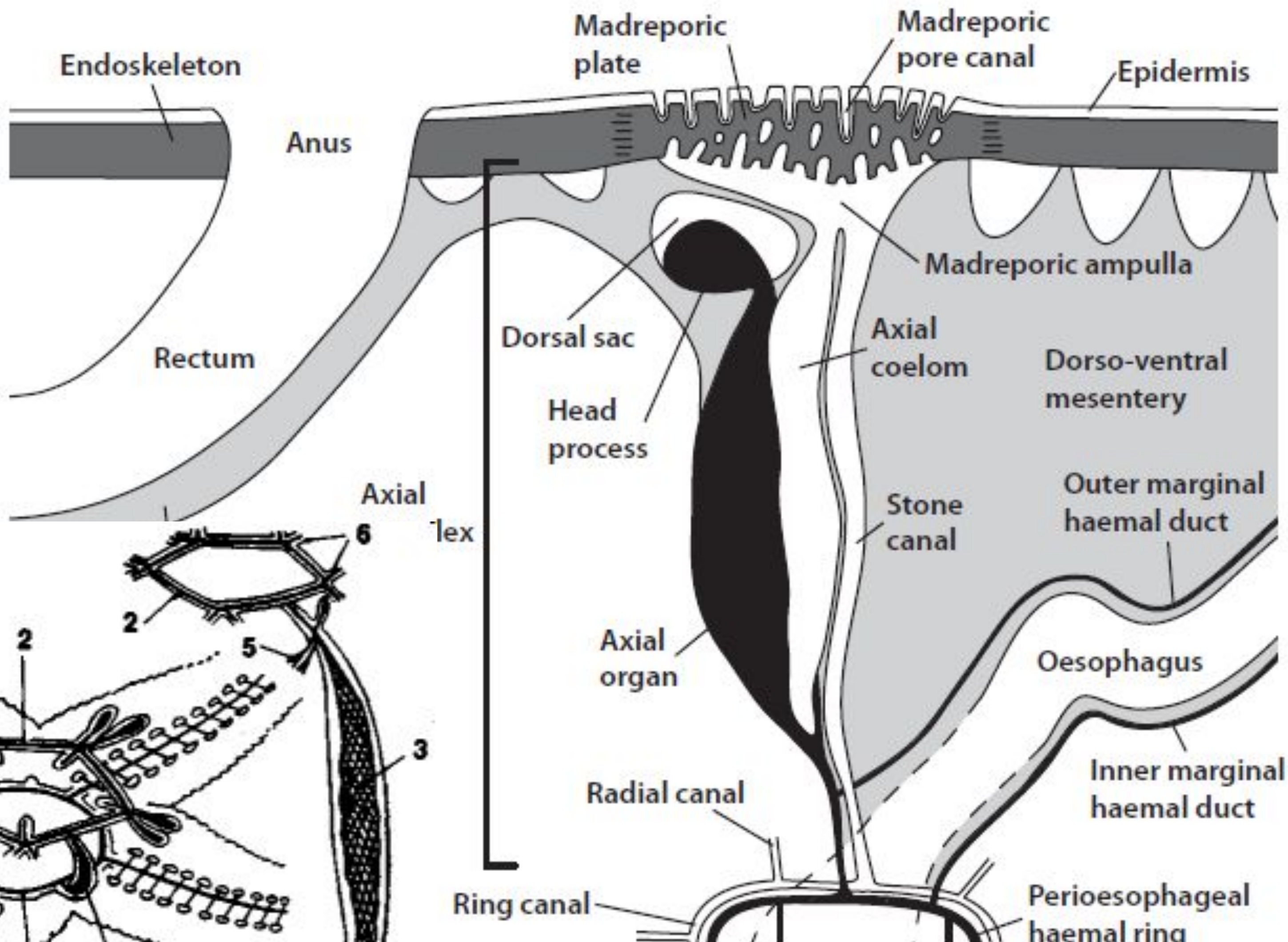
Общая схема строения морского ежа

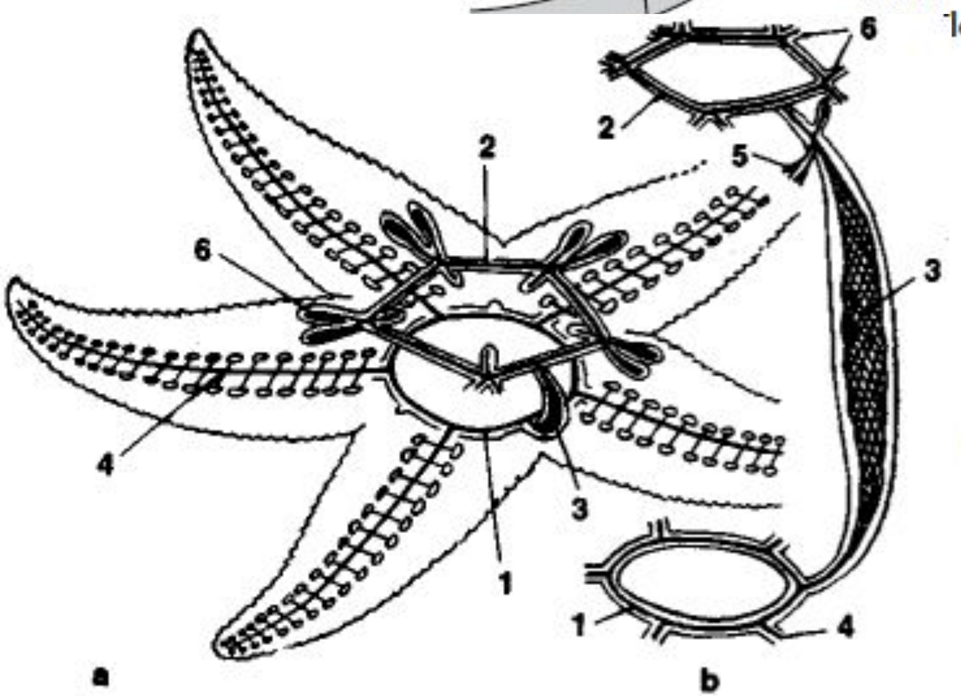


Характеристика генов иммунной системы иглокожих и хордовых

	Amphioxus[a]	Sea squirt[b]	Sea urchin[c]	Human[d]
Complement				
C3/C4/C5[e]	3	2	4	4
Bf/C2[f]	2	3	3	2
MASP[g]/Clr,s[h]	5/44[i]	4	0/2[i]	4
TCC[j]	9	11	0	6
Clq[k]-like	39	2	4	23
LRR-containing				
TLR[l]	72	2	222	10
NLR[m]	118	0/28[n]	203	25
LRR-Ig[o]	125	ND[p]	22	30
Other mediators				
SRCR[q]	270	5	218	16
PGRP[r]	18	0	5	6
GNBP[s]	5	3	3	0
CTL[t]	1200/717[u]	ND[p]	104	81
VCBP[v]	5/10[w]	4	0	0
Cytokines				
TNF[x]	21	4	4	20
TNFR[y]	31	3	9	26
IL-17[z]	9	2	30	9

Аксиальный орган иглокожих



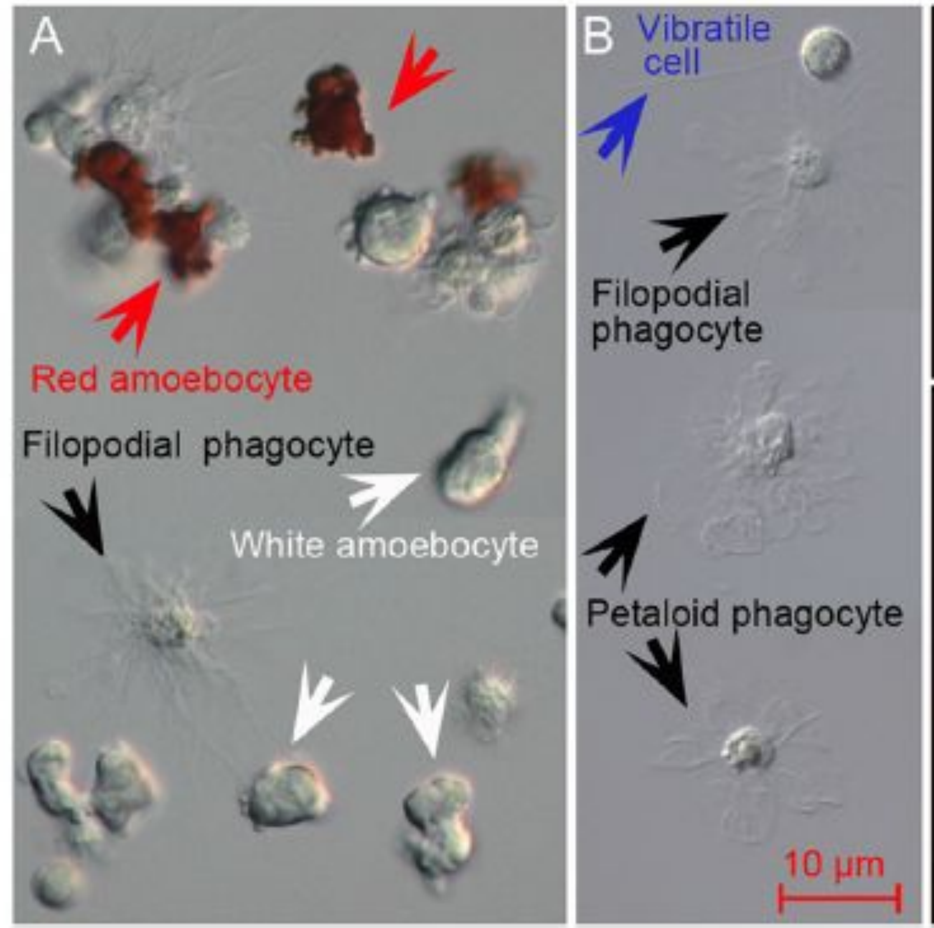


«Формула» целомоцитов морского ежа

Table 1. Coelomocytes in sea urchins

Cell Type	% in Coelomic Fluid	Function
Phagocyte Types Type 1—Discoidal cells Type 2—Polygonal cells Type 3—Small phagocytes	Total phagocytes *Sp** 40-80% *Sd* 67% *Pl* 80%	Encapsulation, Opsonization, Graft rejection, Chemotaxis, Phagocytosis, Antibacterial activity, Cellular clotting
Red spherule cells	*Sp* 7-40% *Sd* 8% *Pl* 4.7%	Oxygen transport. Antibacterial activity from echinochrome A.
Colorless spherule cells	*Sp* 3.7-25% *Sd* 6.5% *Pl* 7.8%	Cytotoxicity, Clotting?
Vibratile cells	*Sp* 11.9-20% *Sd* 18.5% *Pl* 7.5%	Movement or agitation of coelomic fluid? Associated with clotting.

Целомоциты морского ежа:



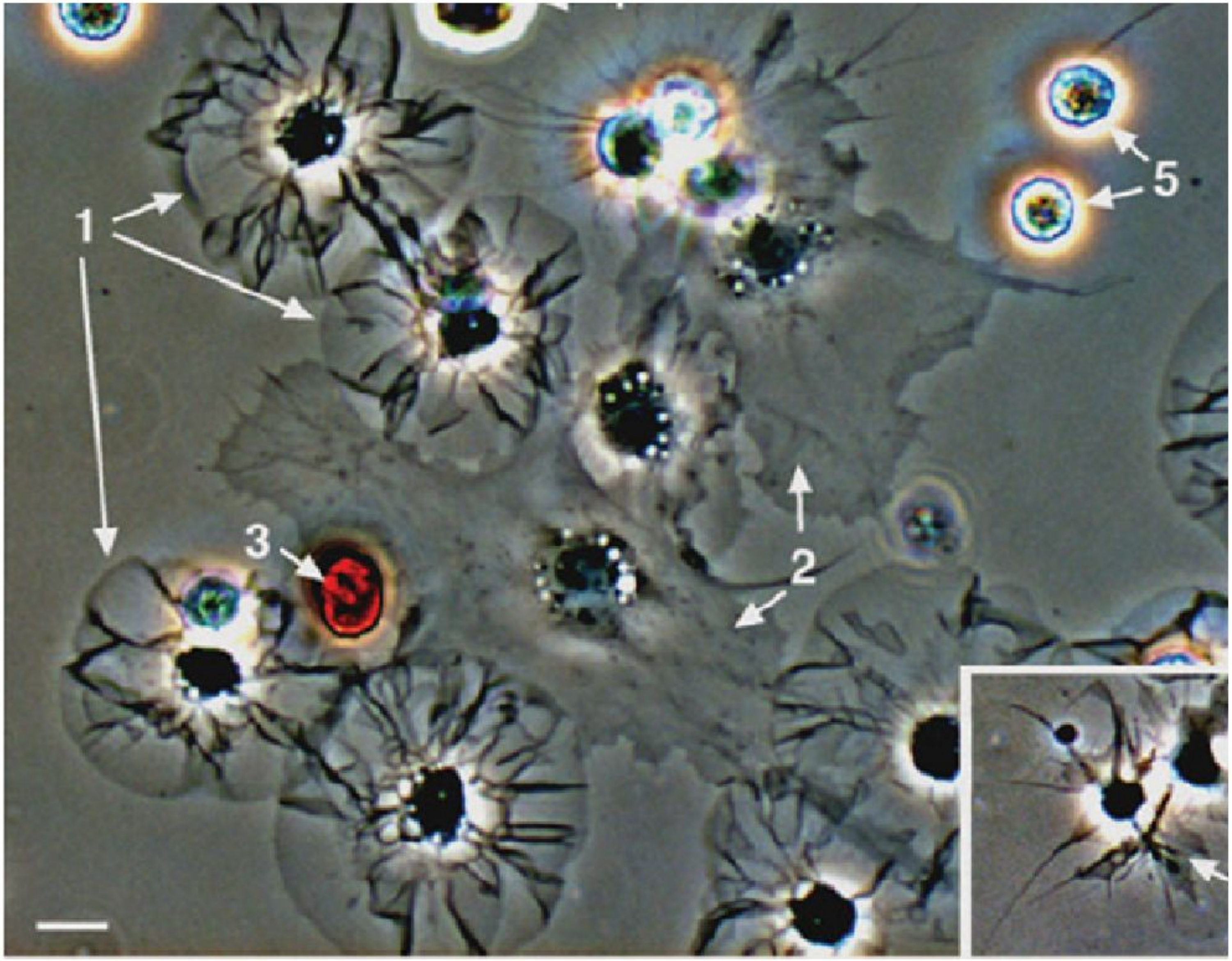
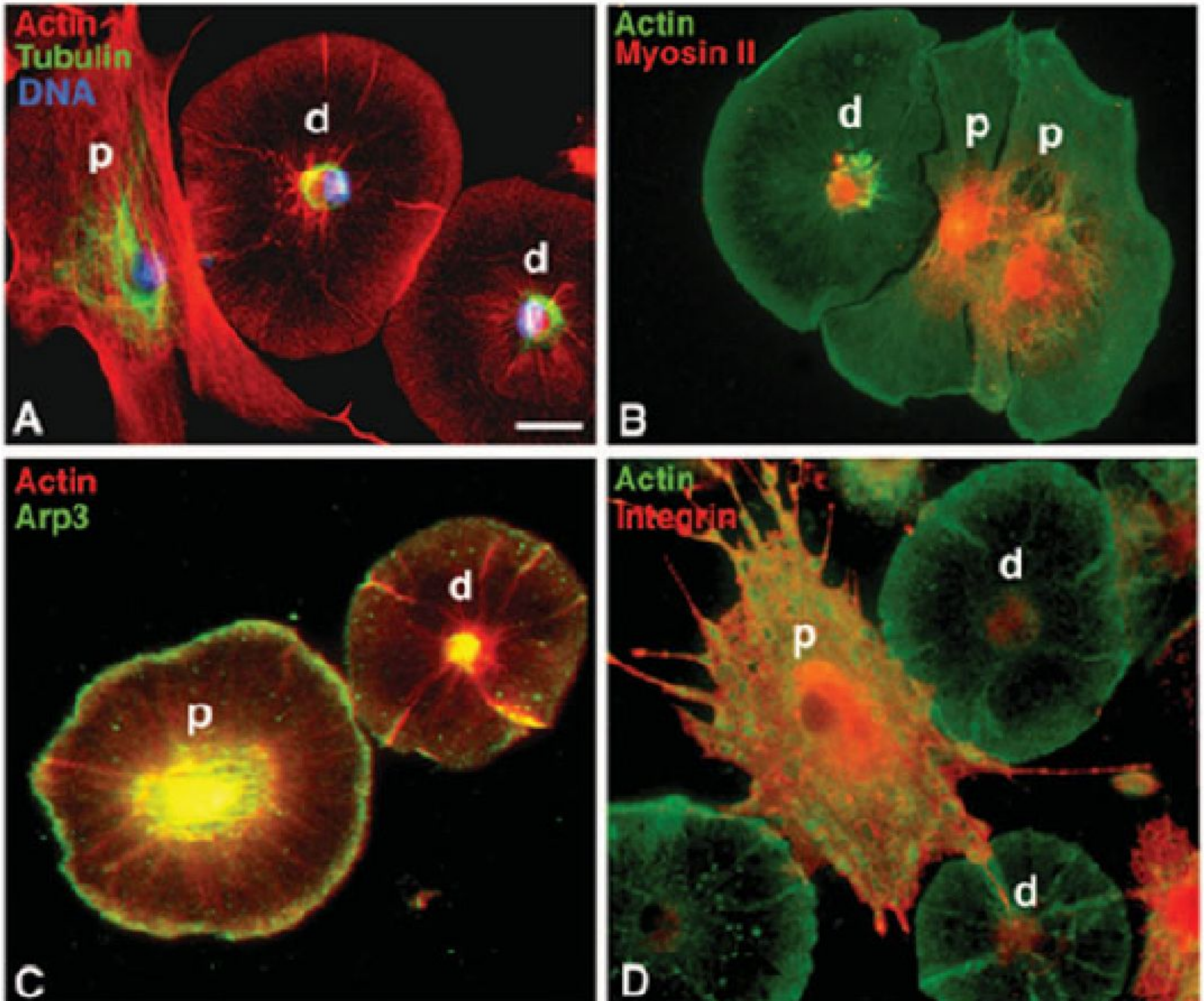
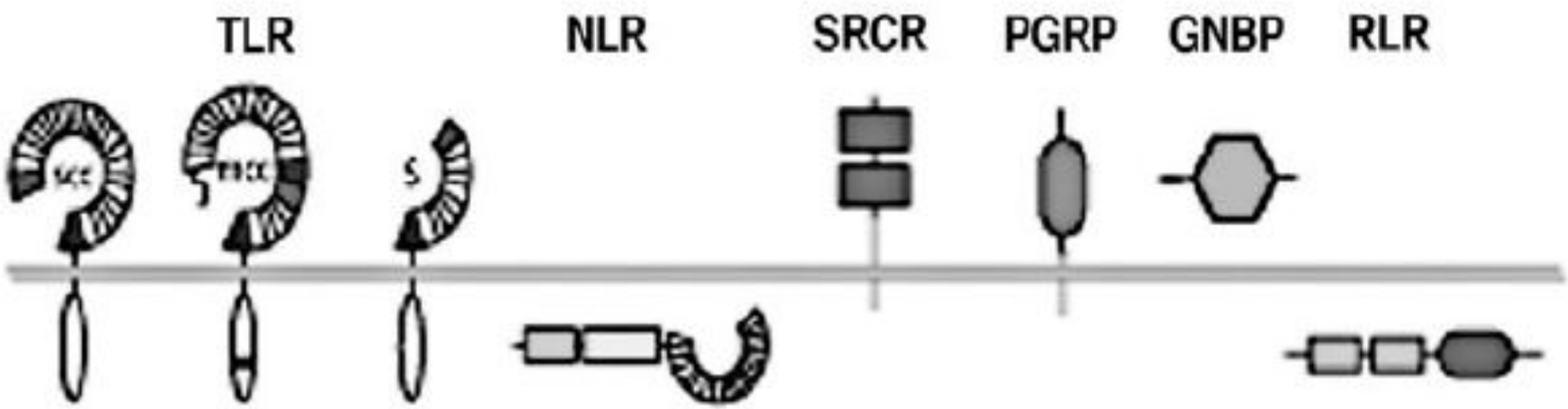


Figure 2. Coelomocytes from the sea urchin *S. droebachiensis*. Cells were withdrawn in anticoagulant and settled onto a glass coverslip. All cell types are shown and labeled with numbers. Large phagocytes; 1 = discoidal phagocyte; 2 = polygonal phagocyte; 3 = red spherule cell; 4 = colorless spherule cell; 5 = vibratile cell (the lower cell has lost the prominent flagellum seen in the upper cell). Inset; 6 = small phagocyte. Bar = 10 microns.

Полигональные и дисковидные фагоциты отличаются организацией цитоскелета

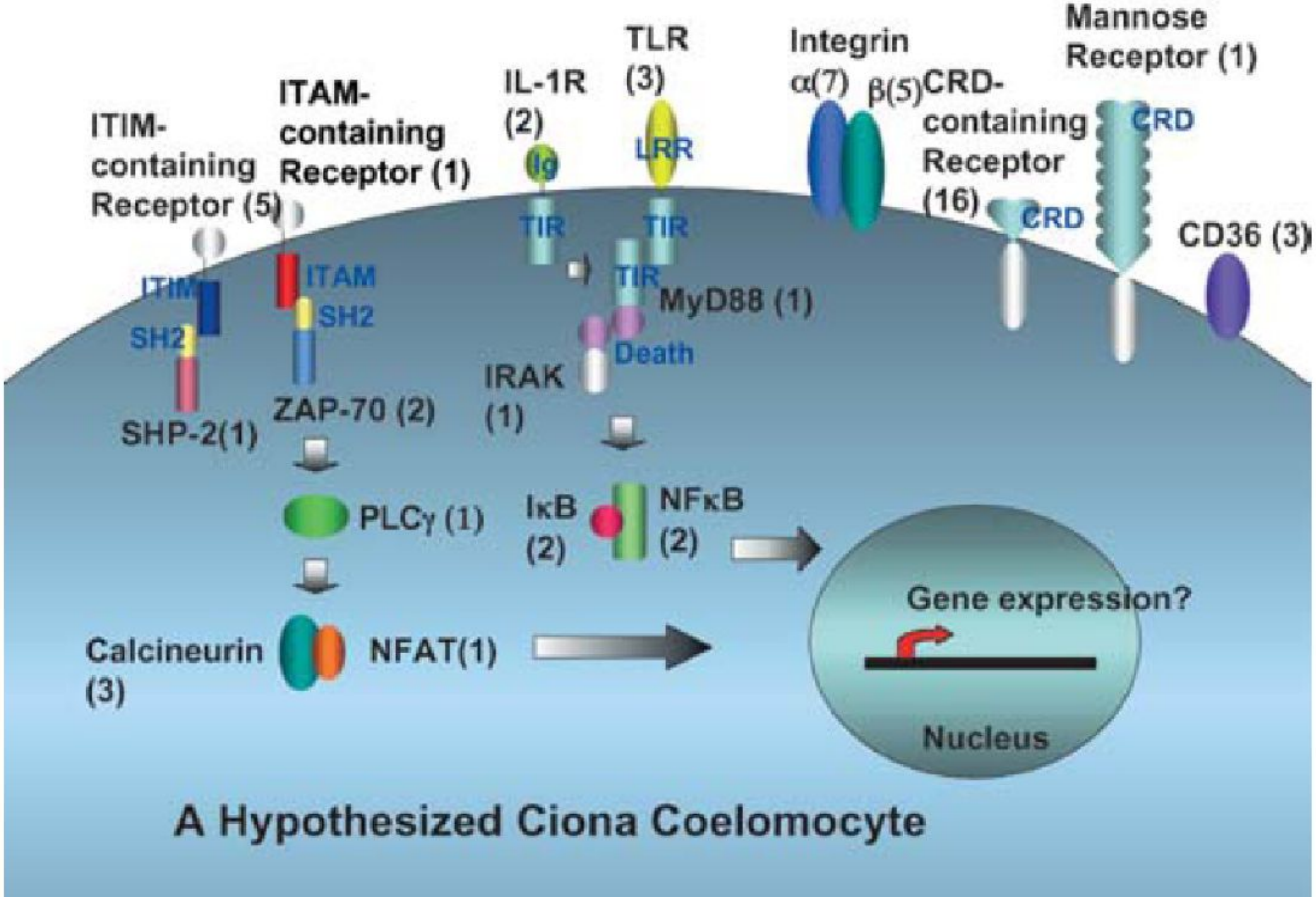


Рецепторные белки иглокожих

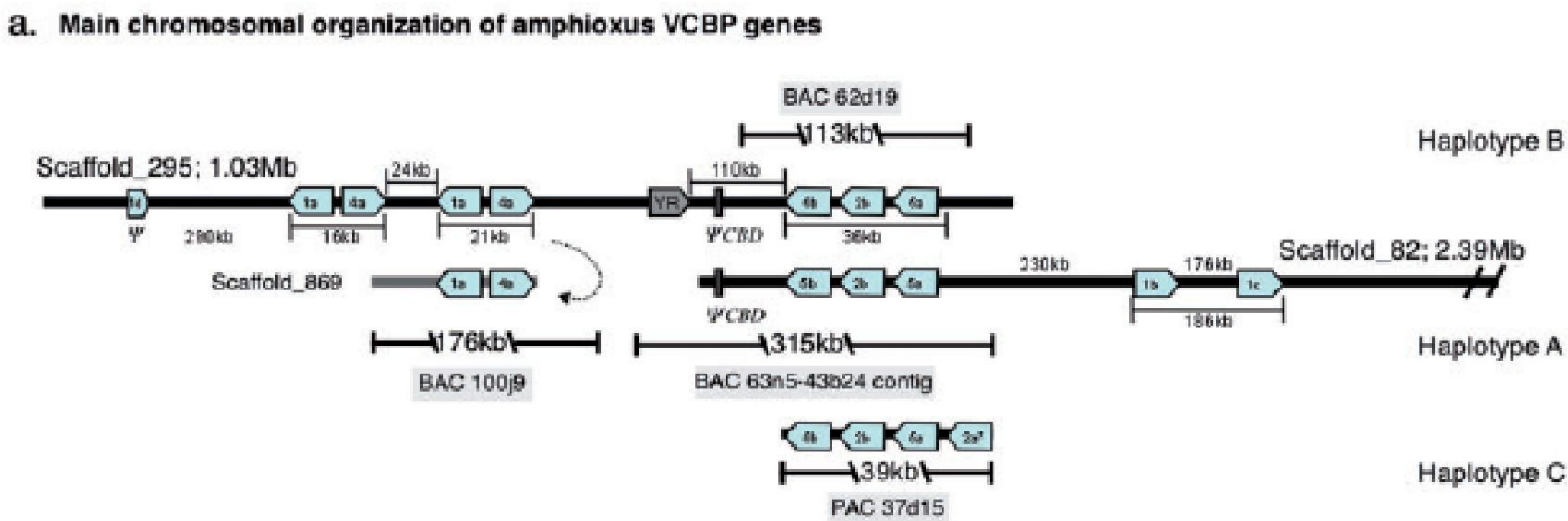


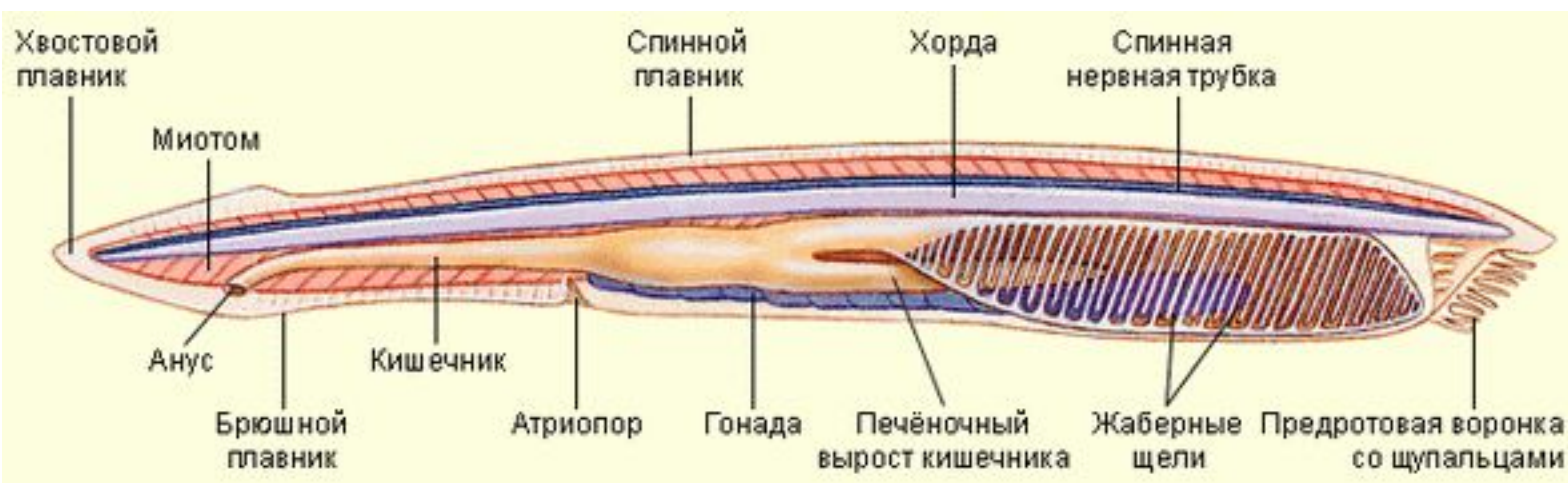
H.s.	10(+1Ψ)	0	0	22	81(16)	6	0	3
M.m.	13	0	0	33	118(27)	4	0	3
S.p.	**214**	**3**	**5**	**>200**	**1095(218)**	**5**	**3**	**12**
D.m.	1	8	0	0	14(7)	15	4	0
C.e.	0	1	0	0	3(1)	0	0	0

Рецепторы целомоцита асцидии



Гены VCBP у ланцетника

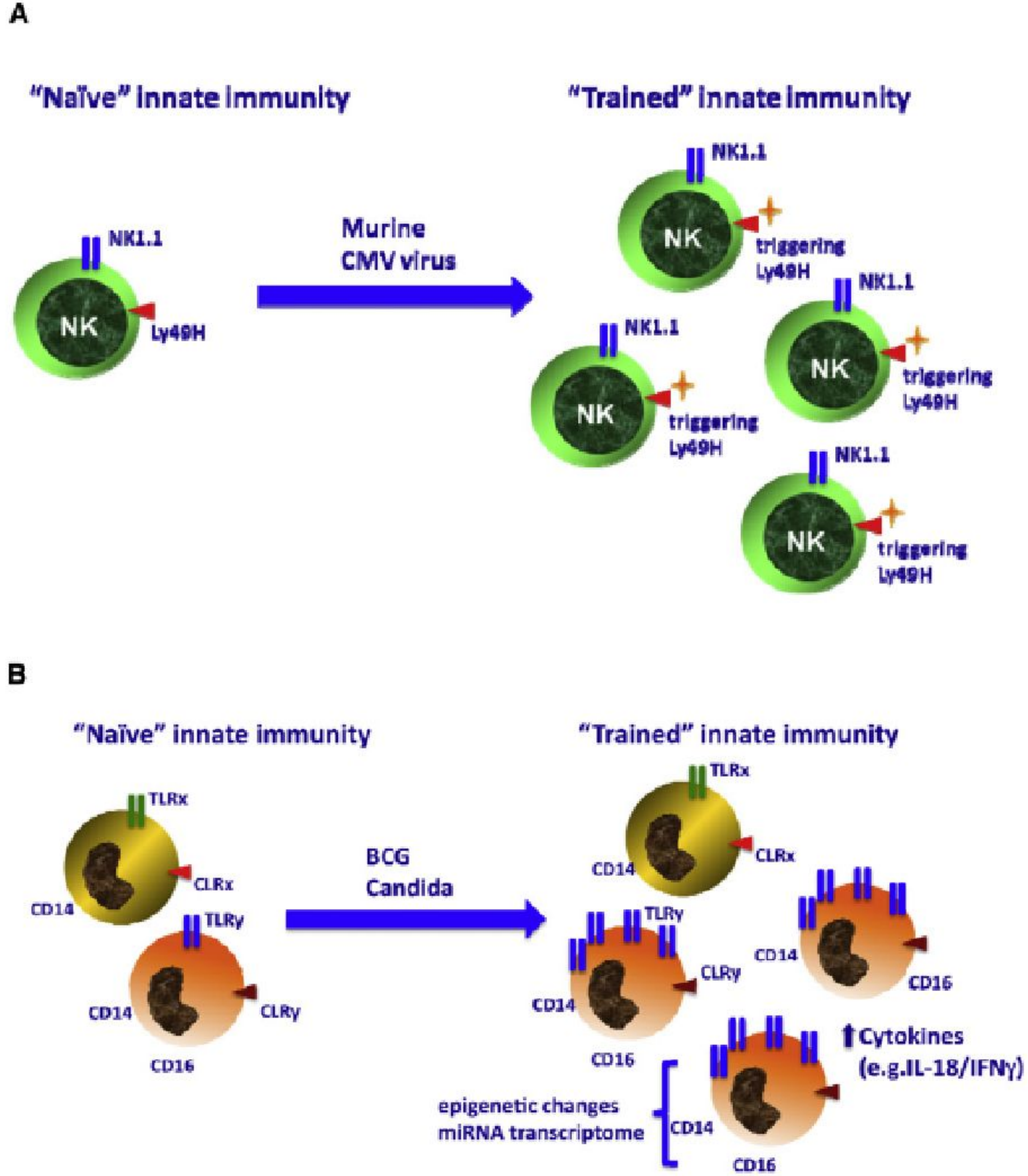




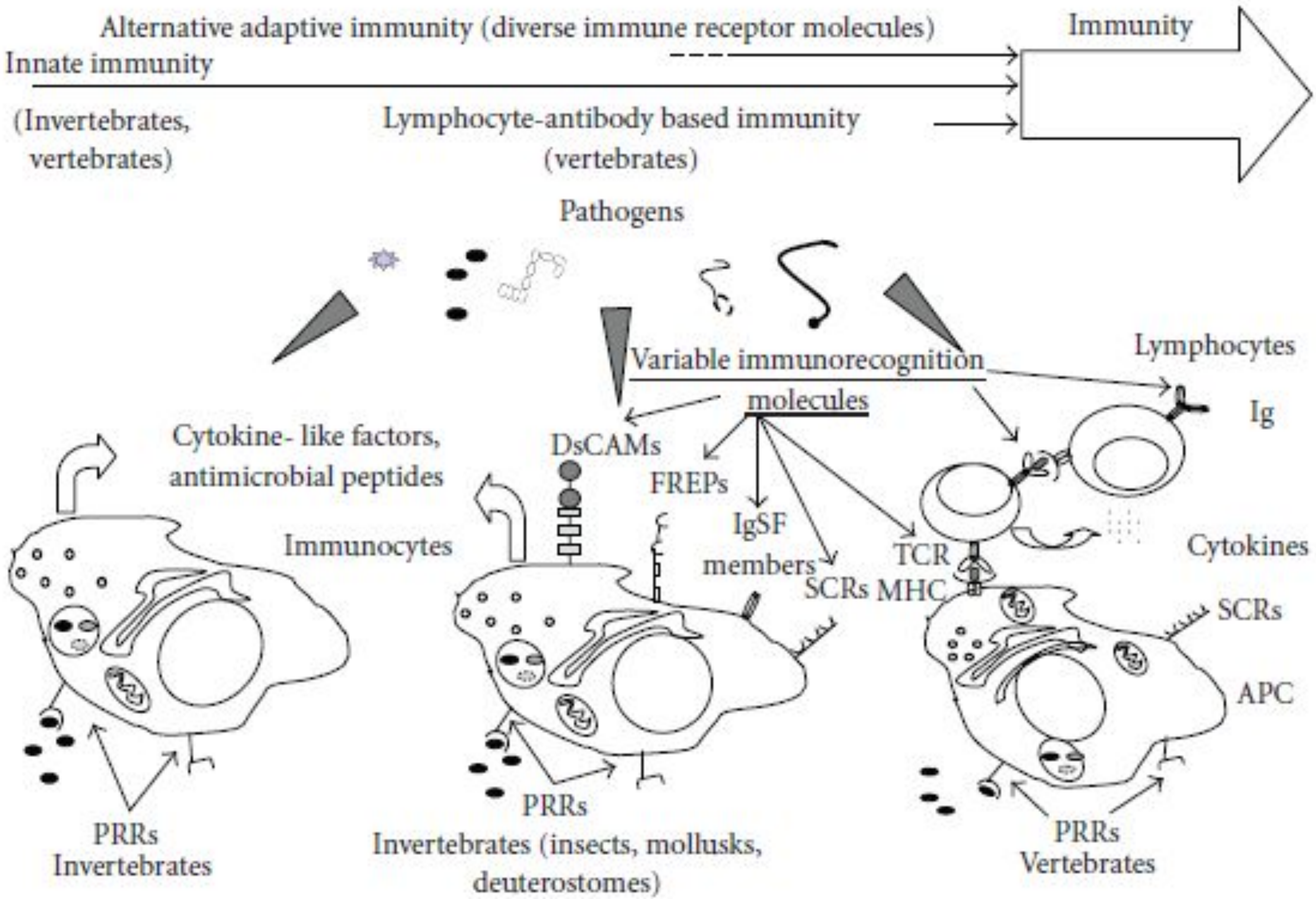
«Тренированный» врождённый иммунитет – аналог адаптивного?

Table 1. Selected Experimental Models in which Biological Activity Compatible with the Concept of Trained Innate Immunity Has Been Reported

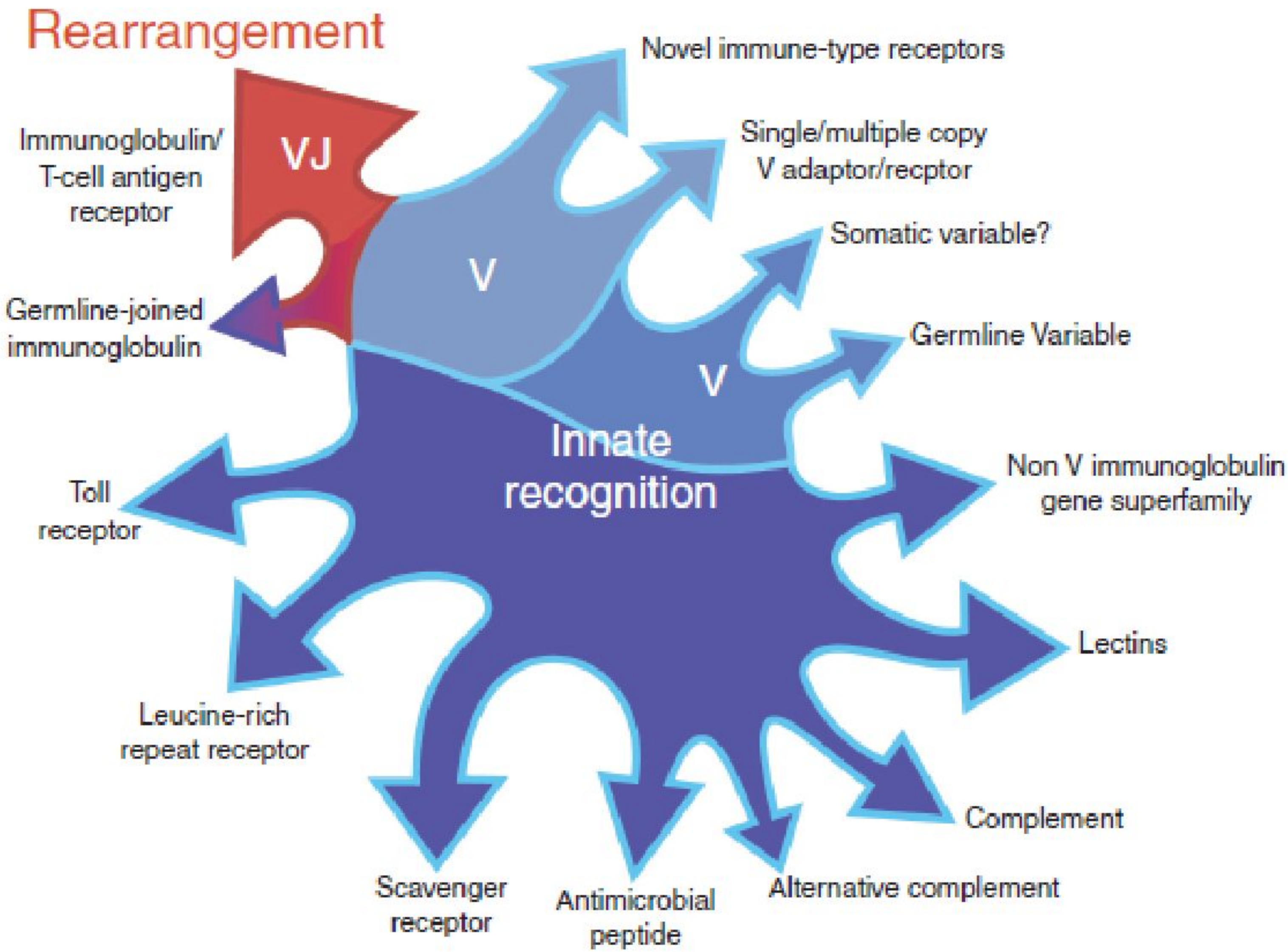
Organism	Experimental Model	Biological Effect	Specificity	References
Plants—Systemic Acquired Resistance				
Large variety of plants	Viruses, bacteria, fungi	Protection against reinfection	Variable	Durrant and Dong, 2004; Sticher et al., 1997
Nonvertebrates				
Mealworm beetle	LPS, or bacterial prechallenge	Protection against secondary infection	No	Moret and Siva-Jothy, 2003
Drosophila	*S. pneumoniae* prechallenge	Protection against *S. pneumoniae*	Uncertain	Pham et al., 2007
Anopheles gambiae	*Plasmodium* prechallenge	Protection against *Plasmodium*	No	Rodrigues et al., 2010
Sponges	Transplantation	Rejection	Yes	Hildemann et al., 1979
Corals	Transplantation	Rejection	Yes	Hildemann et al., 1977
Vertebrates				
Mice	BCG	Protection against candidiasis	No	Van 't Wout et al., 1992
Mice	*Candida* vaccination	T/B cell-independent protection	No	Bistoni et al., 1986, 1988
Mice	Murine CMV infection	NK-dependent protection	No	Sun et al., 2009
Humans	BCG	Nonspecific protection to secondary infections	No	Garly et al., 2003


A
"Naïve" innate immunity
NK1.1
NK
Ly49H
Murine
CMV virus
"Trained" innate immunity
NK1.1
NK
triggering
Ly49H
B
"Naïve" innate immunity
TLRx
CLRx
CD14
TLRy
CLRy
CD16
BCG
Candida
"Trained" innate immunity
Cytokines
(e.g.IL-18/IFNγ)
epigenetic changes
miRNA transcriptome

Граница между врожденным и адаптивным иммунитетом



Направления эволюции иммунных рецепторов



- Следующая лекция 26 марта – о трансплантационном иммунитете и возникновении адаптивного иммунитета