Эволюционная иммунология
Лекция 9 «Возникновение адаптивного иммунитета»

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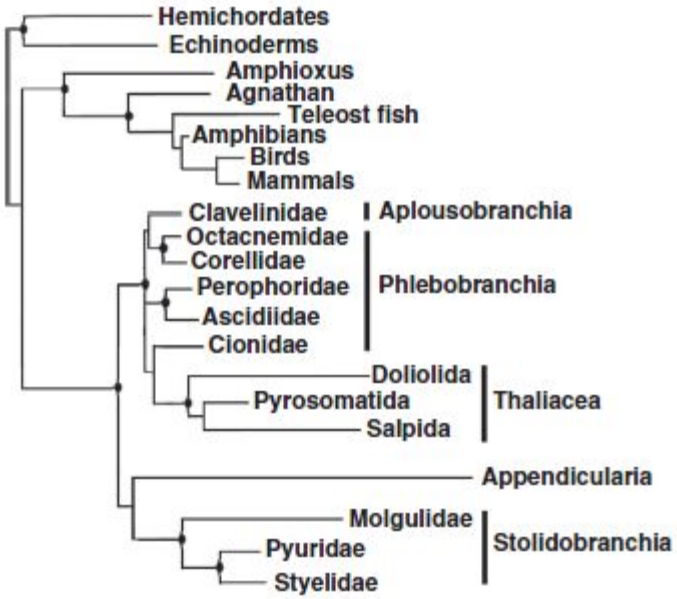
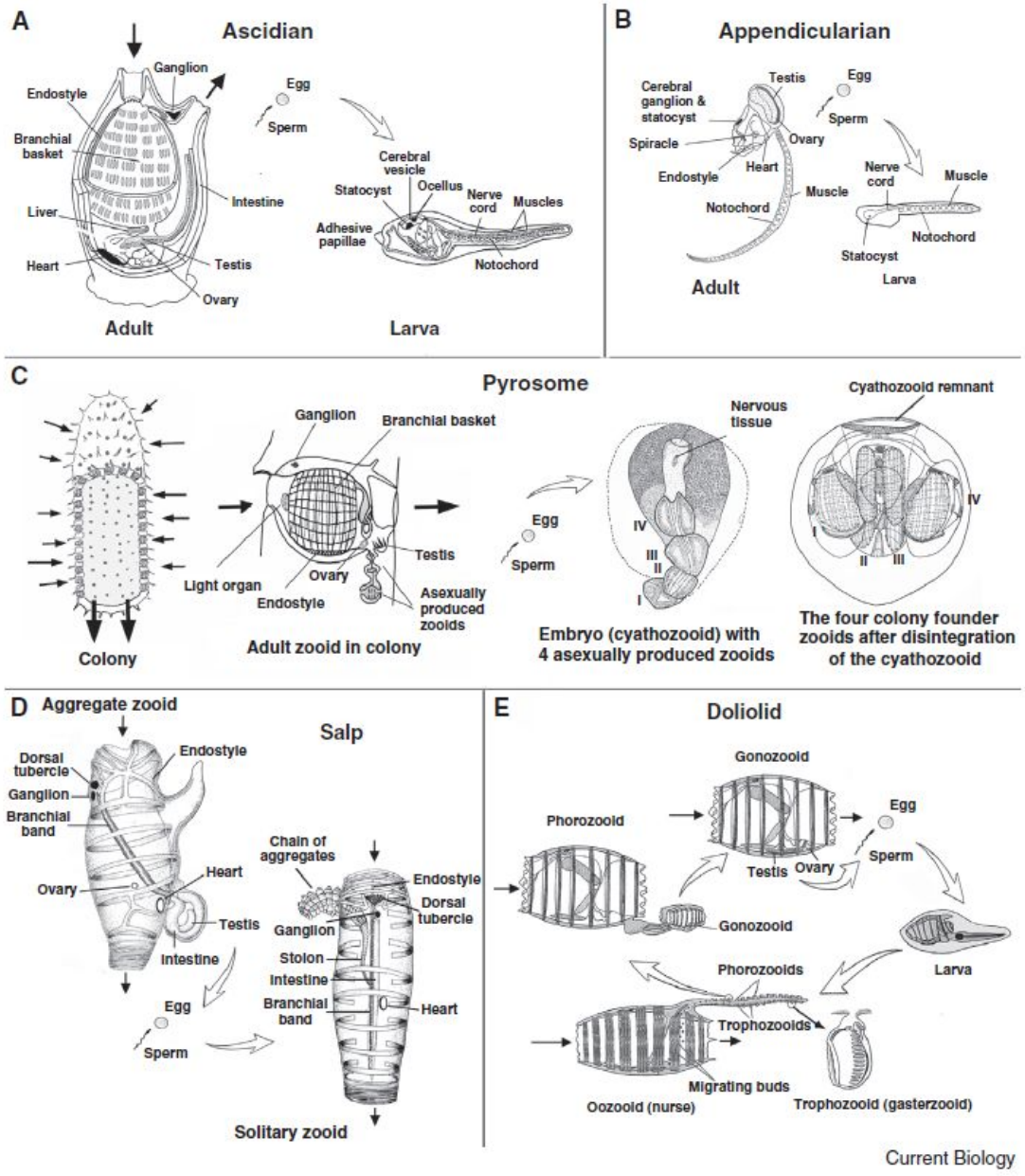
9 апреля 2018

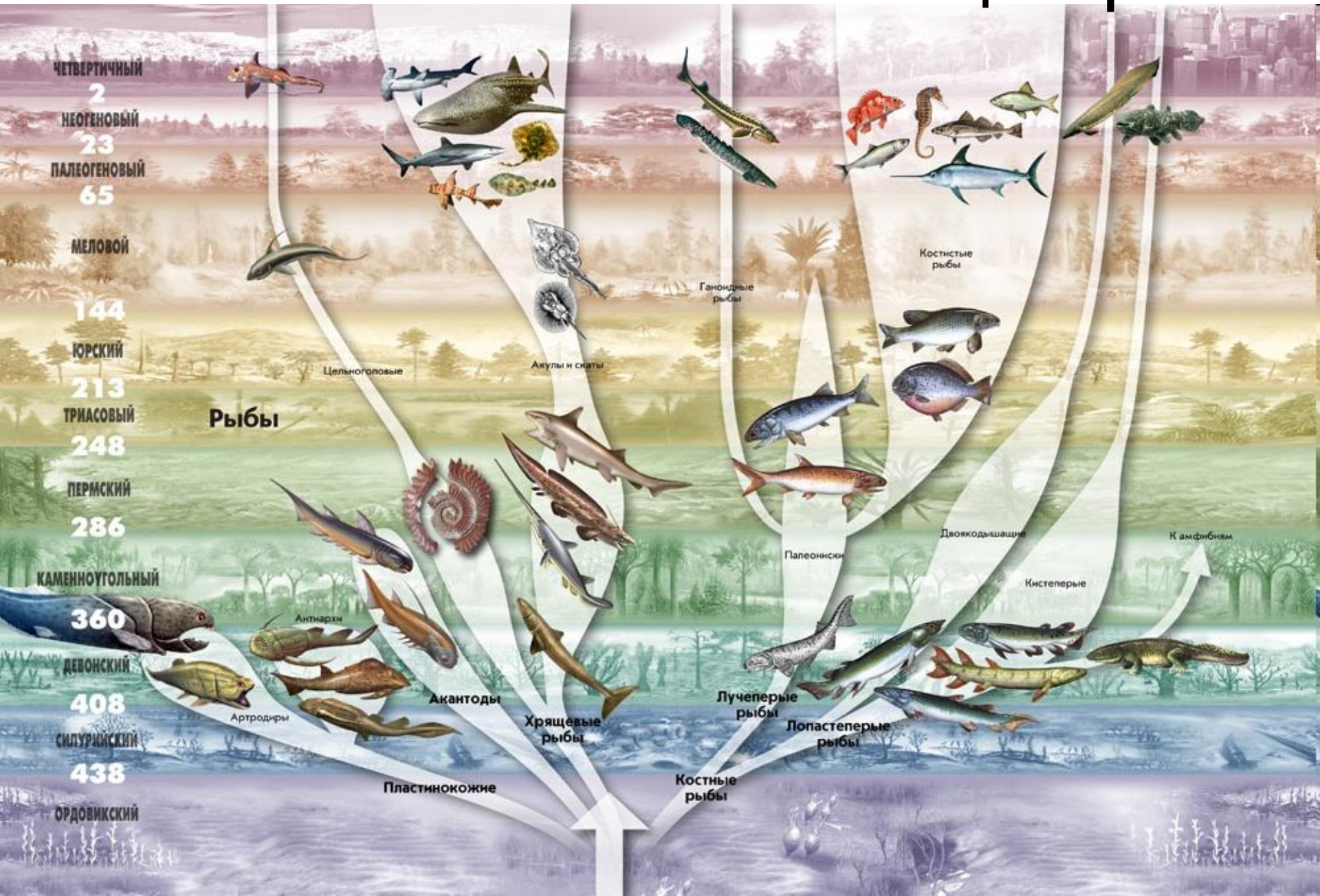
Эволюция иммунной системы на фоне филогенетического дерева животных

Систематика и эволюция оболочников

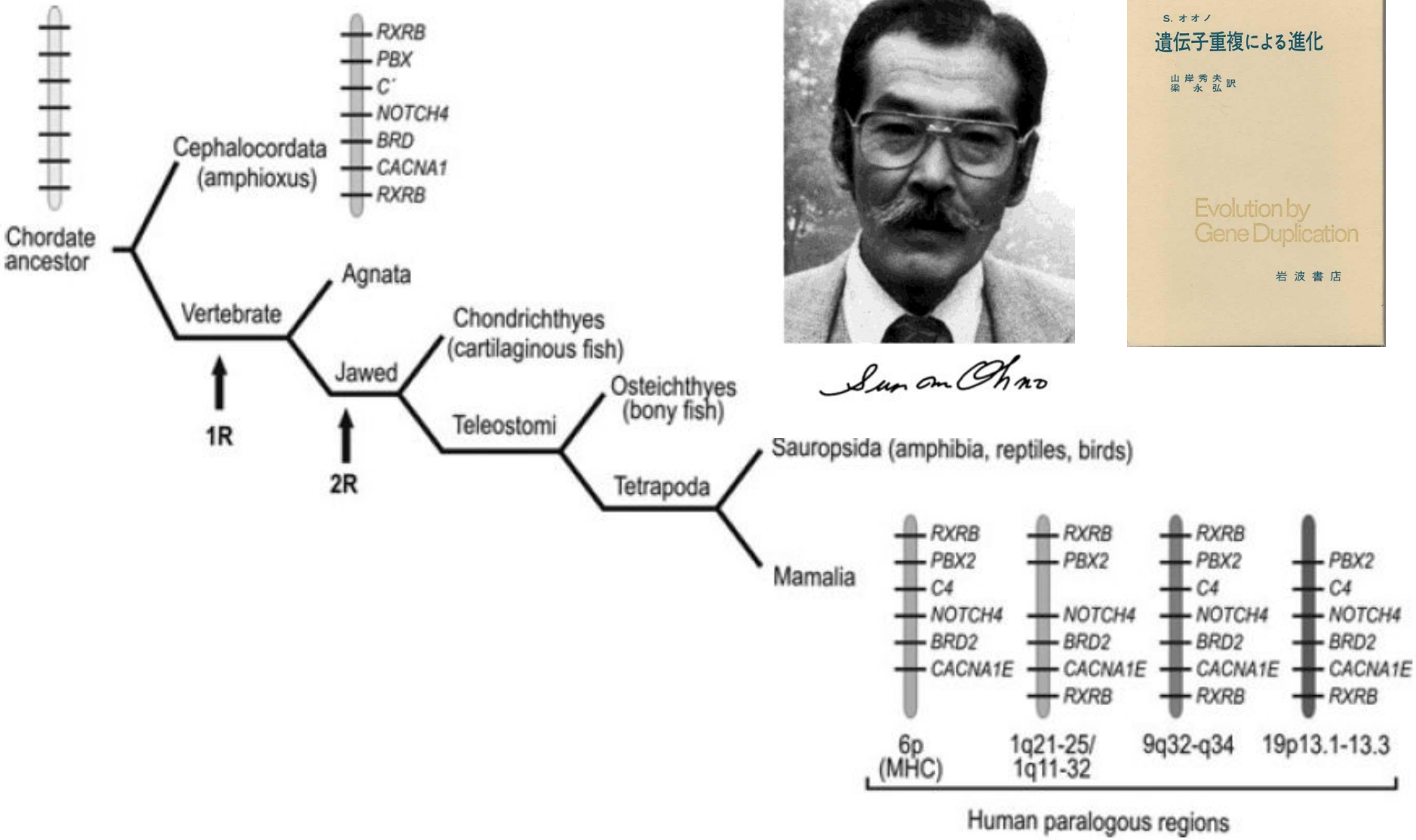




Систематика и эволюция рыб



Две полногеномные дупликации как источник разнообразия паралогов



Синергичность компонентов адаптивного иммунитета создаёт проблемы с пониманием, как он мог возникнуть

- Что возникло раньше, антитела или Т-клеточные рецепторы?
- Что возникло раньше, Т-клеточные рецепторы или МНС?
- Что возникло раньше, МНС I или МНС II?
- Что возникло раньше, трансплантационный иммунитет, или презентация антигена?
- Что возникло раньше, связывающая бороздка или механизмы загрузки антигенных пептидов?

По поводу чего уже есть консенсус:

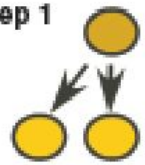
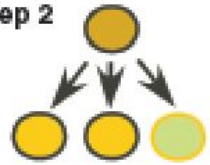
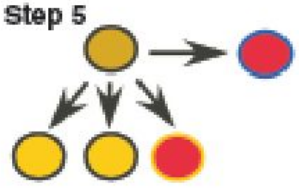
Древнее всего генетические программы, регулирующие гематопоэз.

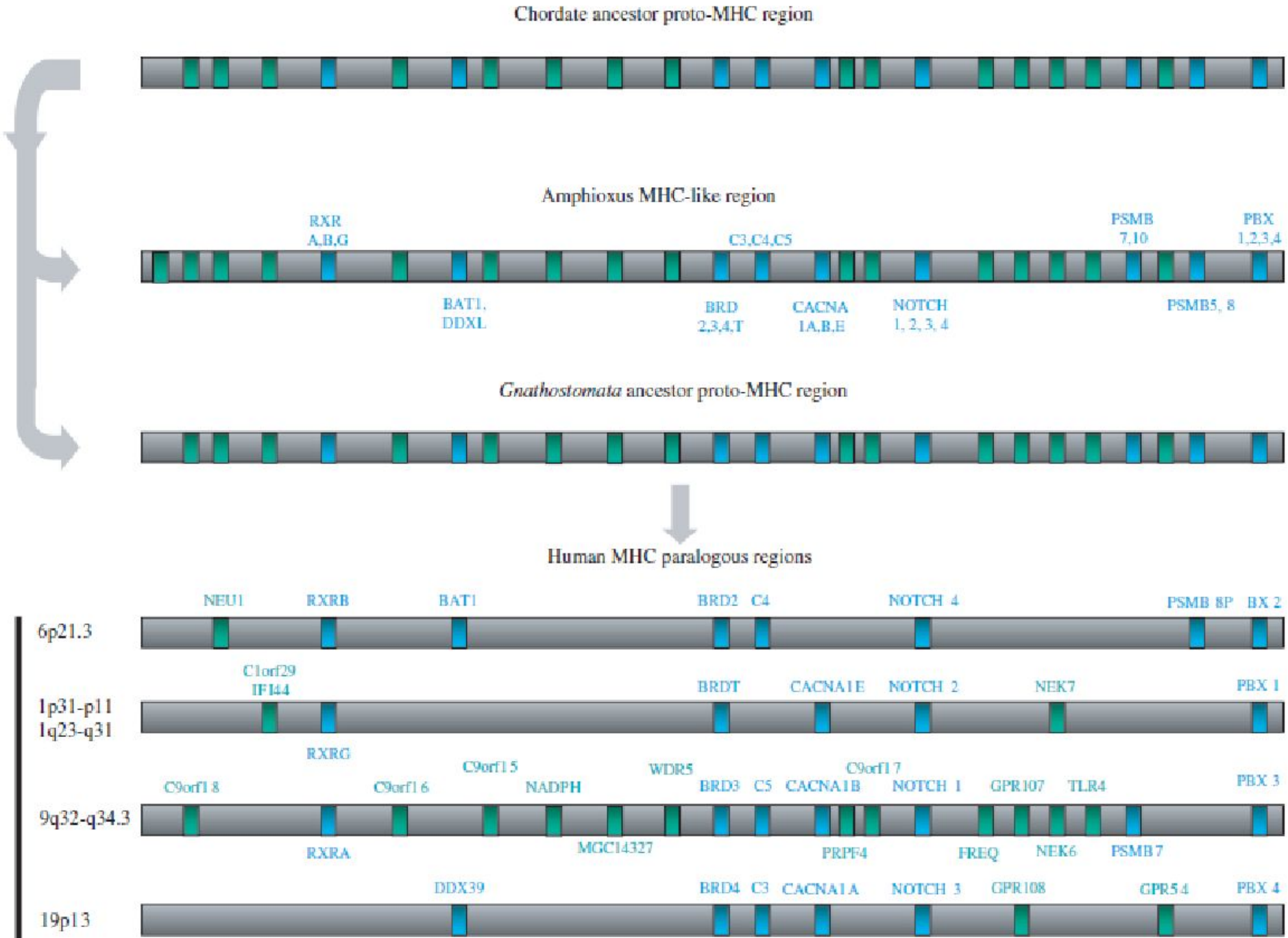
Гамма/дельта Т-клеточные рецепторы древнее, чем альфа/бета Т-клеточные рецепторы

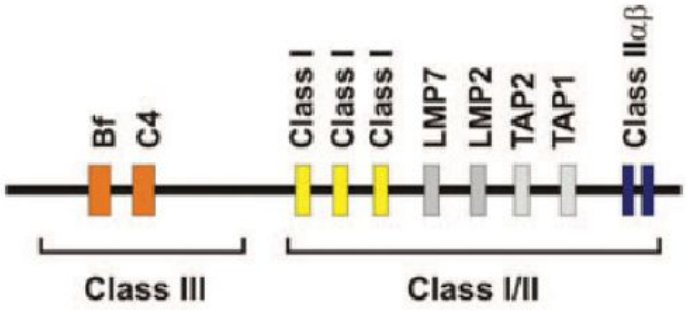
Гипотеза T. Boehm

- Hematopoietic stem cell
- Myeloid cells, including phagocytes
- (B) lymphocyte–like cell expressing structurally diverse antigen receptors
- Proto–T cell expressing monomorphic proto-TCR
- T cell expressing modern TCR based on VDJ recombination
- B cell expressing modern BCR based on VDJ recombination

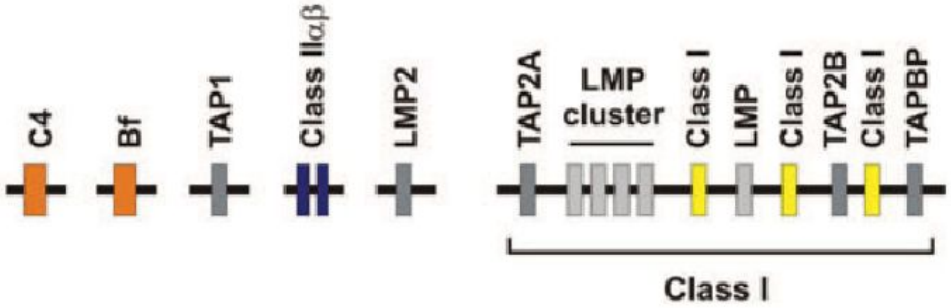
Evolutionary time

Lymphocyte-like cells	Lymphoid organs	Comments
Step 1 	Myeloid tissue	**Invertebrates:** Hematopoietic system gives rise to phagocytes that express germline-encoded pattern-recognition receptors (such as TLRs); somatic quality control unnecessary
Step 2 	Lympho-myeloid tissue (typhlosole, spleen)	**Jawless vertebrates:** Hematopoietic system additionally gives rise to lymphocyte-like cells that express somatically diversified antigen receptors (such as VLR in lamprey); somatic quality control unnecessary
Step 3	Lympho-myeloid tissue (typhlosole, spleen, proto-thymus?)	**Hypothetical intermediate I:** Hematopoietic system additionally gives rise to a second lineage of lymphocyte-like cells that express structurally invariant proto-TCR; development may occur in a dedicated microenvironment; somatic quality control unnecessary
Step 4	Lympho-myeloid tissue (bone marrow or equivalent); thymus	**Hypothetical intermediate II:** Transposon-mediated insertion transforms structurally invariant proto-TCR into somatically diversifiable VDJ-type TCR; development and somatic quality control for self compatibility in dedicated primary lymphoid organ
Step 5 	Lympho-myeloid tissue (bone marrow or equivalent); thymus	**Jawed vertebrates:** Hematopoietic system additionally gives rise to B lymphocytes that express somatically diversified antigen receptors; somatic quality control distinct from that for TCR expressing cells

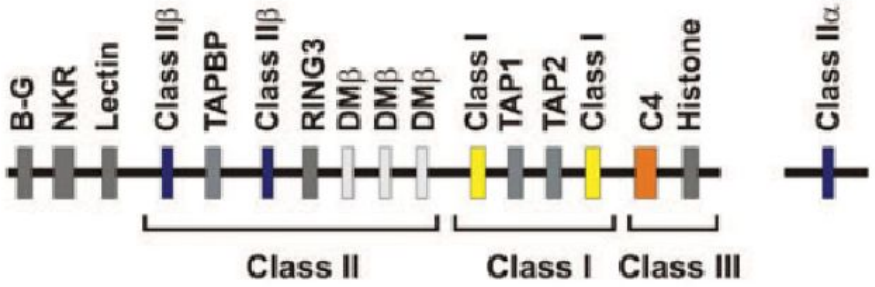

Chordate ancestor proto-MHC region
Amphioxus MHC-like region
RXR
A,B,G
C3,C4,C5
PSMB
7,10
PBX
1,2,3,4
BAT1,
DDXL
BRD
2,3,4,T
CACNA
1A,B,E
NOTCH
1, 2, 3, 4
PSMB5, 8
Gnathostomata ancestor proto-MHC region
Human MHC paralogous regions
6p21.3
NEU1
RXRB
BAT1
BRD2
C4
NOTCH 4
PSMB 8P
BX 2
1p31-p11
1q23-q31
C1orf29
IFI44
BRDT
CACNA1E
NOTCH 2
NEK7
PBX 1
9q32-q34.3
RXRG
C9orf15
WDR5
C9orf17
C9orf18
C9orf16
NADPH
BRD3
C5
CACNA1B
NOTCH 1
GPR107
TLR4
PBX 3
RXRA
MGC14327
PRPF4
FREQ
NEK6
PSMB7
19p13
DDX39
BRD4
C3
CACNA1A
NOTCH 3
GPR108
GPR54
PBX 4



Хрящевые рыбы

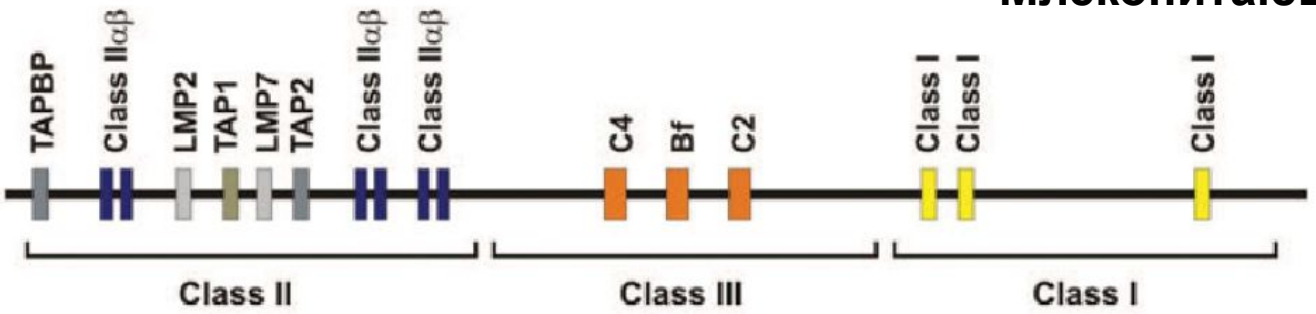


Костные рыбы



Птицы

Млекопитающие



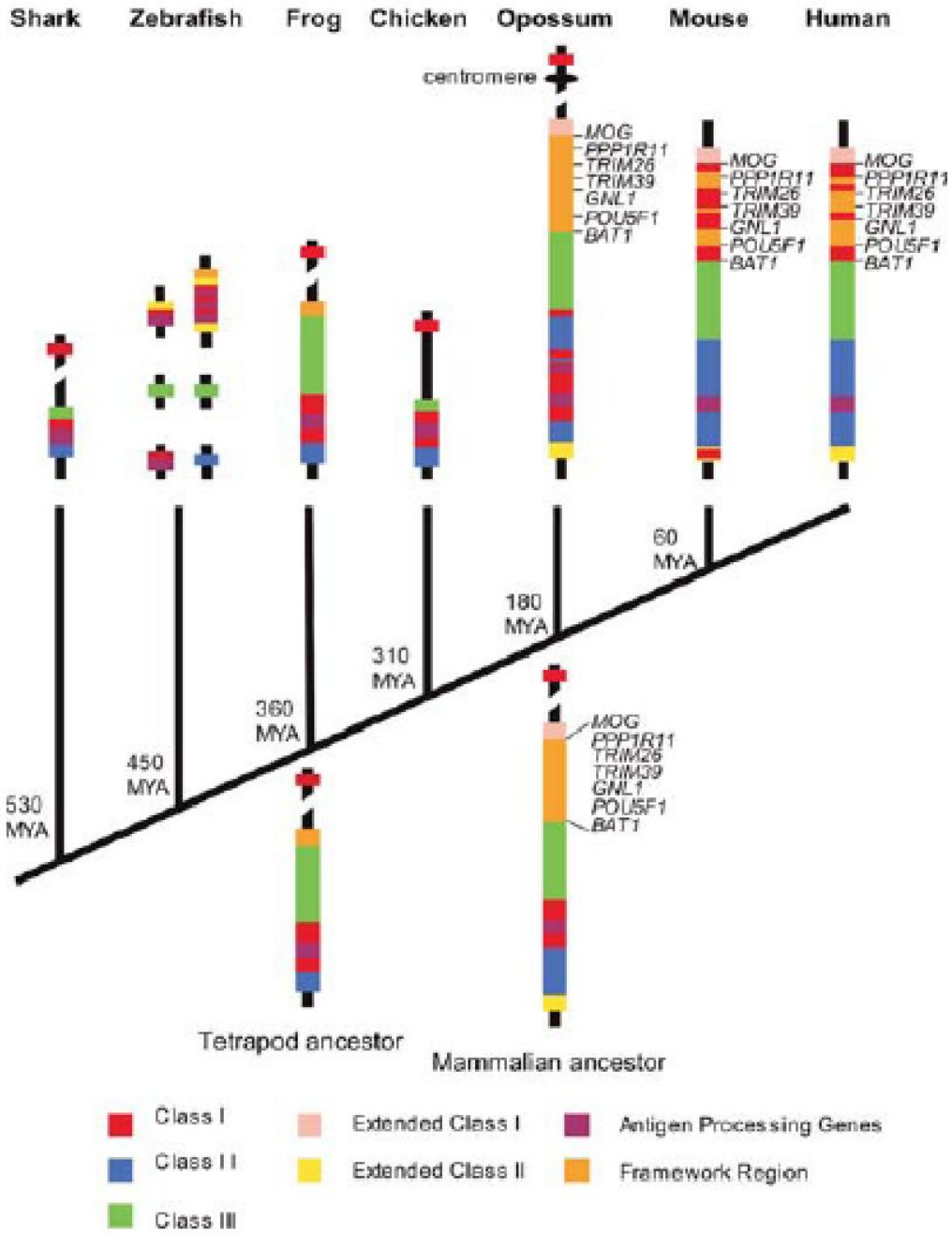
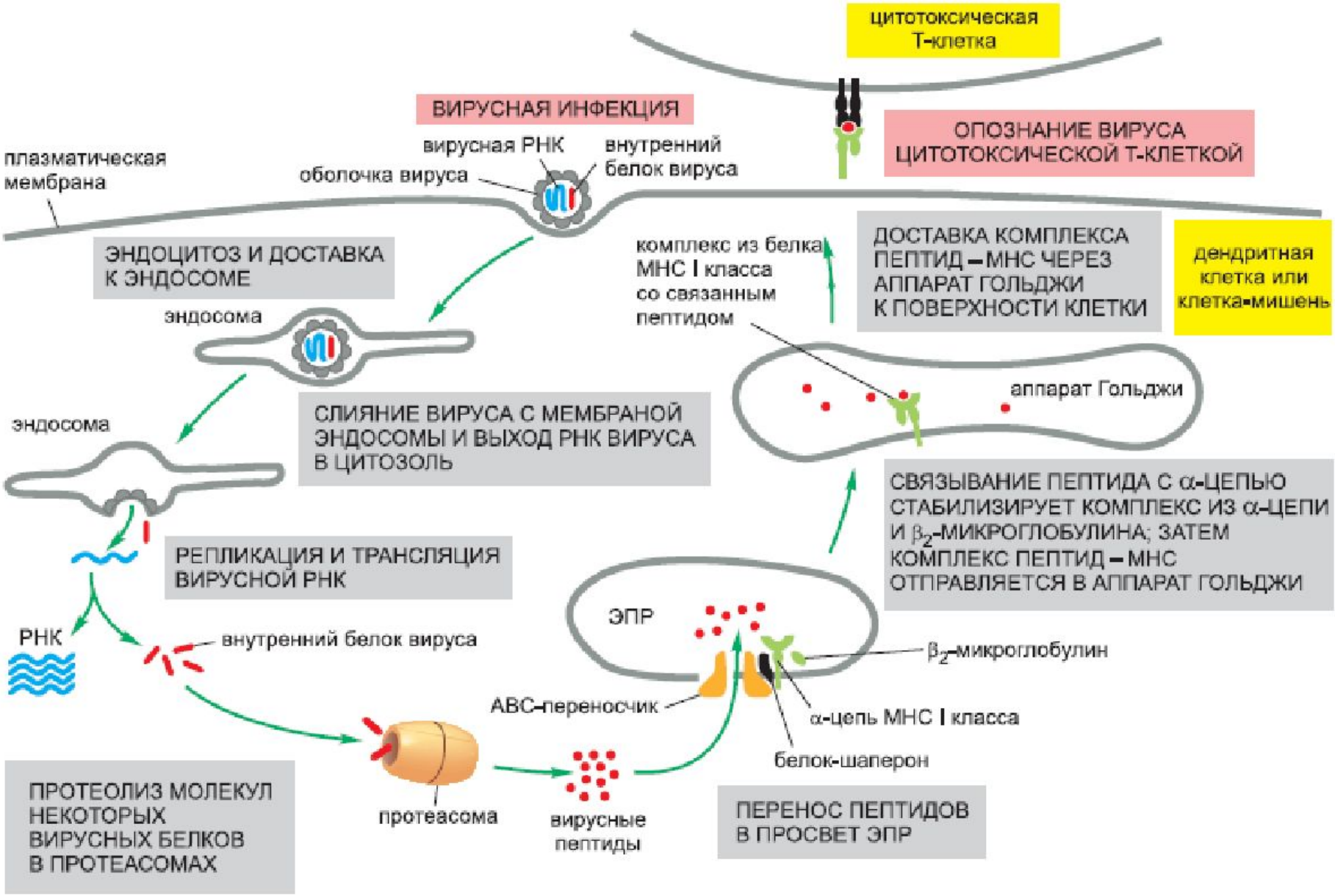
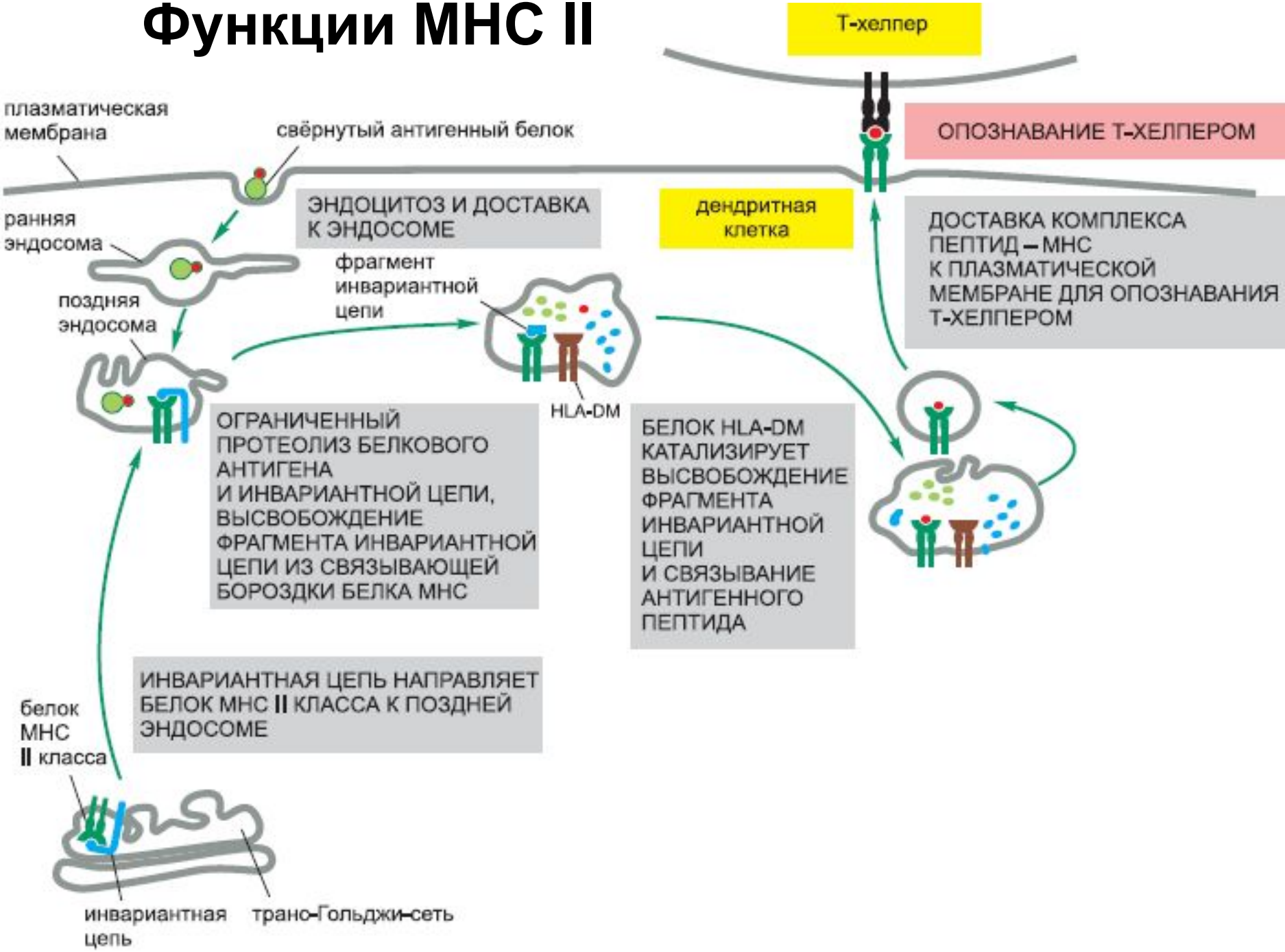


Figure 4. A Model of the Evolution of the Mammalian MHC

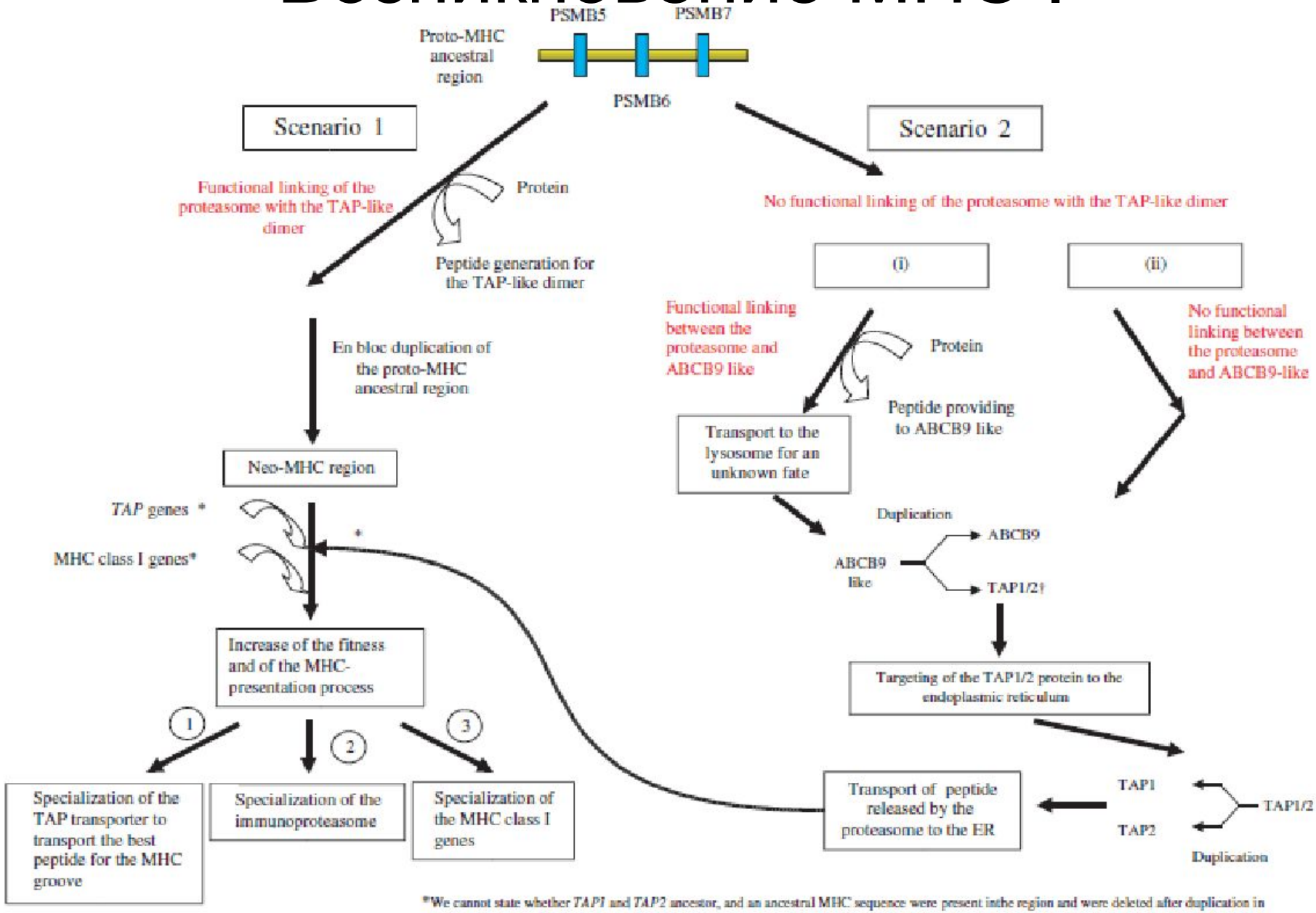
Функции МНС I



Функции МНС II



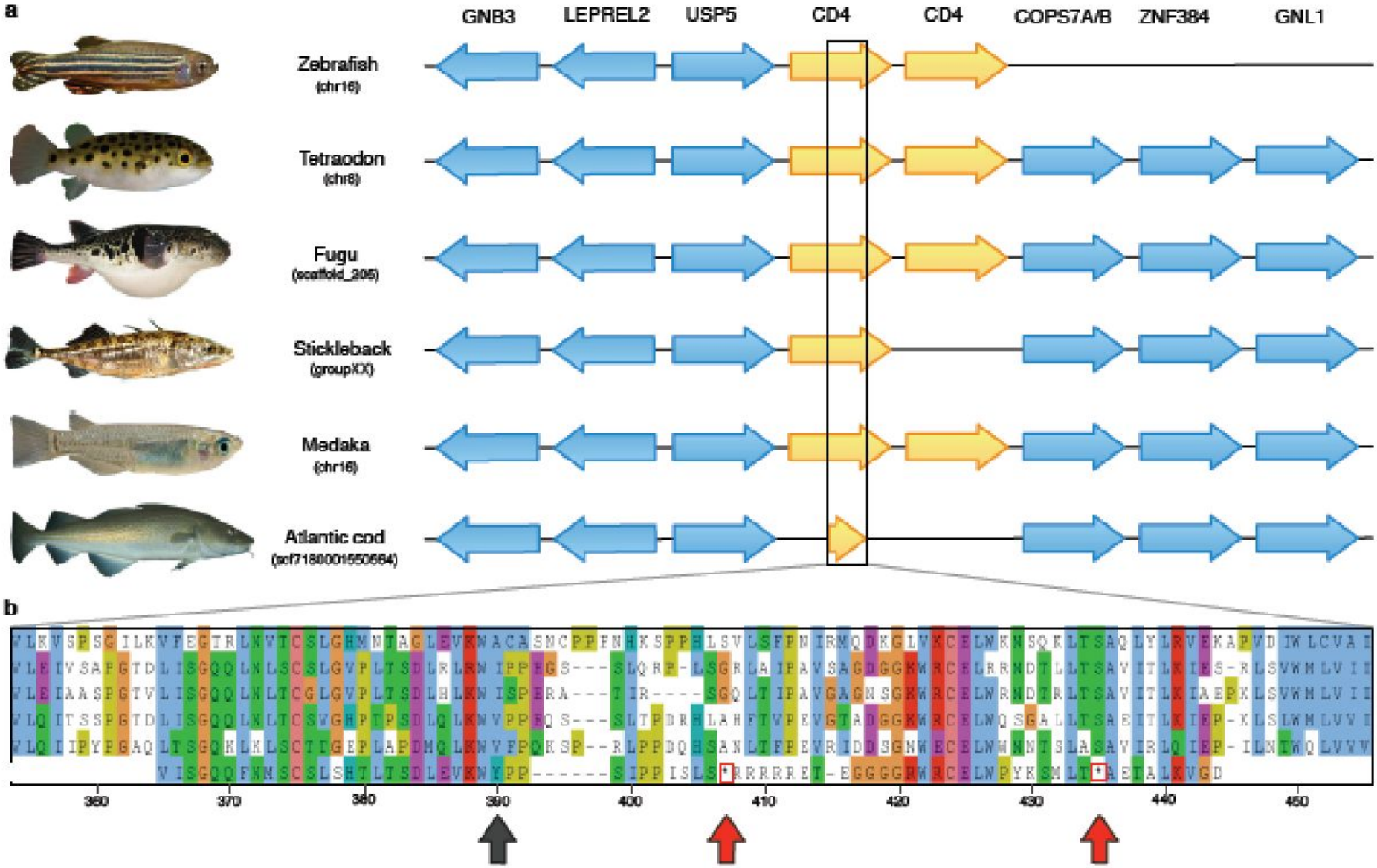
Возникновение MHC I



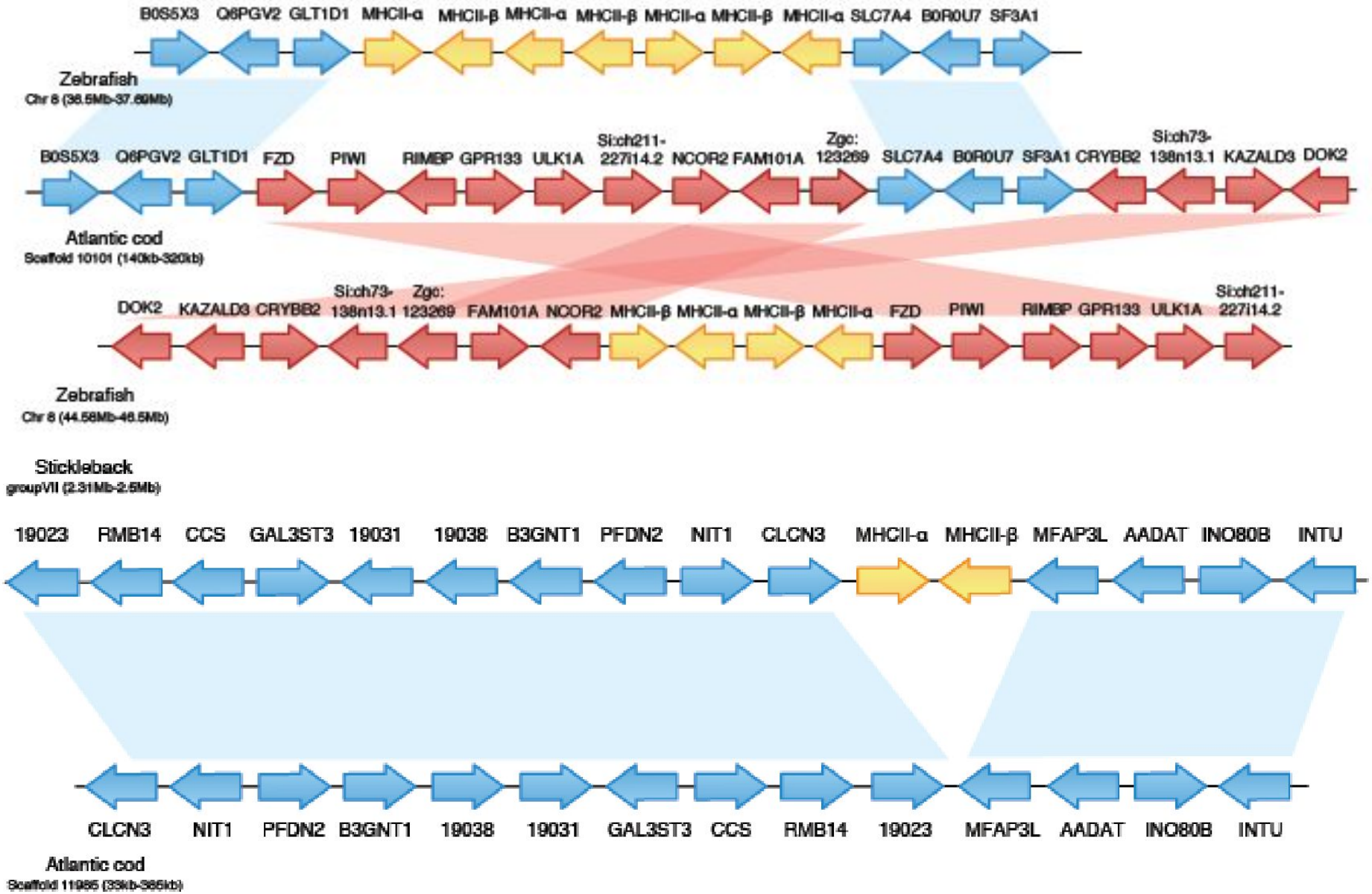
*We cannot state whether *TAP1* and *TAP2* ancestor, and an ancestral MHC sequence were present inthe region and were deleted after duplication in the MHC sister regions or if the TAP-like and the MHC-like ancestral sequences were translocated into the neo-MHC genomic region

†In scenario 2 (ii), TAP1/2 underwent mutations that allowed the acquisition of the peptide transport function.

Треска не имеет функционального набора генов молекул MHCII, и рецептора CD4



Это является результатом цепочки хромосомных перестроек, затрагивающих локус МНС

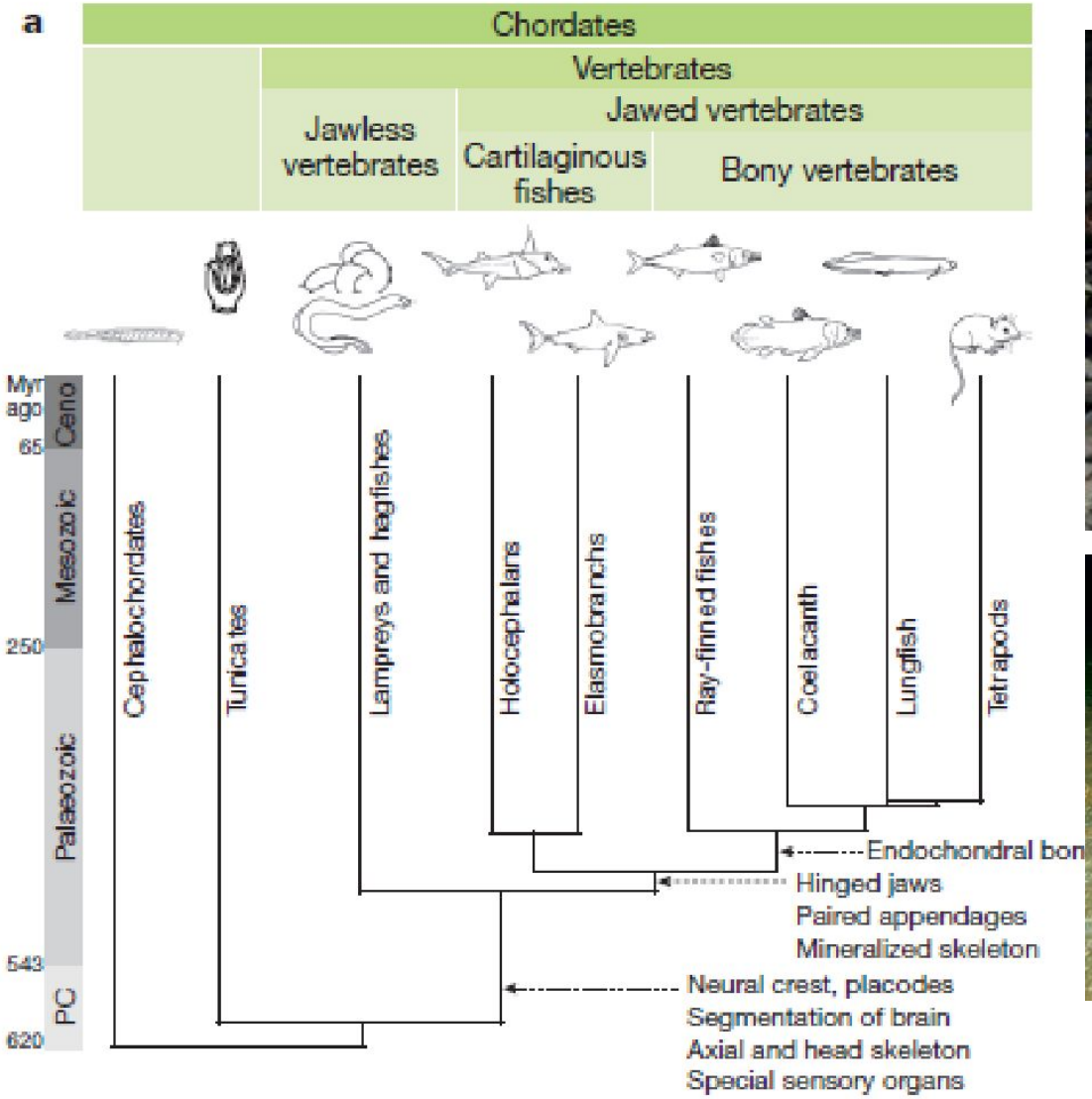


Рыбы, экономящие на Т-хелперной ветви

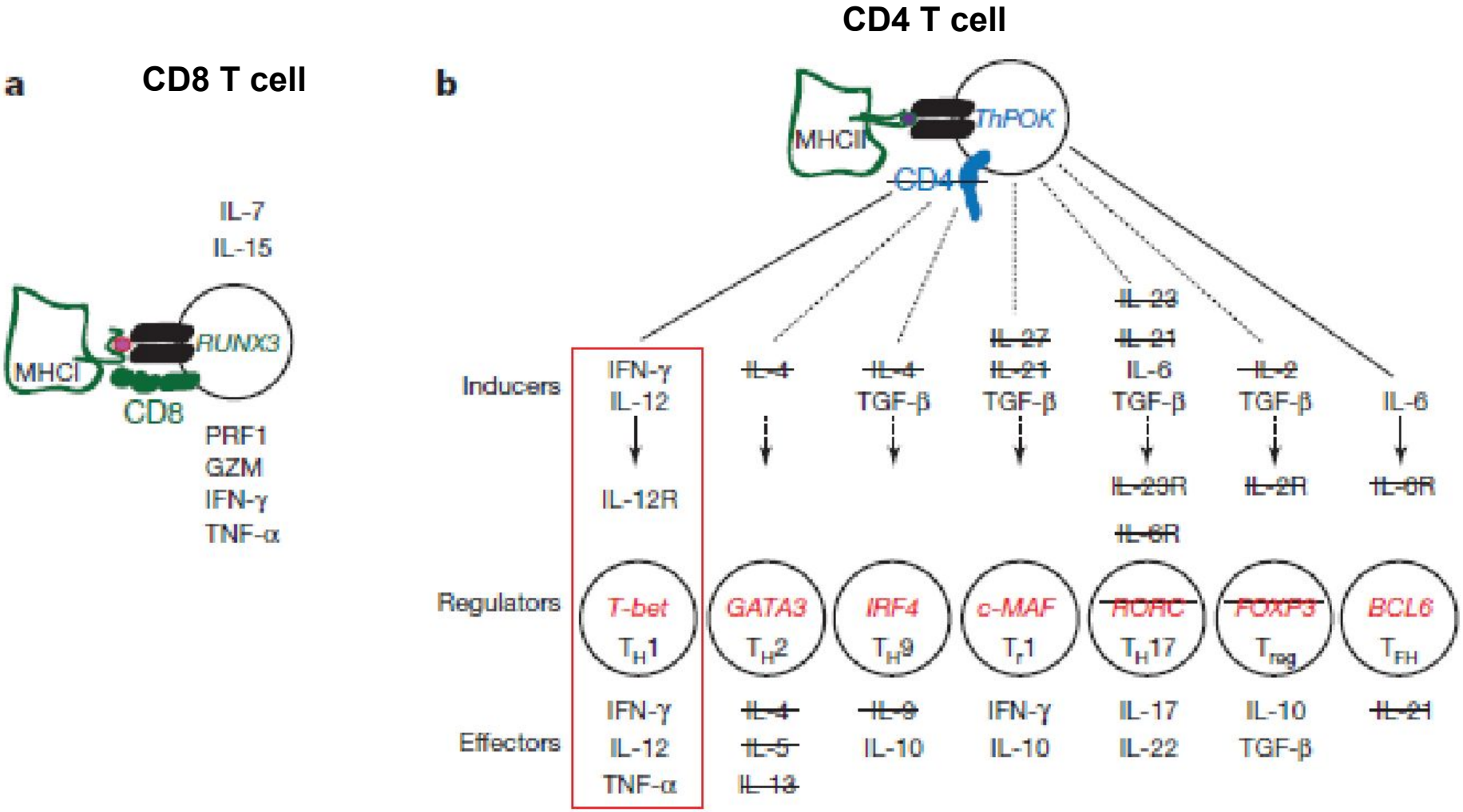
Table 3
Teleost fishes known until now without or with a minimal MHCII system and adopted compensatory strategies.

Scientific name	Common name	MHCII a and b chain genes	CD4	CD74	Compensatory mechanism
Gadus morhua	Atlantic cod	Absent	Pseudogene	Absent	Expansion of MHC I, TLR and other innate-immunity related gene families
Other Gadoidei	Euopean hake, haddock, whiting, burbot, etc.	Absent or not expressed	Absent or not expressed	Absent or not expressed	Possibly same as in cod
Syngnathus typhle	Broadnosed pipefish	Absent	Absent	Present, but possibly not functional	Unknown
Hippocampus abdominalis	Big-belly seahorse	Minimal system, single locus	Present	Present	Increased intralocus variability and interlocus recombination in MHCII loci
Salmonids	Atlantic salmon, rainbow trout, etc.	Minimal system, single locus	Present	Present	Increased intralocus variability and interlocus recombination in MHCII loci
Other teleosts		Multiple loci	Present	Present	/

Химера *Callorhinchus milii* утратила CD4…

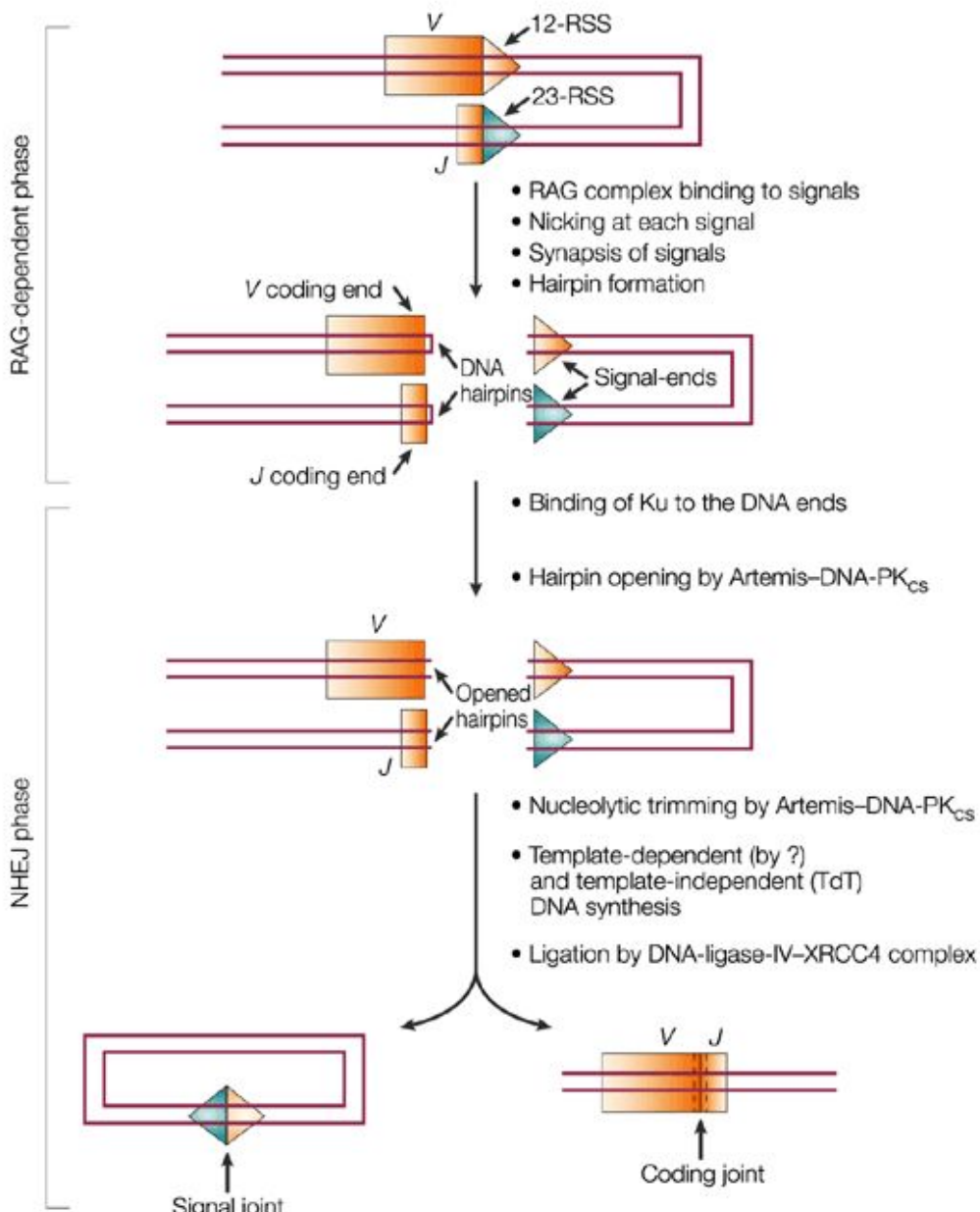


… и несколько цитокинов и транскрипционных факторов



(Venkatesh et al, Nature, 2014)

Роль рекомбиназ RAG



David Schatz, клонировал предсказанные Сакано и Тонегавой рекомбиназы

Возникновение RAG генов

John Marchalonis
1941-2007

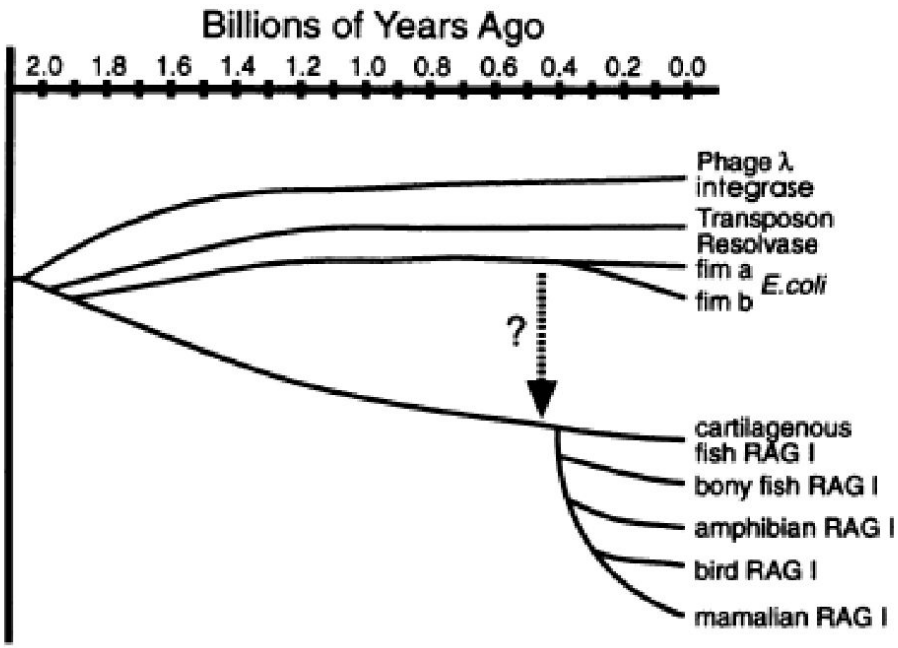
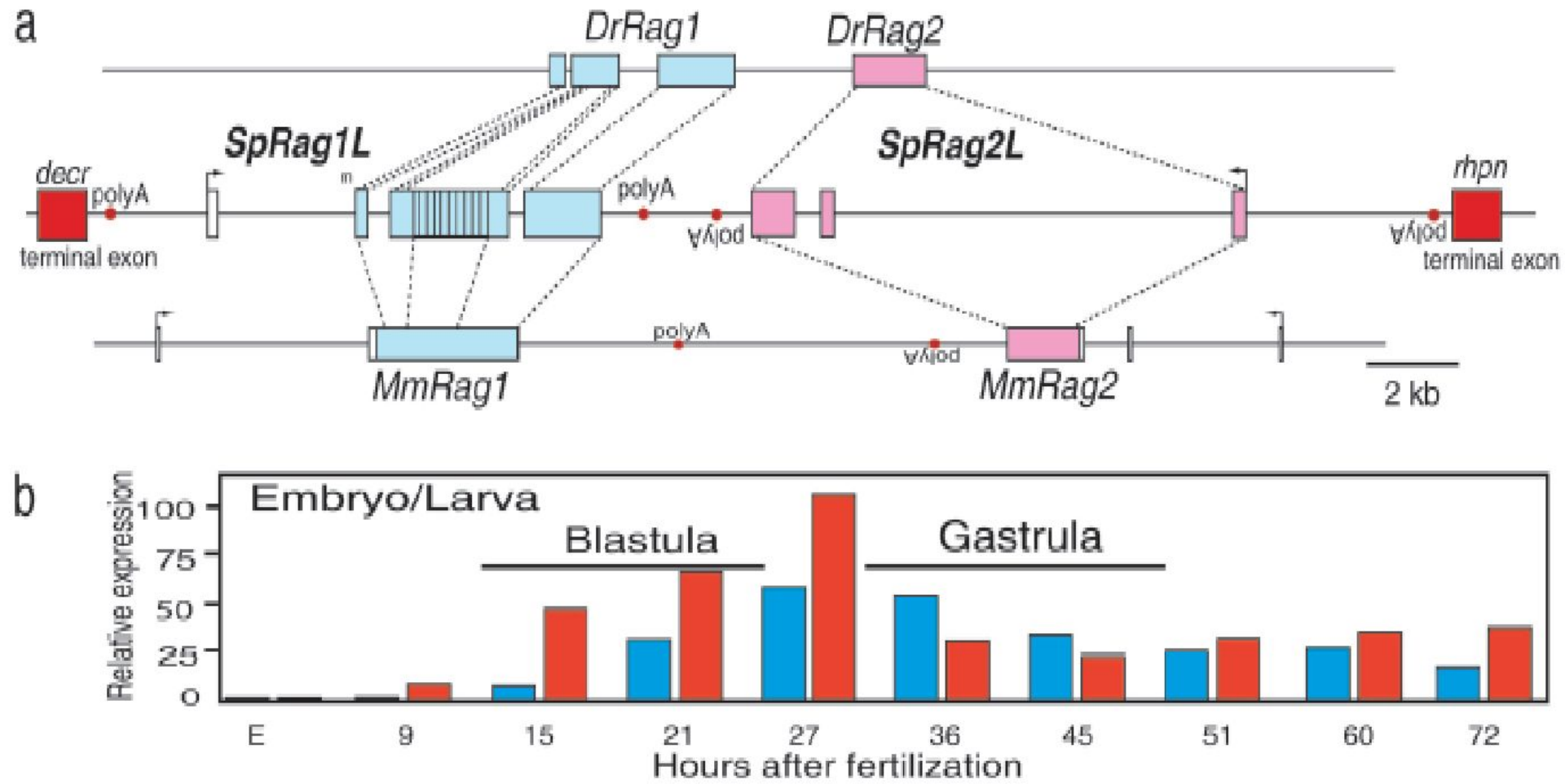


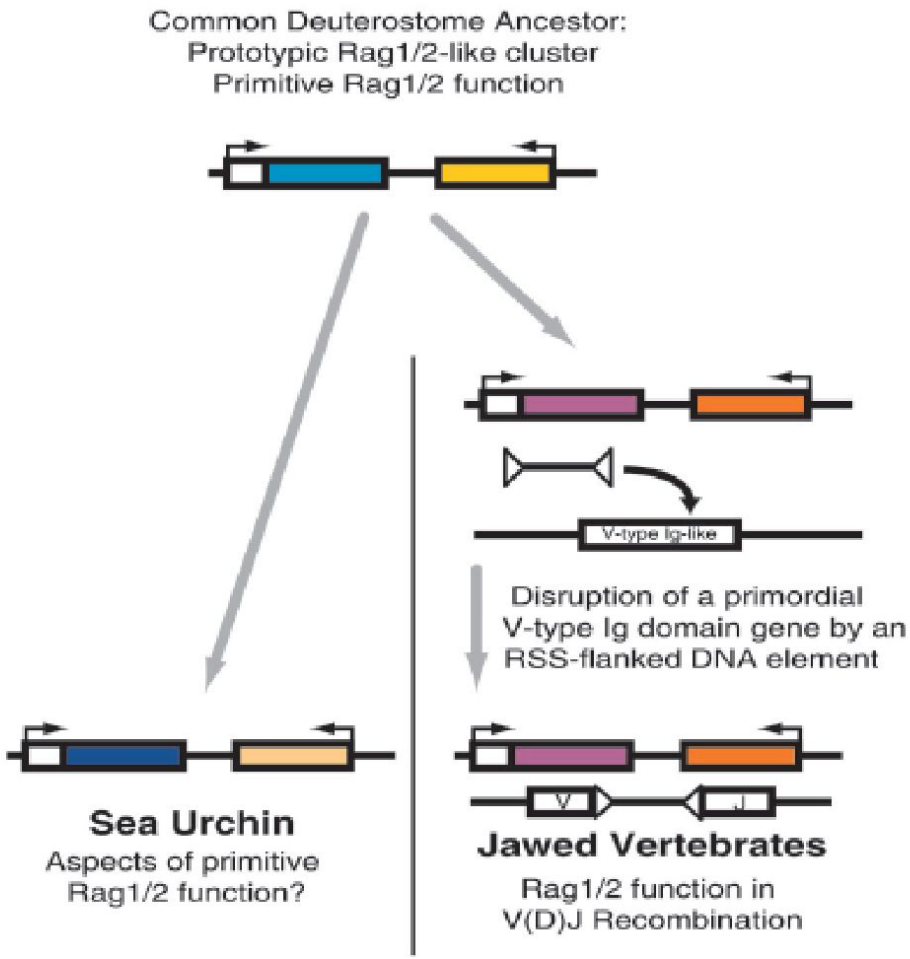
FIG. 5. A phylogenetic tree depicting the evolutionary relationship between members of the INT family of site-specific recombinases. The RAG I INT motif is shown to have diverged prior to 1.8 billion years ago from a common ancestor with the bacterial INT family recombinases. The alternative possibility that the RAG I INT motif was derived by lateral transfer of a microbial INT family gene prior to 0.4 billion years ago is also shown. The date for the divergence of the eukaryotic and prokaryotic lineages, 1.8 billion years ago, is from Doolittle *et al.* (46).

После того, как группа Джона Маркелониса в 1994 году клонировала ген *Rag1* акулы, на основании высокой степени идентичности белков RAG и различных бактериальных интеграз, казалось, что подтвердилась предложенная в 1989 г. гипотеза о горизонтальном переносе генов между первыми Челюстноротыми позвоночными и некими бактериями. Ген Rag1 относили к семейству бактериальных интеграз INT, а ген Rag2 считали гомологом фактора интеграции в хозяина IHF.

Однако гомологи *RAG*-генов нашлись после полного секвенирования генома морского ежа

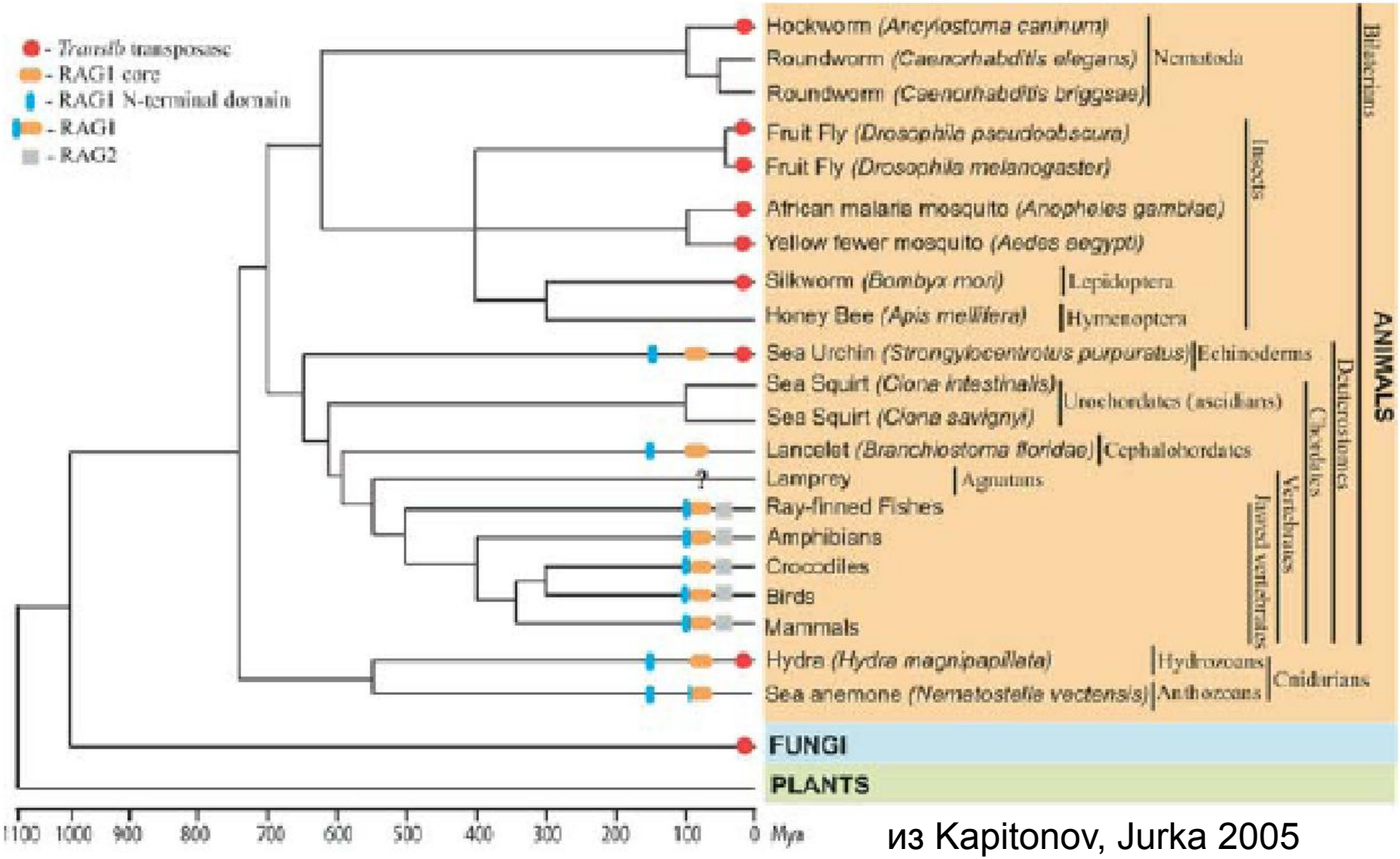


Возникновение RAG генов у общего предка вторичноротых заложило основы для развития адаптивного иммунного ответа



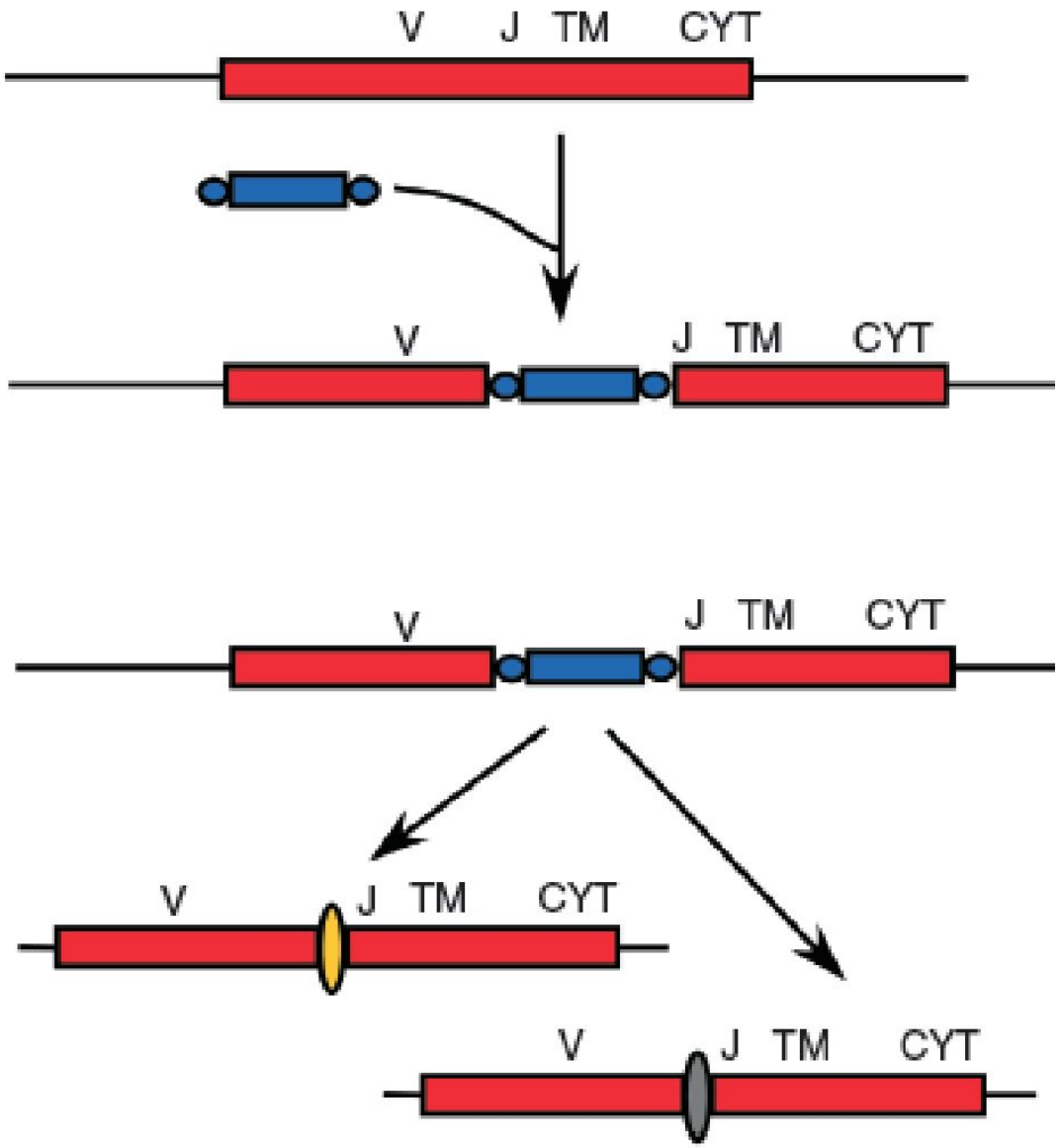
Выяснилось, что гомологи RAG генов есть даже в геноме морского ежа *Strongylocentrotus*, однако отсутствуют во вчетверо меньшем геноме асцидии *Cyona*. Поскольку у морских ежей нет антител и механизма соматической рекомбинации, очевидно, что их рекомбиназы имеют какую-либо другую функцию.

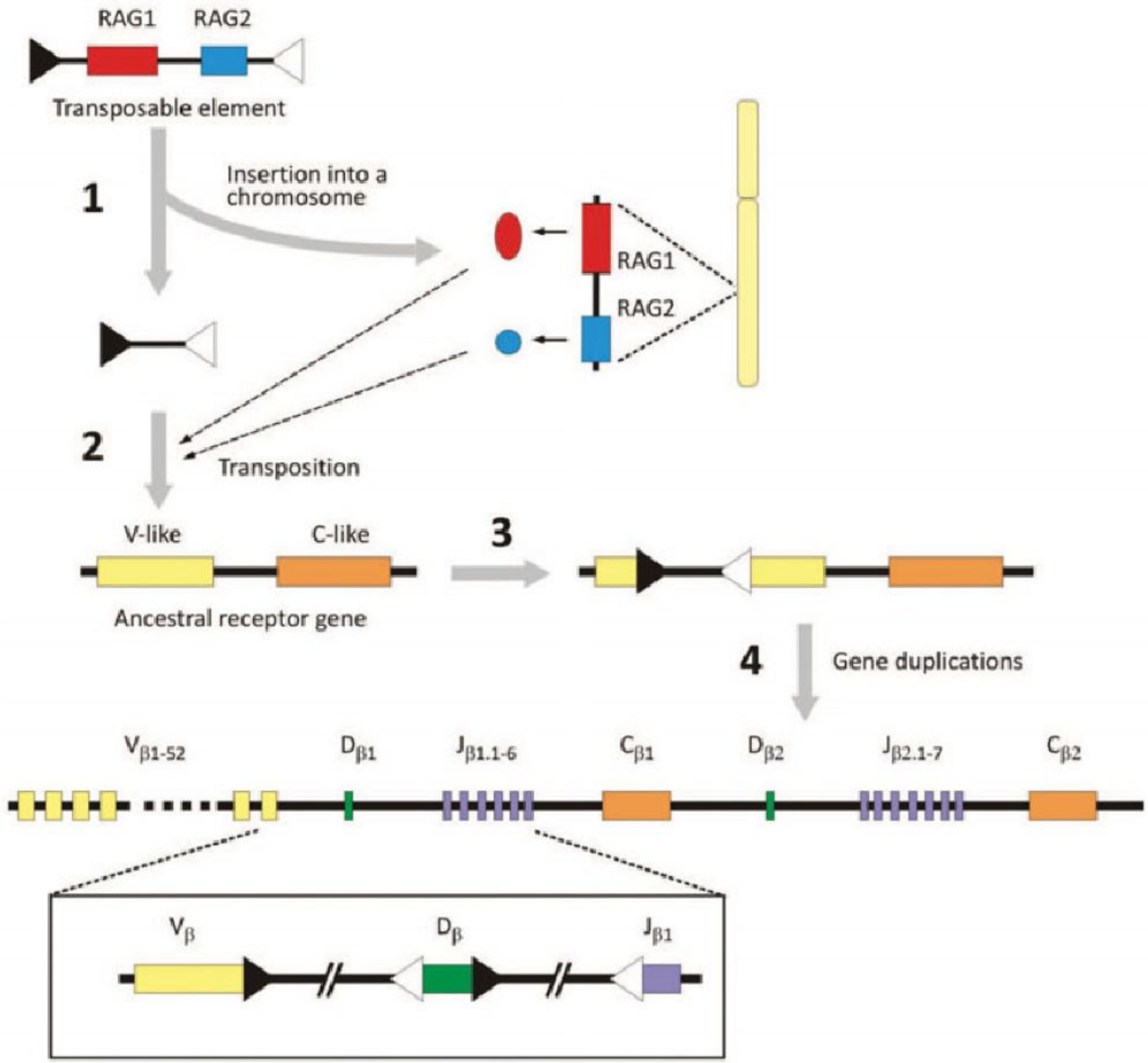
RAG1 сходен с транспозазой Transib

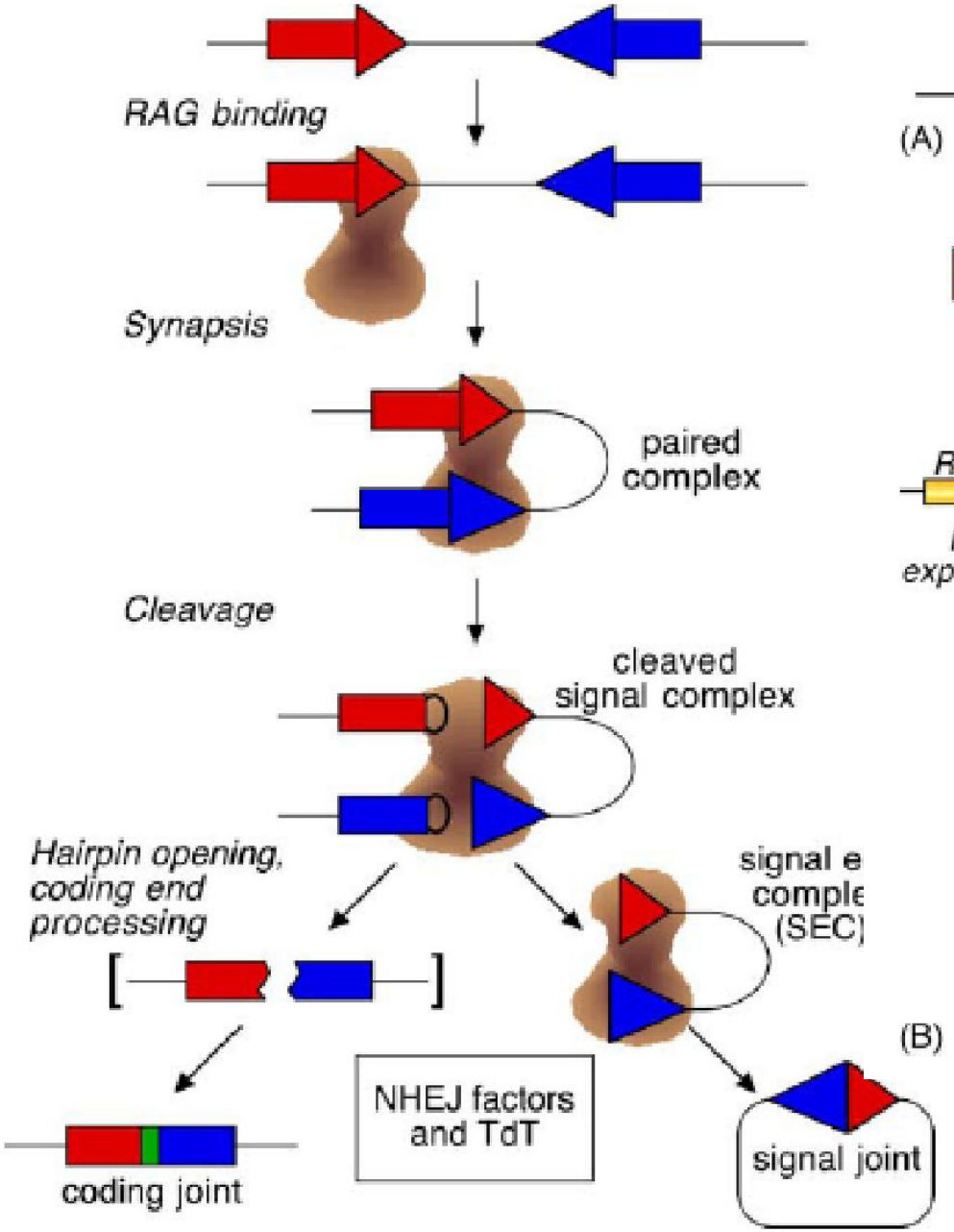


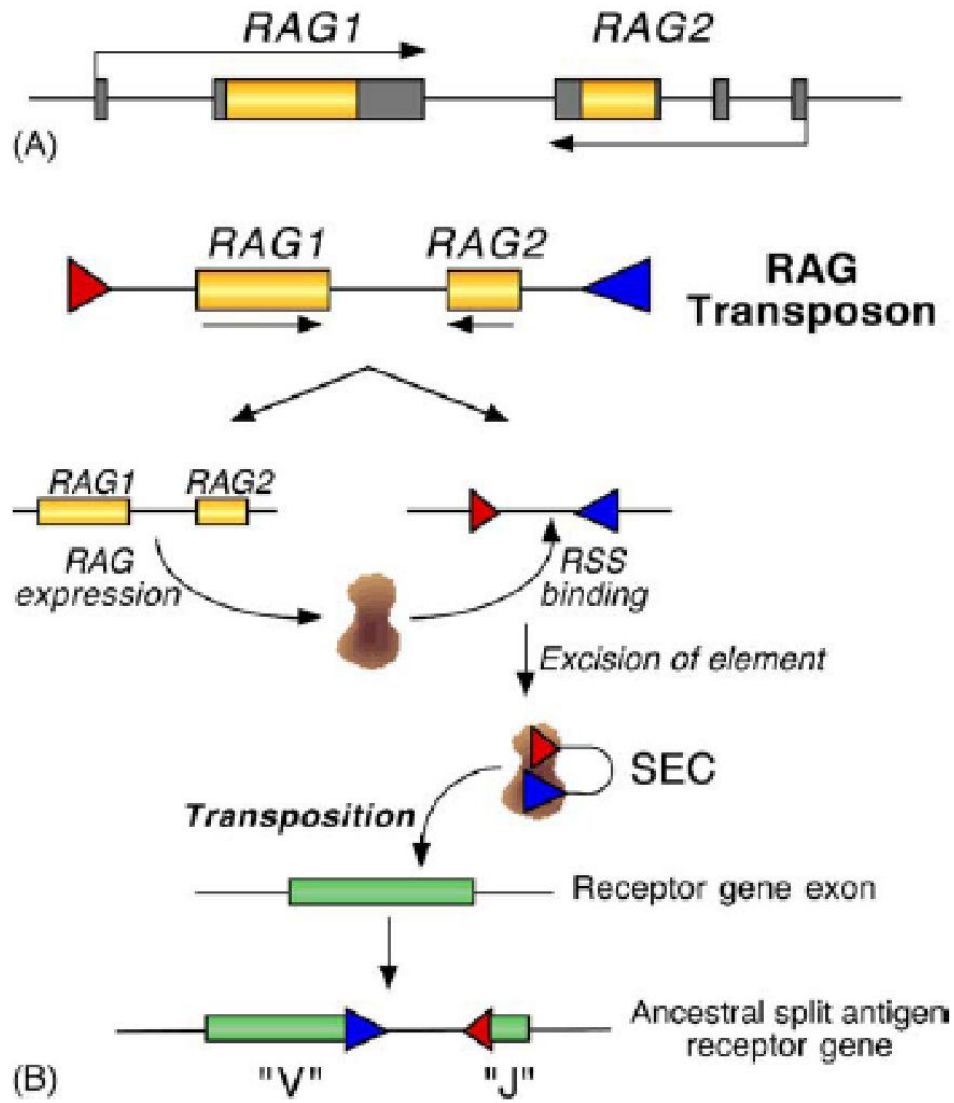
из Kapitonov, Jurka 2005

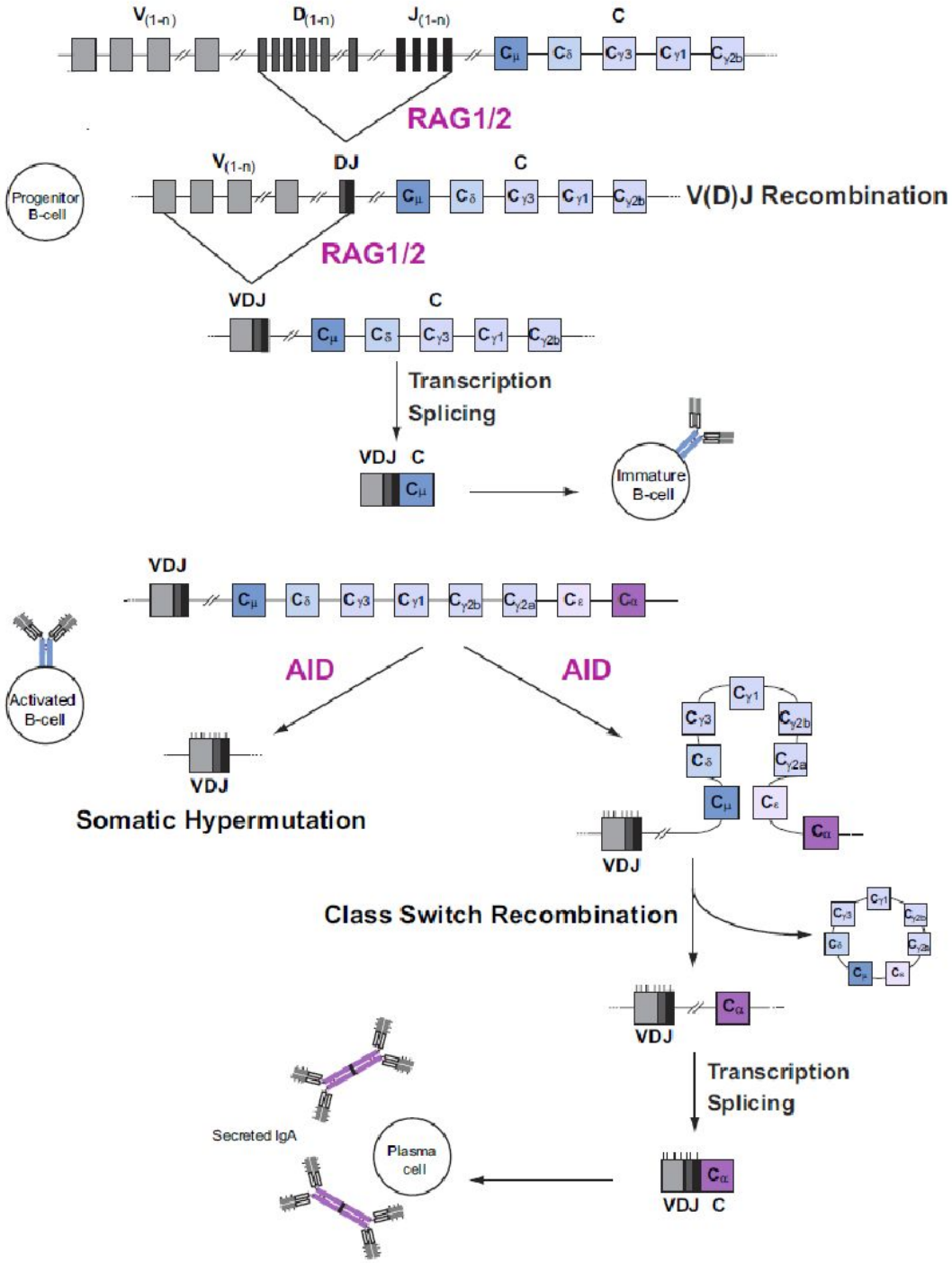
Использование транспозона «в мирных целях»



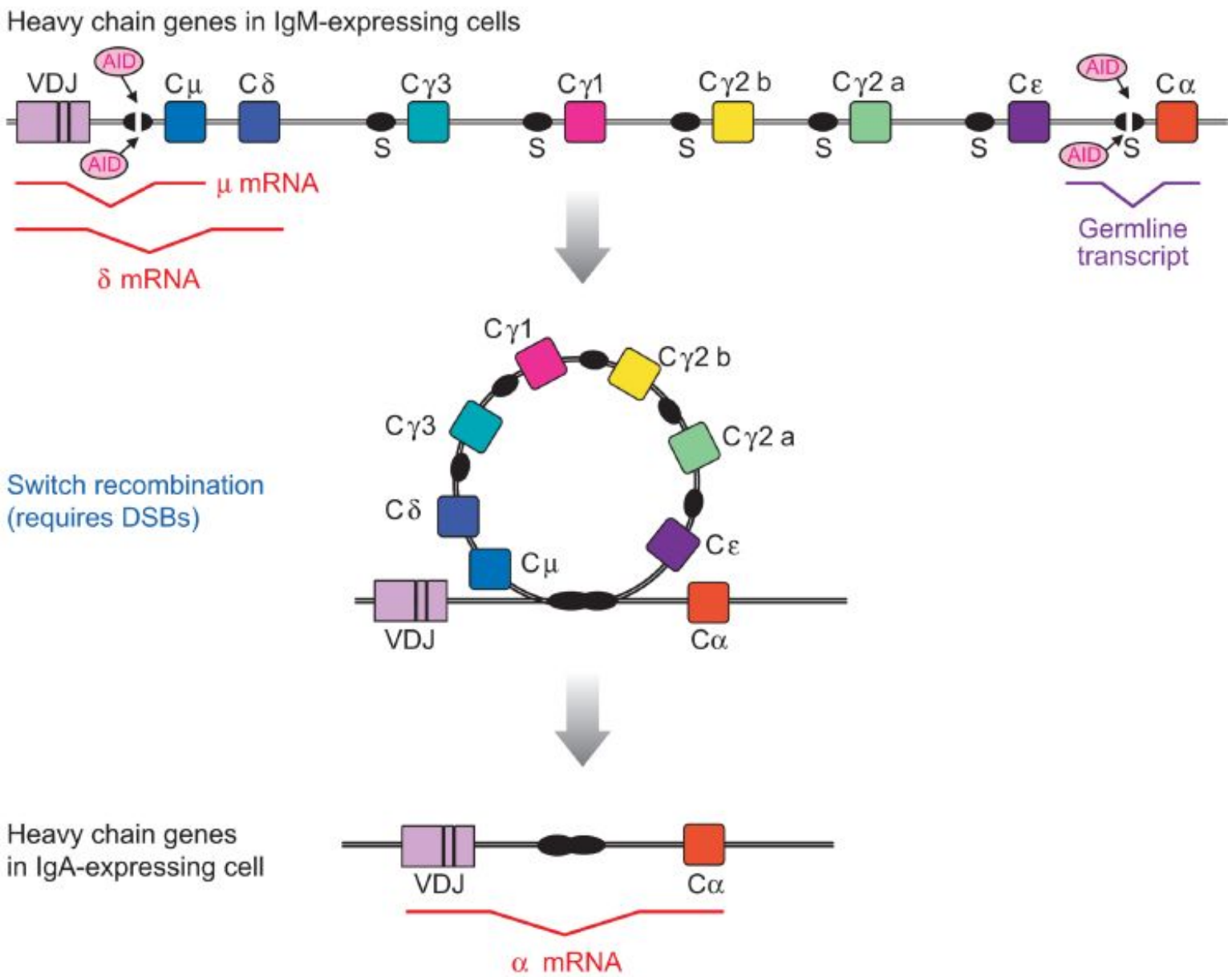

RAG1
RAG2
Transposable element
1
Insertion into a chromosome
RAG1
RAG2
2
Transposition
V-like
C-like
Ancestral receptor gene
3
4
Gene duplications
$V_{\beta 1\text{-}52}$
$D_{\beta 1}$
$J_{\beta 1.1\text{-}6}$
$C_{\beta 1}$
$D_{\beta 2}$
$J_{\beta 2.1\text{-}7}$
$C_{\beta 2}$
V_{β}
D_{β}
$J_{\beta 1}$


RAG binding
Synapsis
paired complex
Cleavage
cleaved signal complex
Hairpin opening, coding end processing
signal e
comple
(SEC)
NHEJ factors and TdT
coding joint
signal joint
(B)


RAG1
RAG2
(A)
RAG1
RAG2
RAG Transposon
RAG1
RAG2
RAG expression
RSS binding
Excision of element
SEC
Transposition
Receptor gene exon
Ancestral split antigen receptor gene
"V"
"J"


V(1-n)
D(1-n)
J(1-n)
C
Cμ
Cδ
Cγ3
Cγ1
Cγ2b
RAG1/2
Progenitor B-cell
V(1-n)
DJ
C
V(D)J Recombination
RAG1/2
VDJ
C
Transcription
Splicing
VDJ C
Immature B-cell
VDJ
Cε
Cα
Cγ2a
Activated B-cell
AID
AID
VDJ
Somatic Hypermutation
VDJ
Class Switch Recombination
VDJ
Transcription
Splicing
Secreted IgA
Plasma cell
VDJ C

Механизм переключения классов антител



Рецепторы врожденного иммунитета могли возникнуть из рецепторов NK-клеток

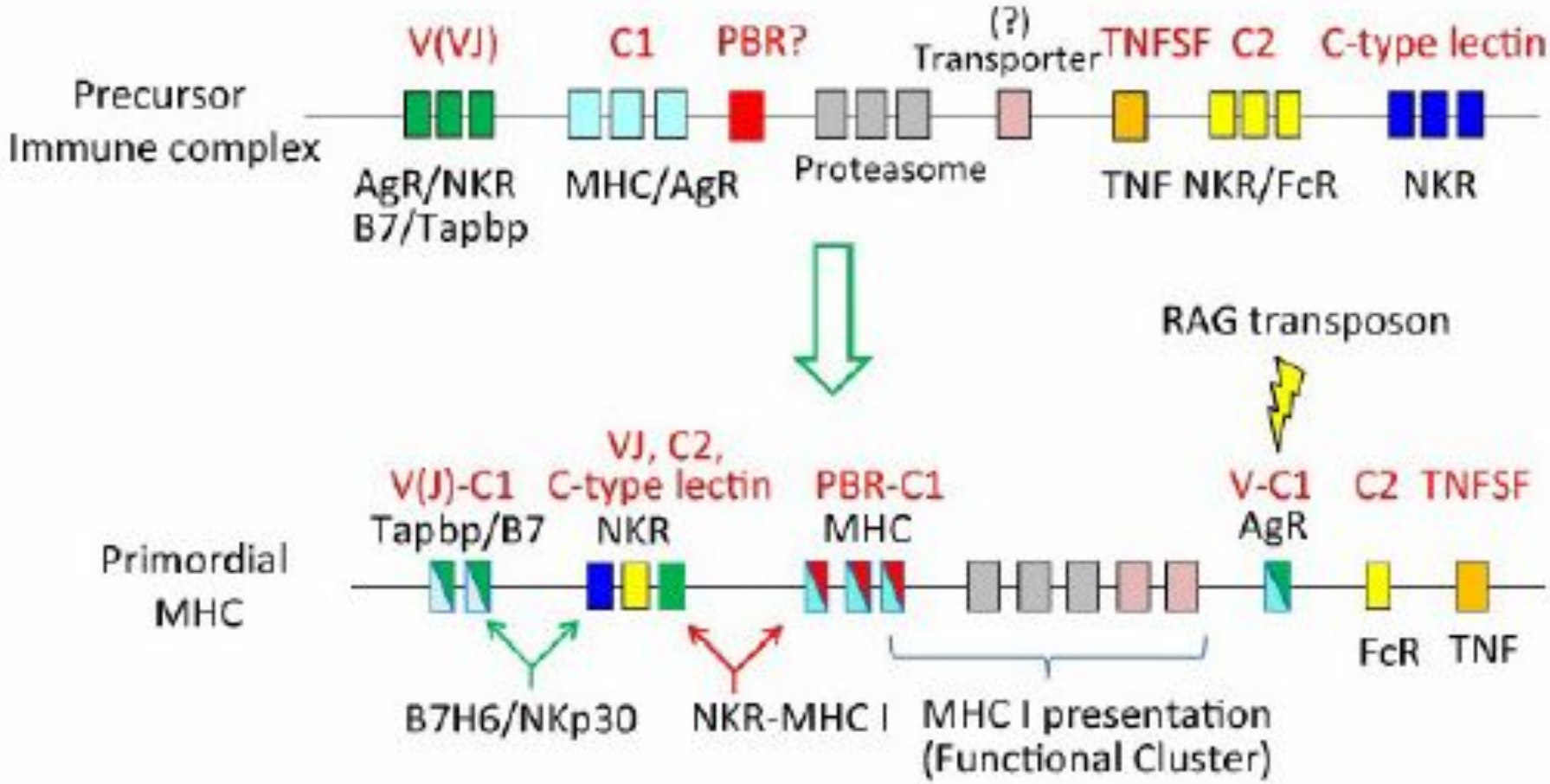


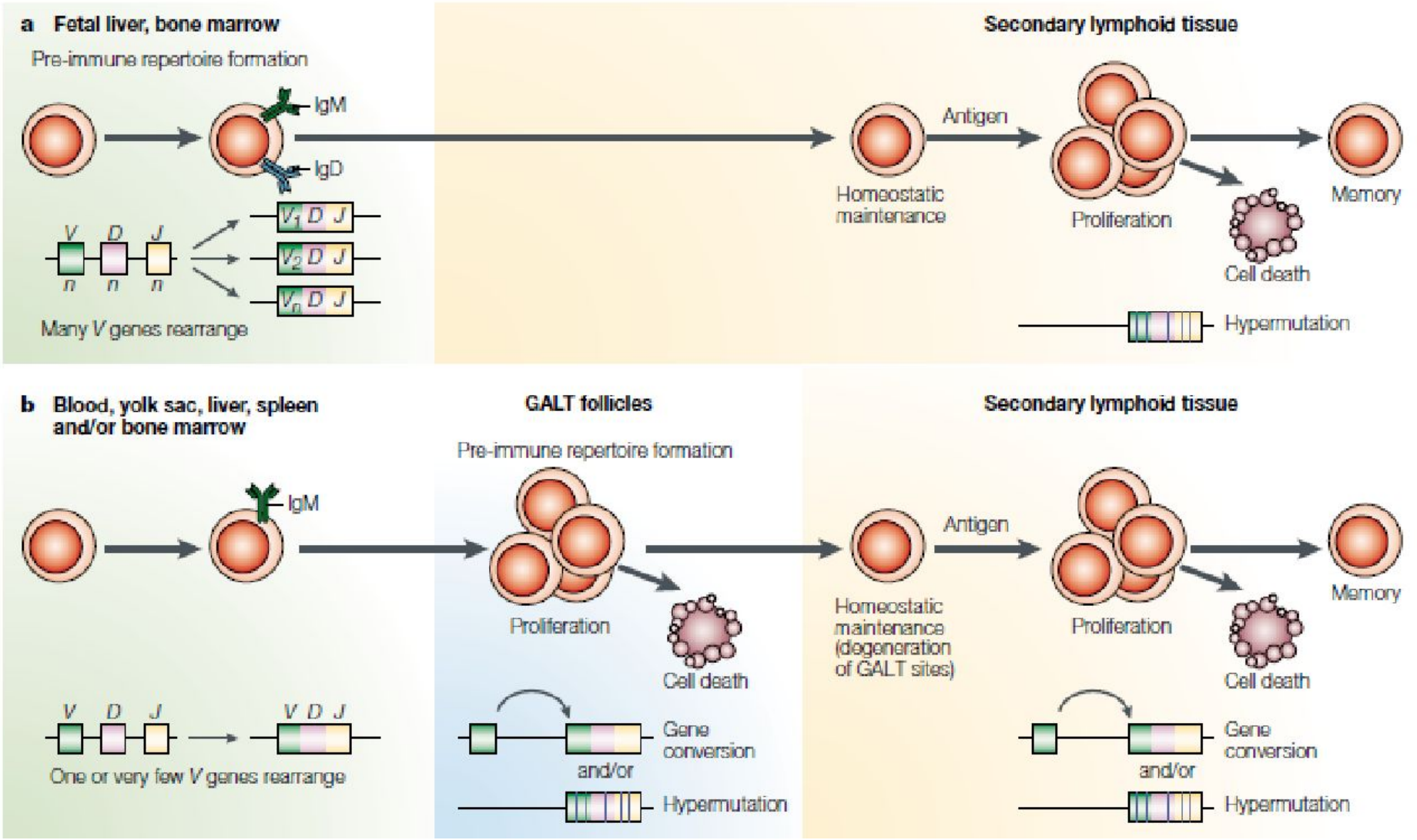
TABLE 1. Ig Gene Diversification System of Mammalian Species and Chicken

	Primary B cell repertoire formation	
	Mechanism	Organ
Human	V(D)J recombination	Bone marrow
Mouse	V(D)J recombination	Bone marrow
Rabbit	Gene conversion and somatic hypermutation	Appendix
Cattle	Gene conversion and somatic hypermutation	Illeal Peyer's partches
Swine	Gene conversion and somatic hypermutation	Illeal Peyer's partches
Horse	Gene conversion and somatic hypermutation	Illeal Peyer's partches
Chicken	Gene conversion and somatic hypermutation	The bursa of Fabricius

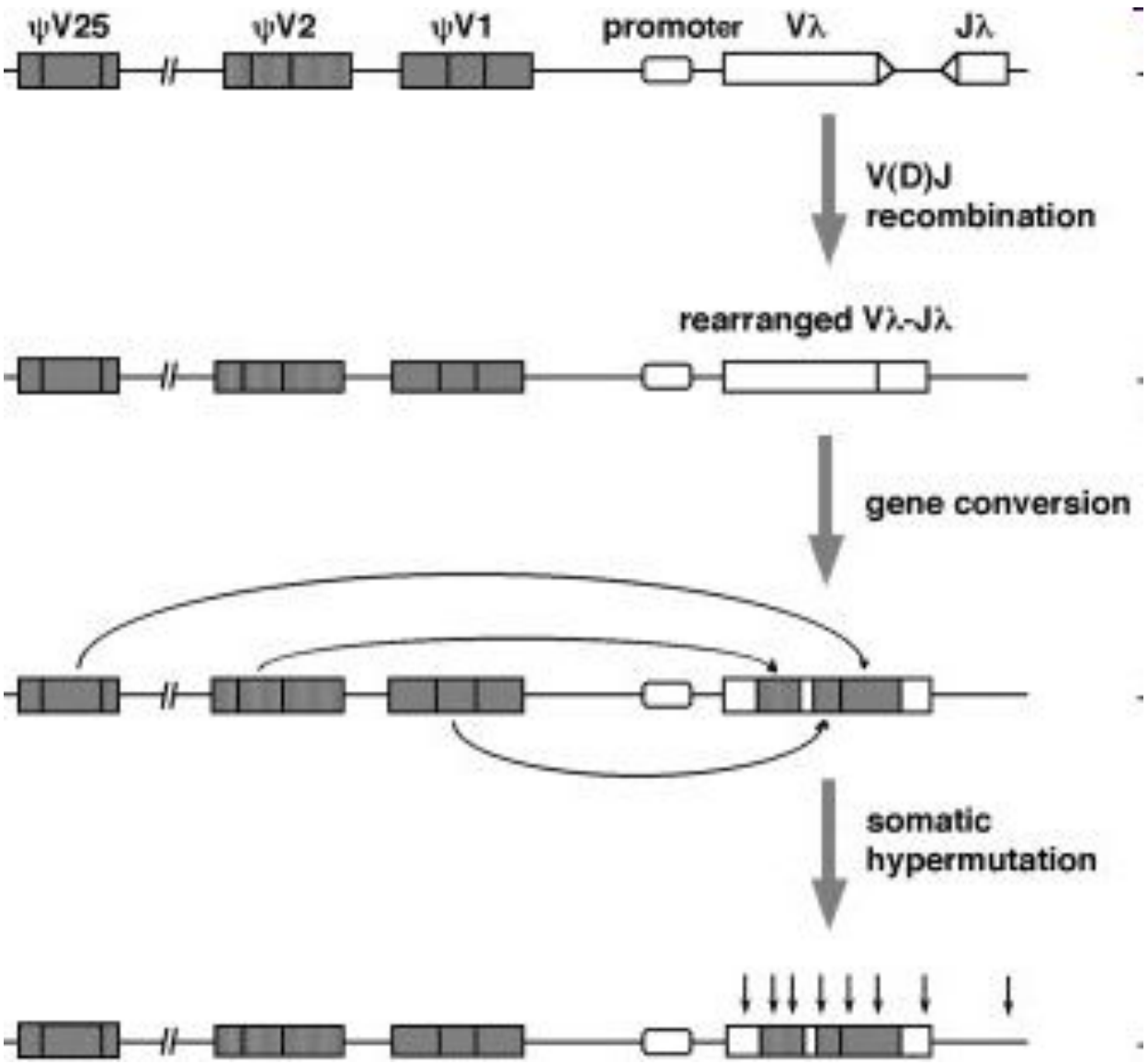
TABLE 2. DT40 Mutants Related to Gene Conversion and Somatic Hypermutation

	Enzyme activity	DT40 mutant phenotype	References
RAG-2	V(D)J recombinase	No defect in gene conversion	Takeda et al., 1992
RAD51	Homologous recombination	Lethal	Sonoda et al., 1998
RAD52	Homologous recombination	Slight reduction of targeted integration	Yamaguchi-Iwai et al., 1998
RAD54	Homologous recombination	Reduction of gene conversion Reduction of targeted integration Hypersensitivity to DNA damaging reagent	Bezzubova et al., 1997
NBS1	Homologous recombination	Reduction of gene conversion Reduction of targeted integration	Tauchi et al., 2002
AID	Cytidine deaminase	No gene conversion activity	Arakawa et al., 2002
RAD51-paralogues (XRCC2, XRCC3, RAD51B)	Homologous recombination	Shift from gene conversion to somatic hypermutation	Sale et al., 2001
UNG	Uracil DNA glycosilase (base excision repair)	Shift of hypermutation pattern from transversion to transition	Di Noia and Neuberger, 2002
REV1	Deoxycytidyl transferase	Reduction of somatic hypermutation	Simpson and Sale, 2003

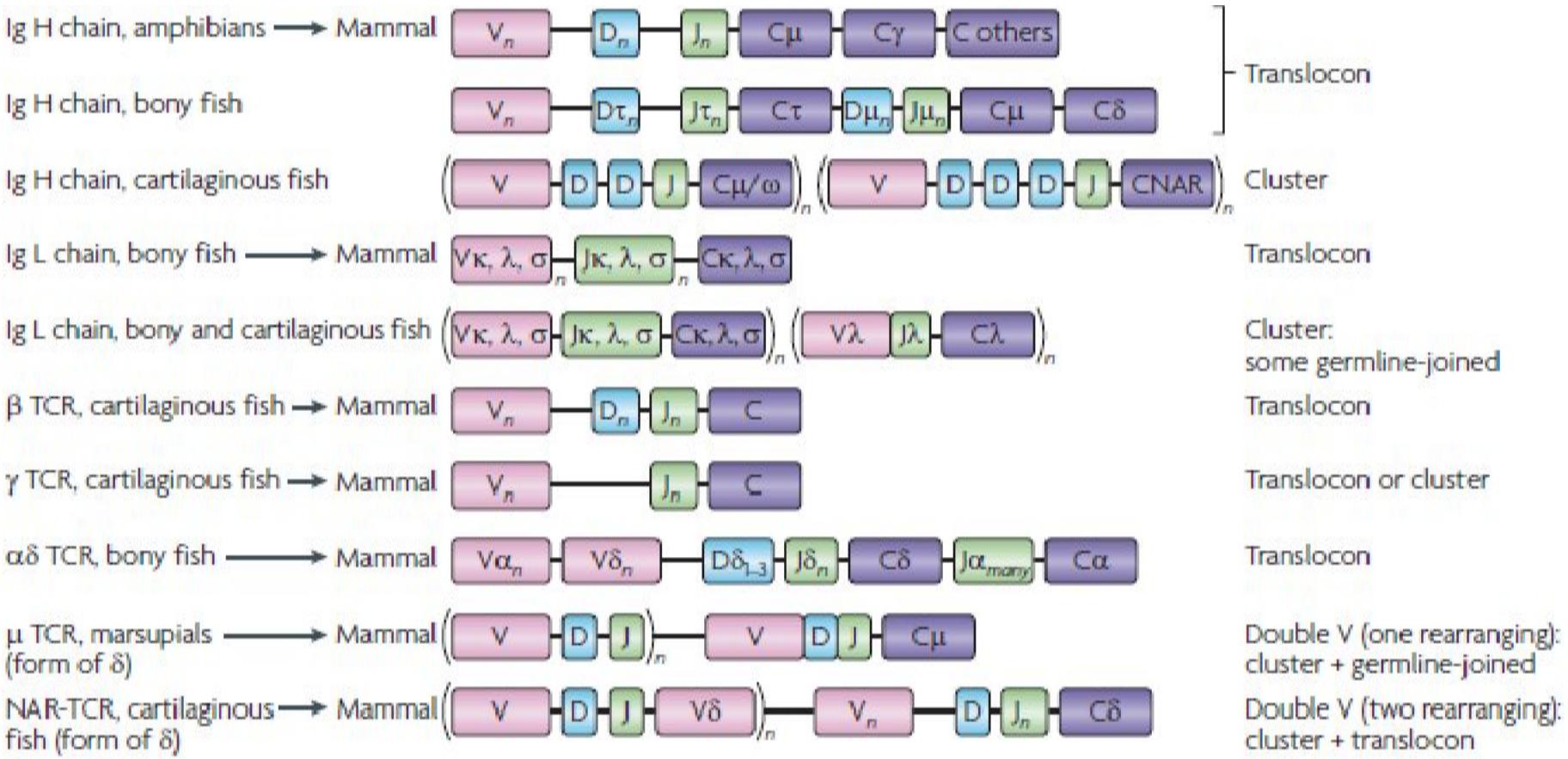
Rag-зависимая рекомбинация или конверсия генов?



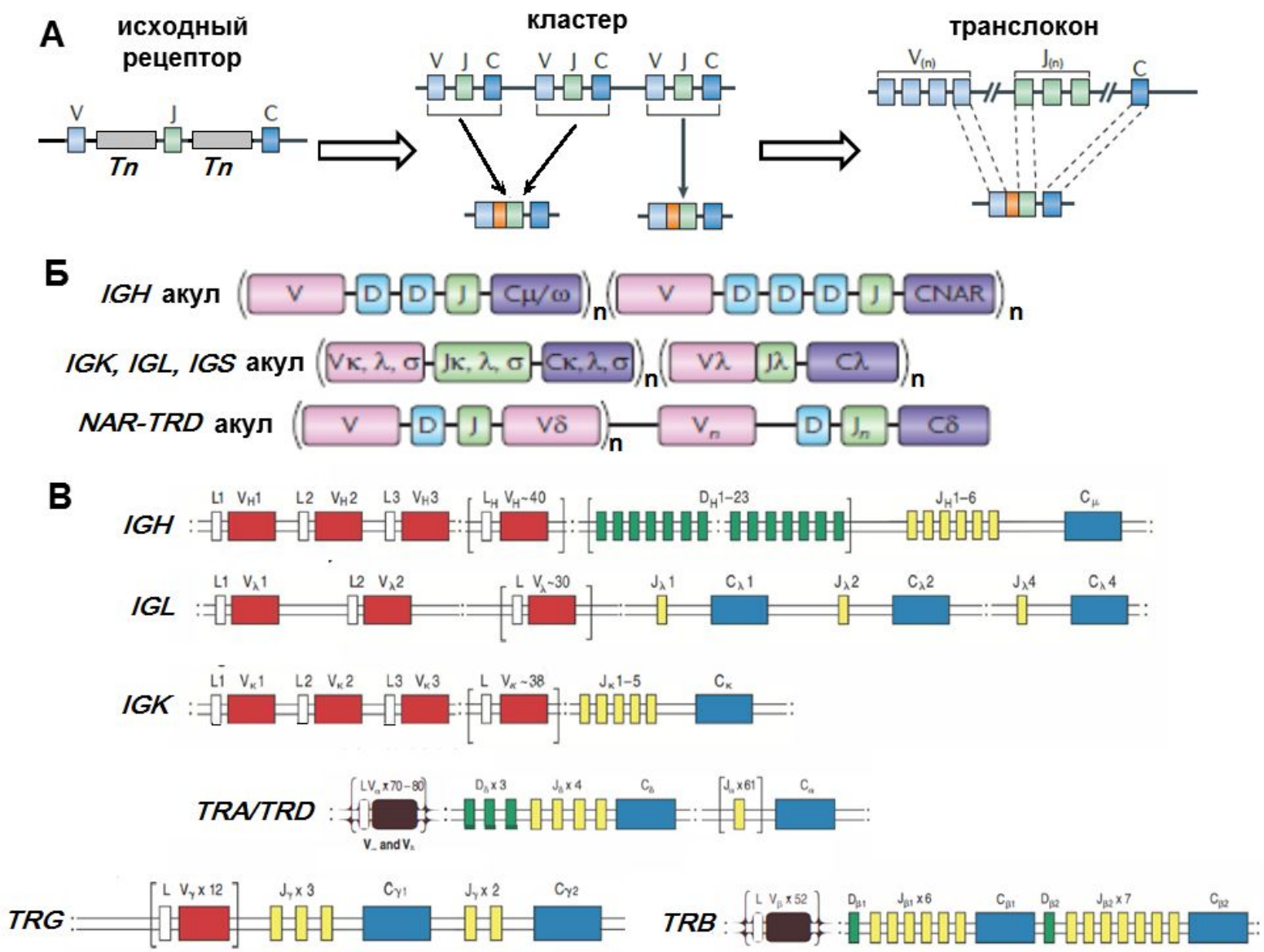
Общая схема конверсии



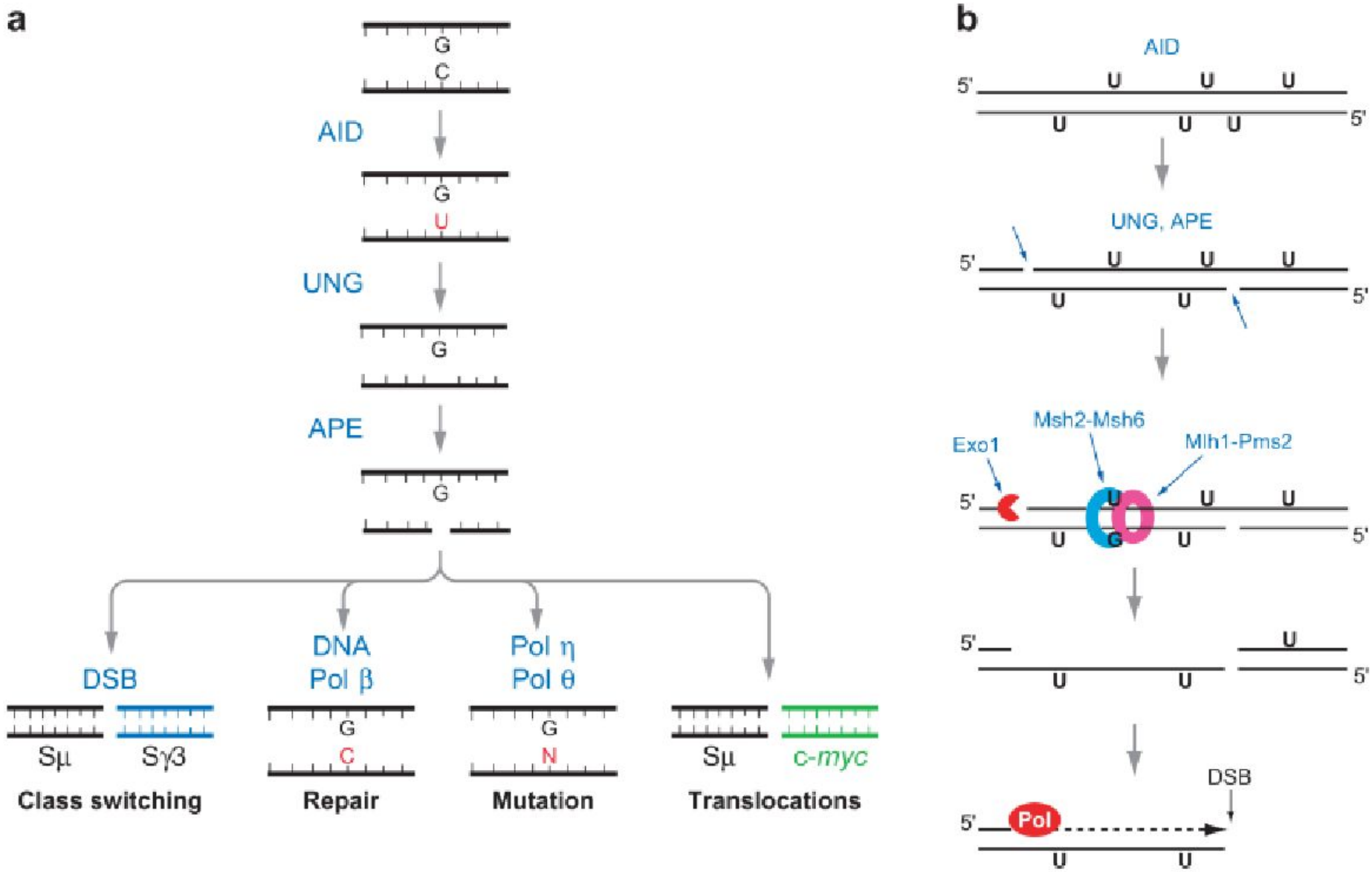
Организация генов в кластеры или транслоконы



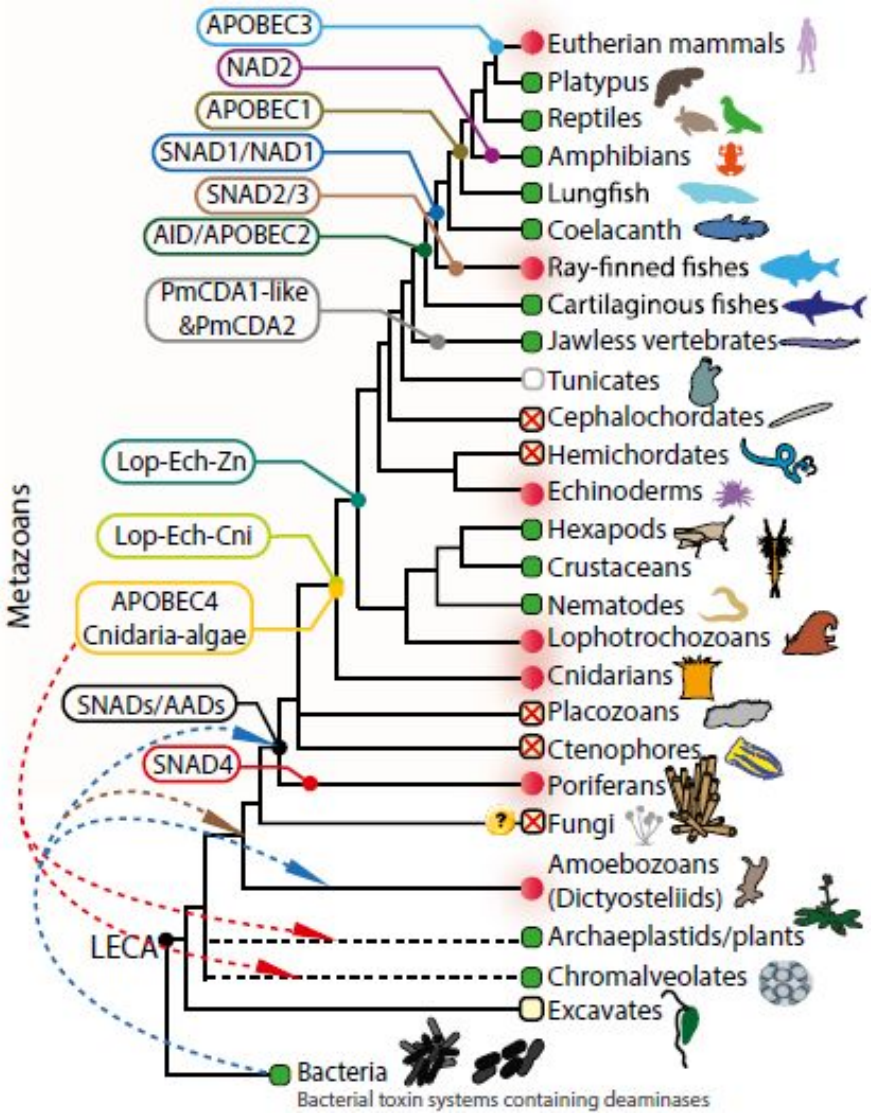
Организации генов в кластеры более примитивна

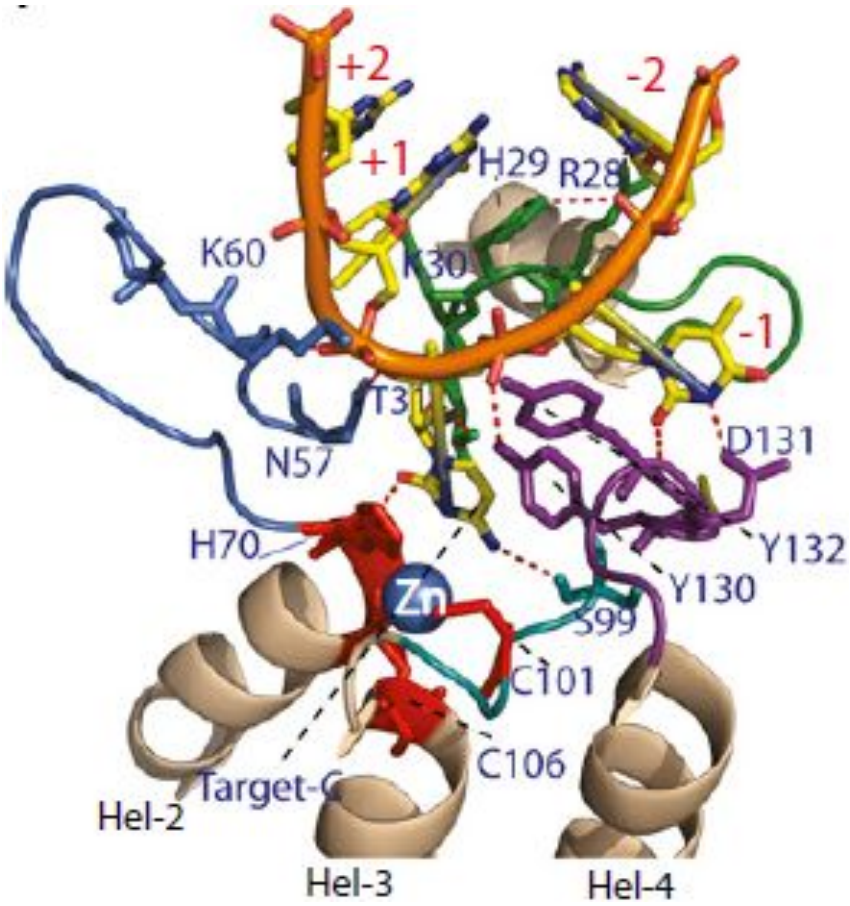


Для переключения классов снова важна цитидин-дезаминаза AID



Эволюция семейств цитидиндезаминаз





- Следующая лекция 16 апреля – об особенностях иммунных систем отдельных классов Челюстноротых