

Эволюционная иммунология

Лекция 9 «Возникновение адаптивного иммунитета»

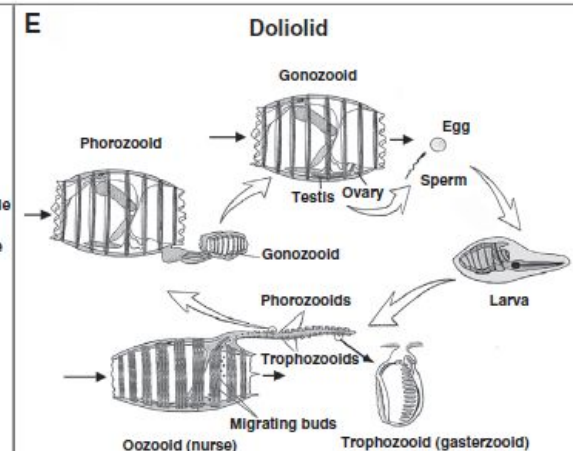
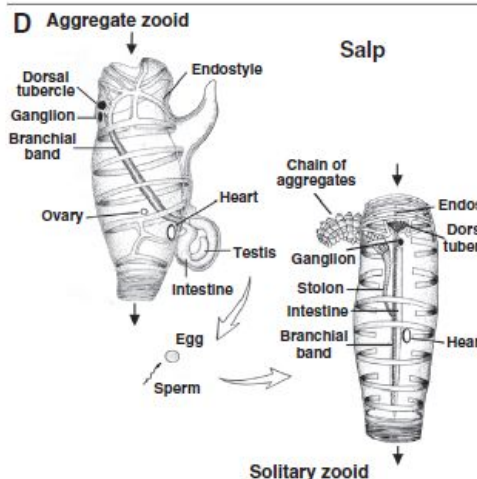
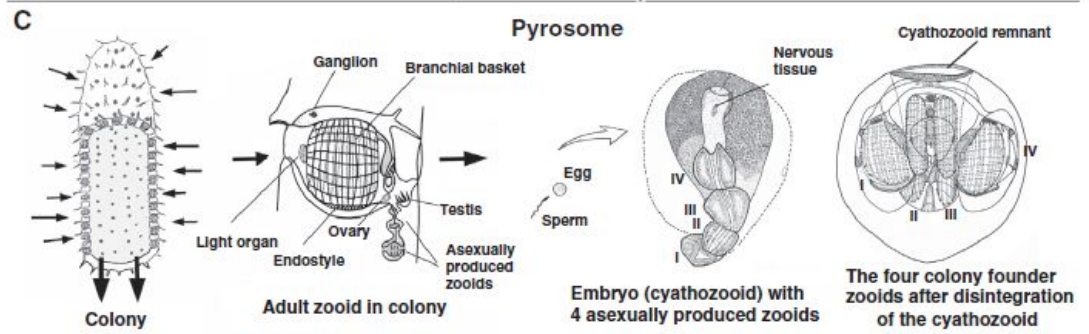
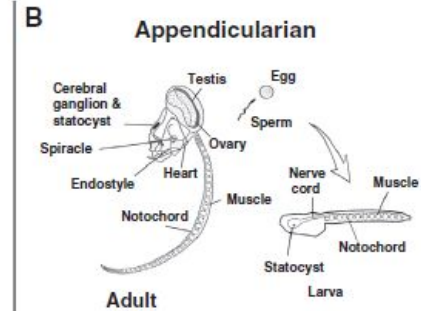
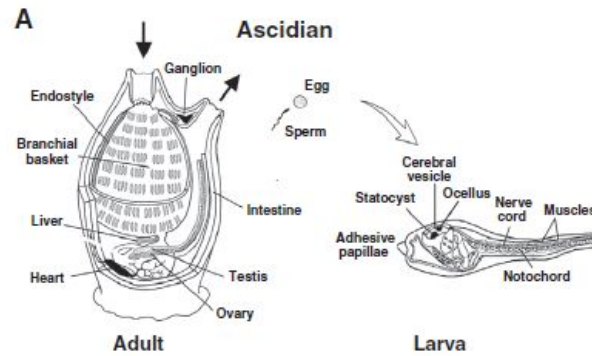
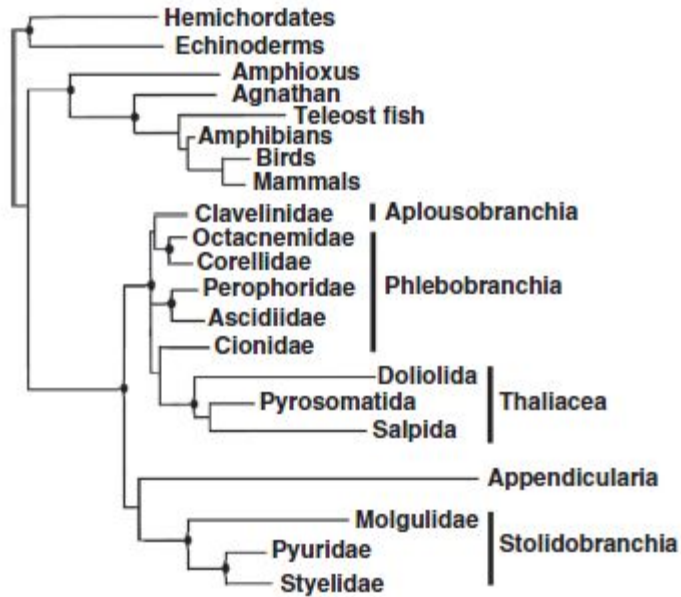


Шилов Е.С.
9 апреля 2018

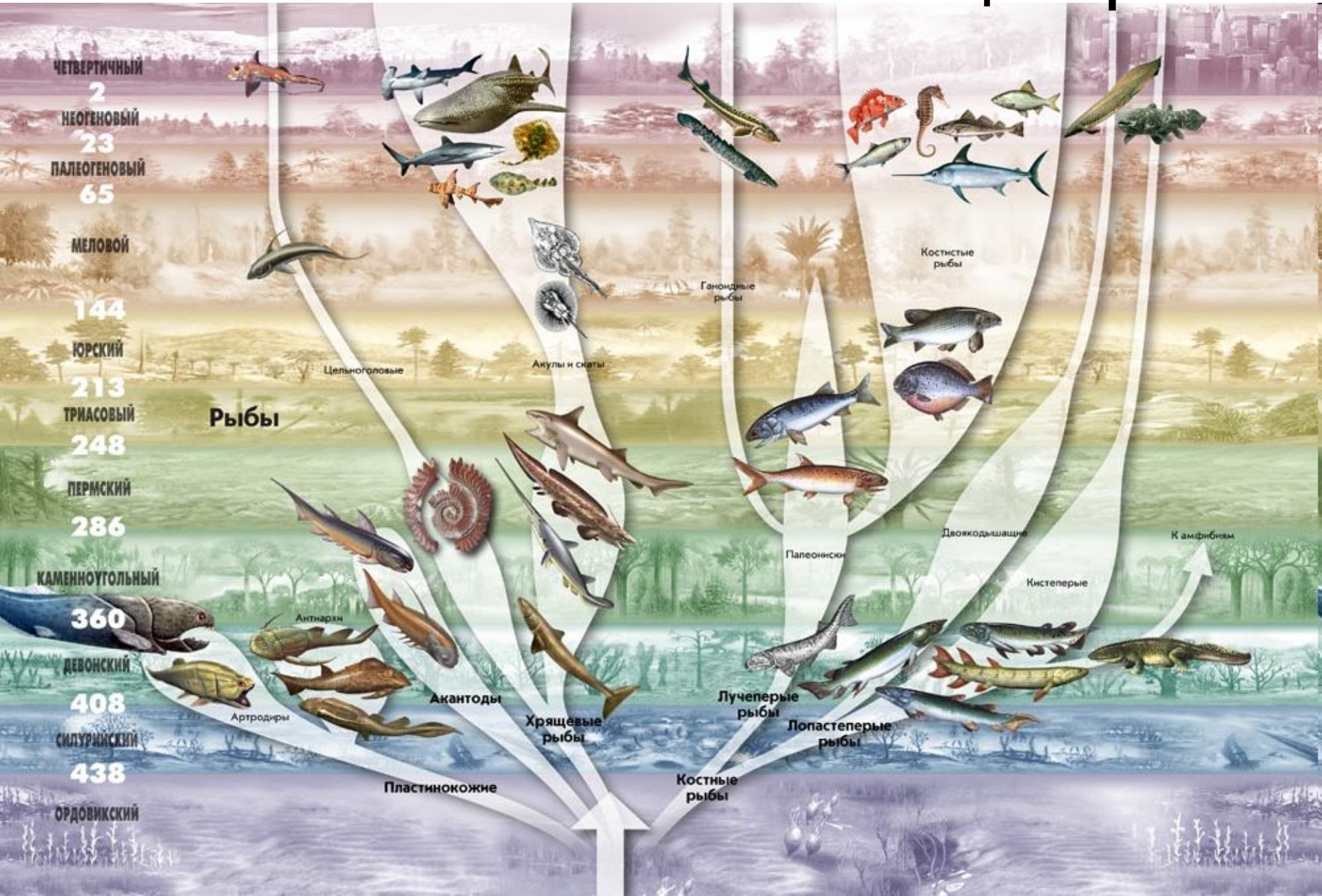


**Эволюция иммунной системы на фоне
филогенетического дерева животных**

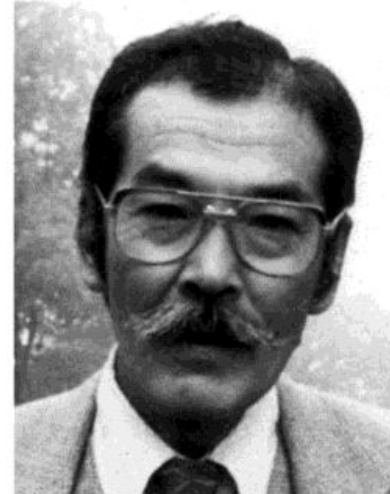
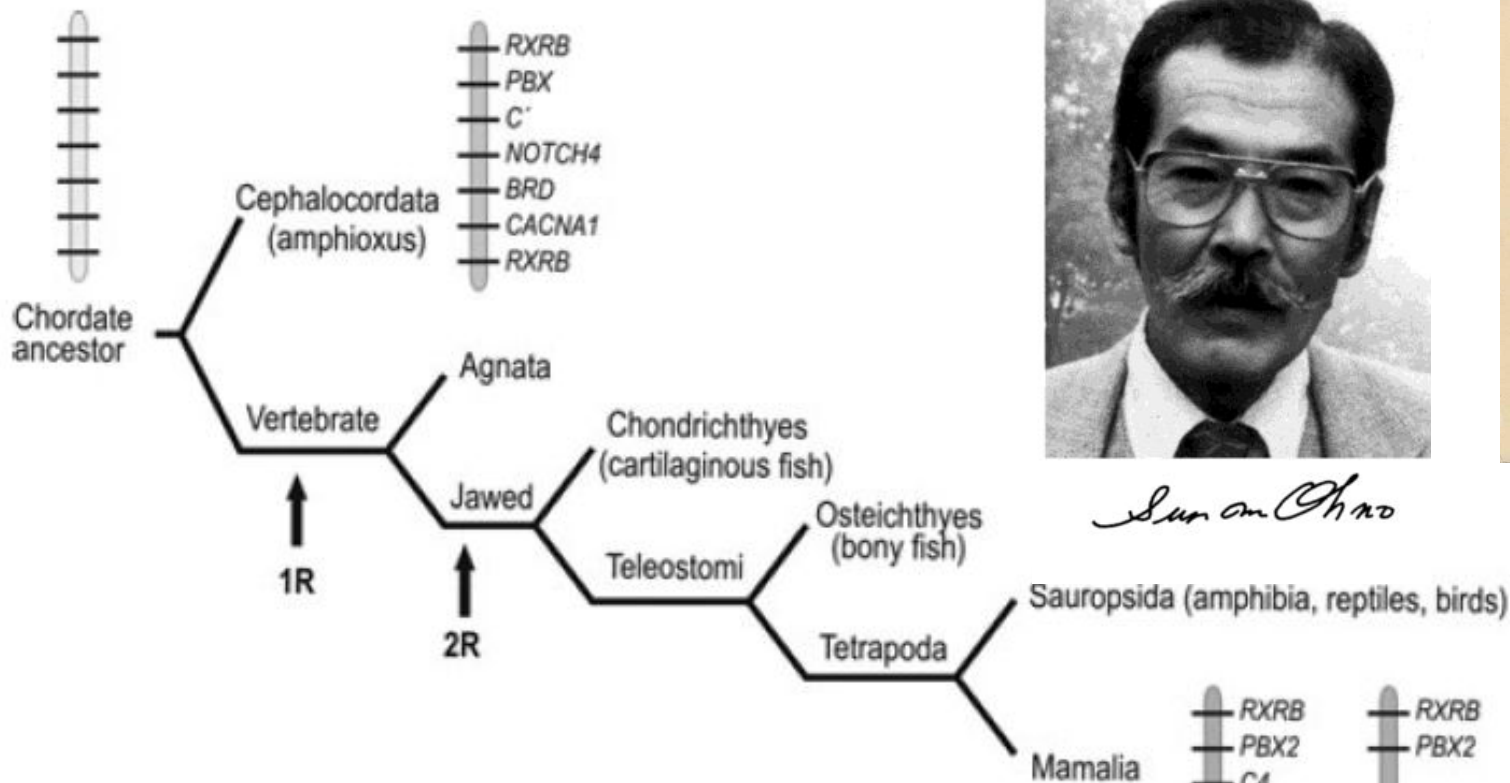
Систематика и эволюция оболочников



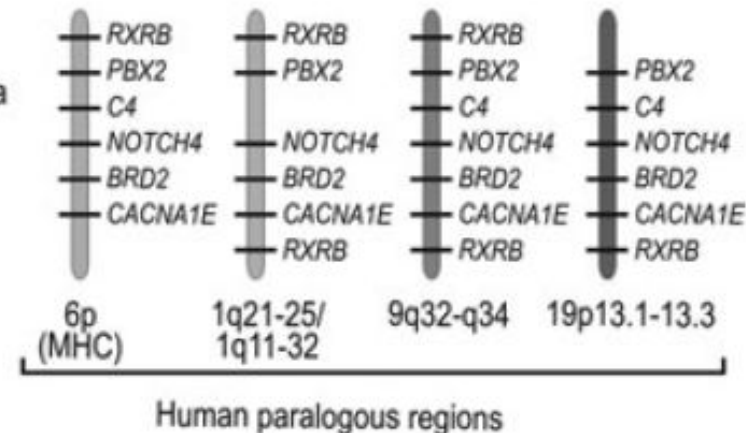
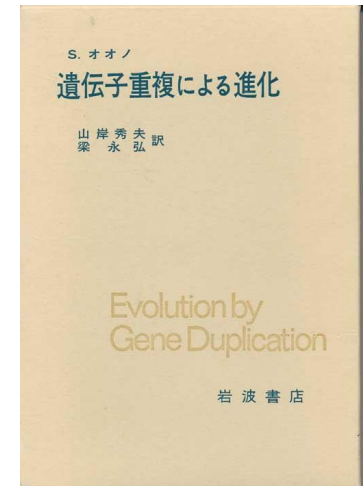
Систематика и эволюция рыб



Две полногеномные дупликации как источник разнообразия паралогов



Susumu Ohno



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

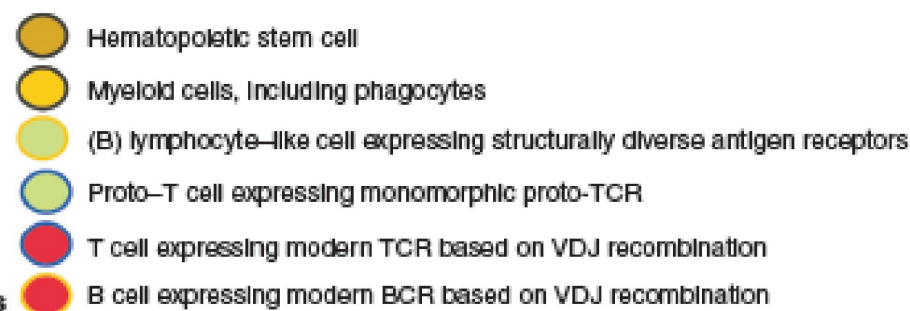
- Что возникло раньше, антитела или Т-клеточные рецепторы?
- Что возникло раньше, Т-клеточные рецепторы или МНС?
- Что возникло раньше, МНС I или МНС II?
- Что возникло раньше, трансплантационный иммунитет, или презентация антигена?
- Что возникло раньше, связывающая бороздка или механизмы загрузки антигенных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

По поводу чего уже есть консенсус:

Древнее всего генетические программы, регулирующие гематопоез.

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

Гипотеза Т. Boehm

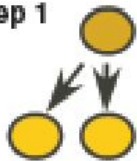


Lymphocyte-like cells

Lymphoid organs

Comments

Step 1

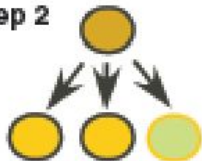


Myeloid tissue

Invertebrates:

Hematopoietic system gives rise to phagocytes that express germline-encoded pattern-recognition receptors (such as TLRs); somatic quality control unnecessary

Step 2

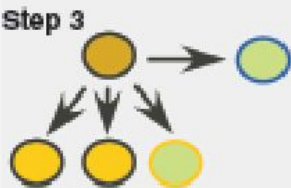


Lympho-myeloid tissue
(typhlosole, spleen)

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

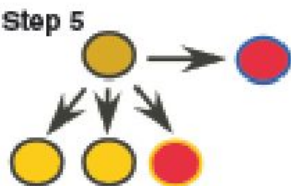


Lympho-myeloid tissue
(bone marrow or
equivalent); thymus

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

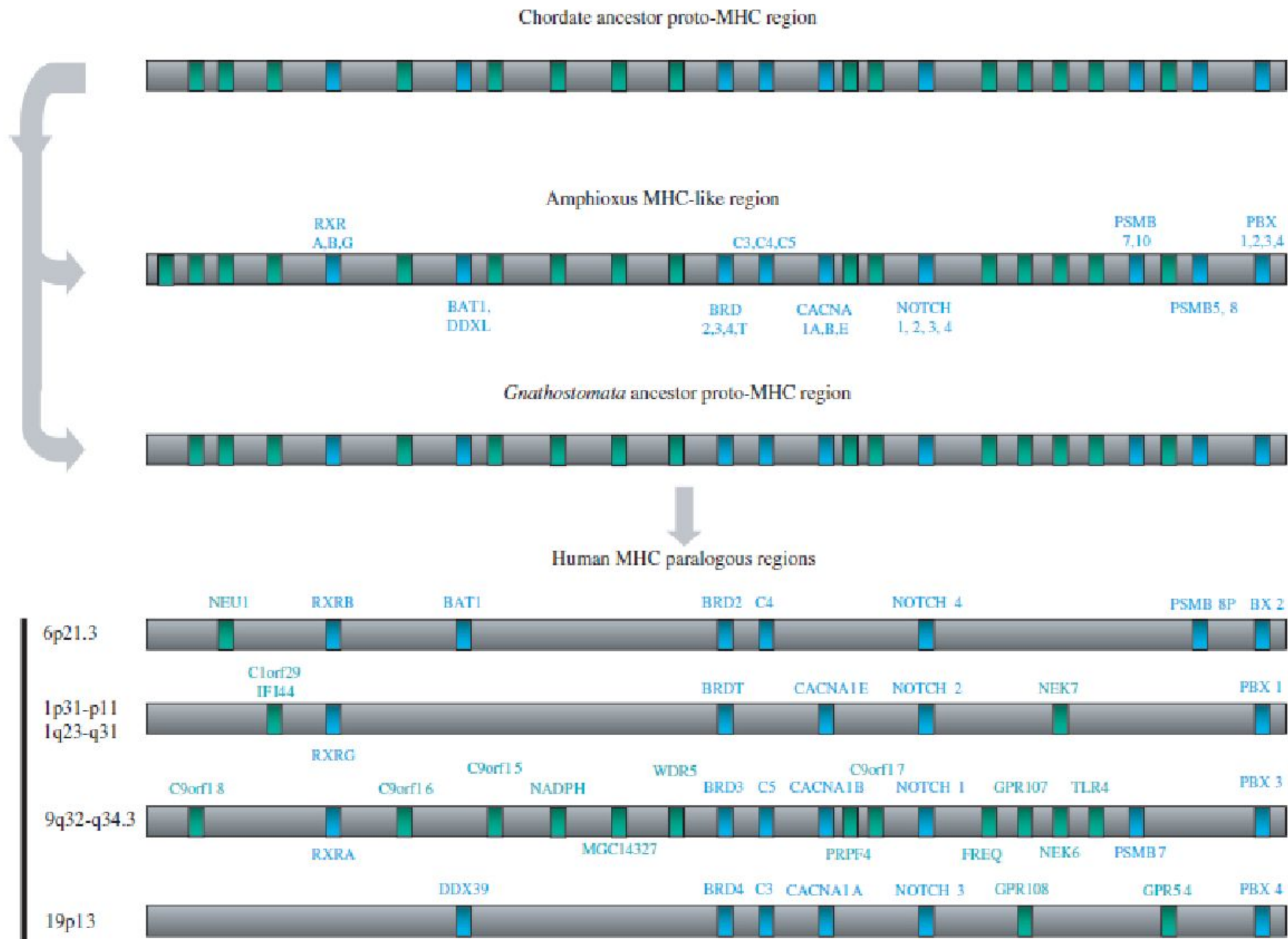


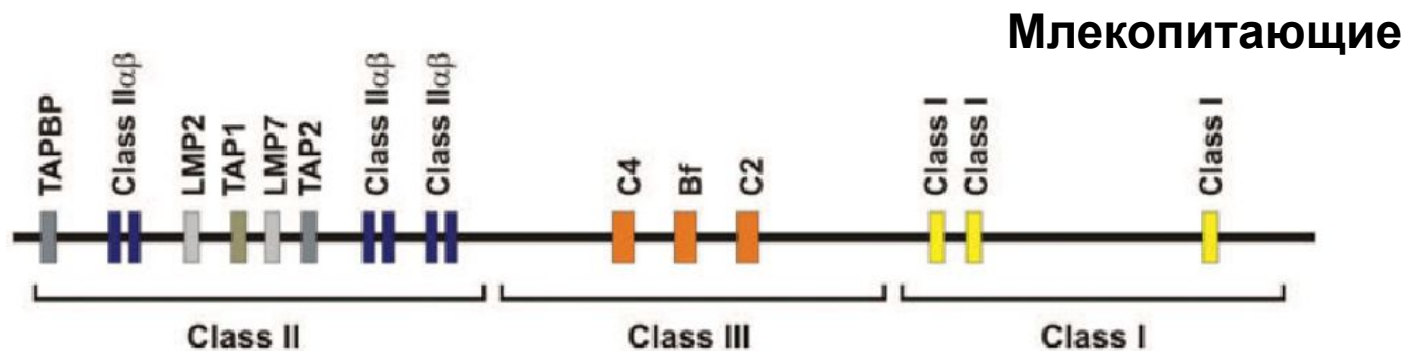
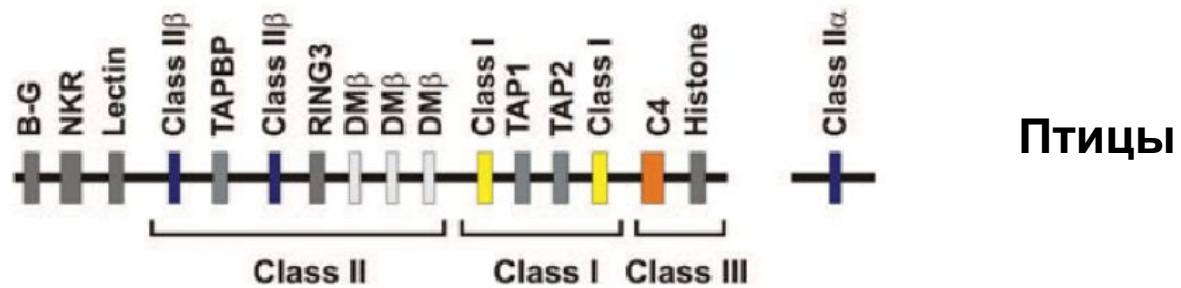
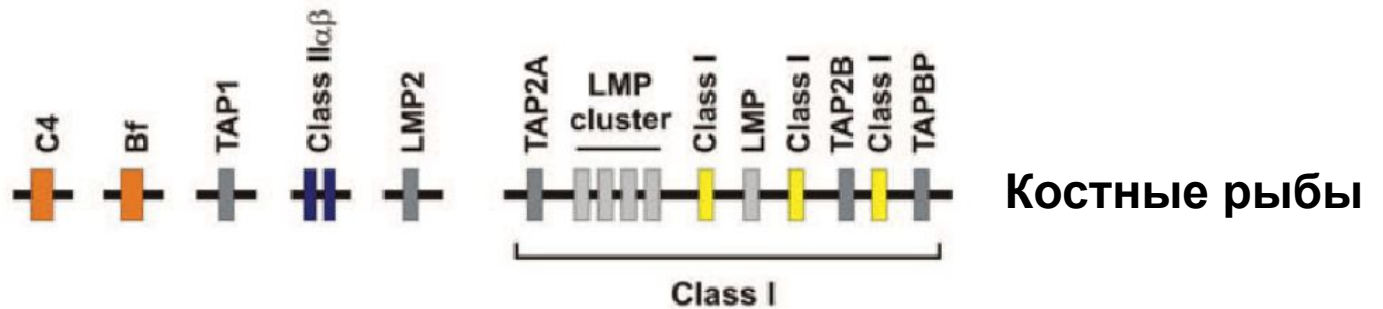
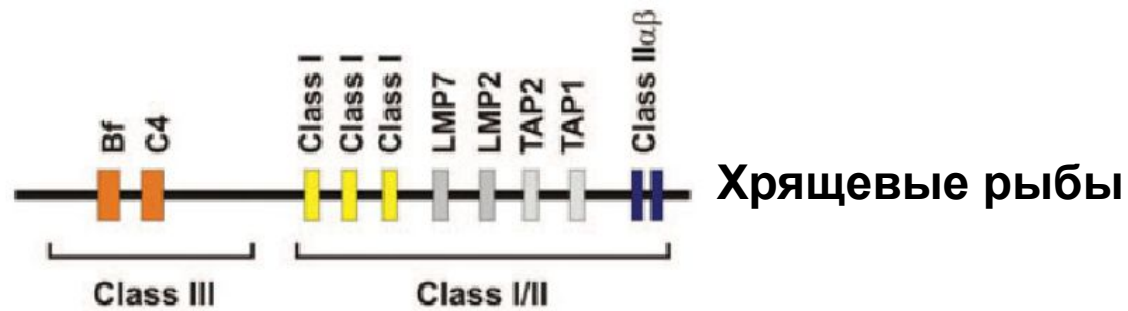
Lympho-myeloid tissue
(bone marrow or
equivalent); thymus

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

Evolutionary time





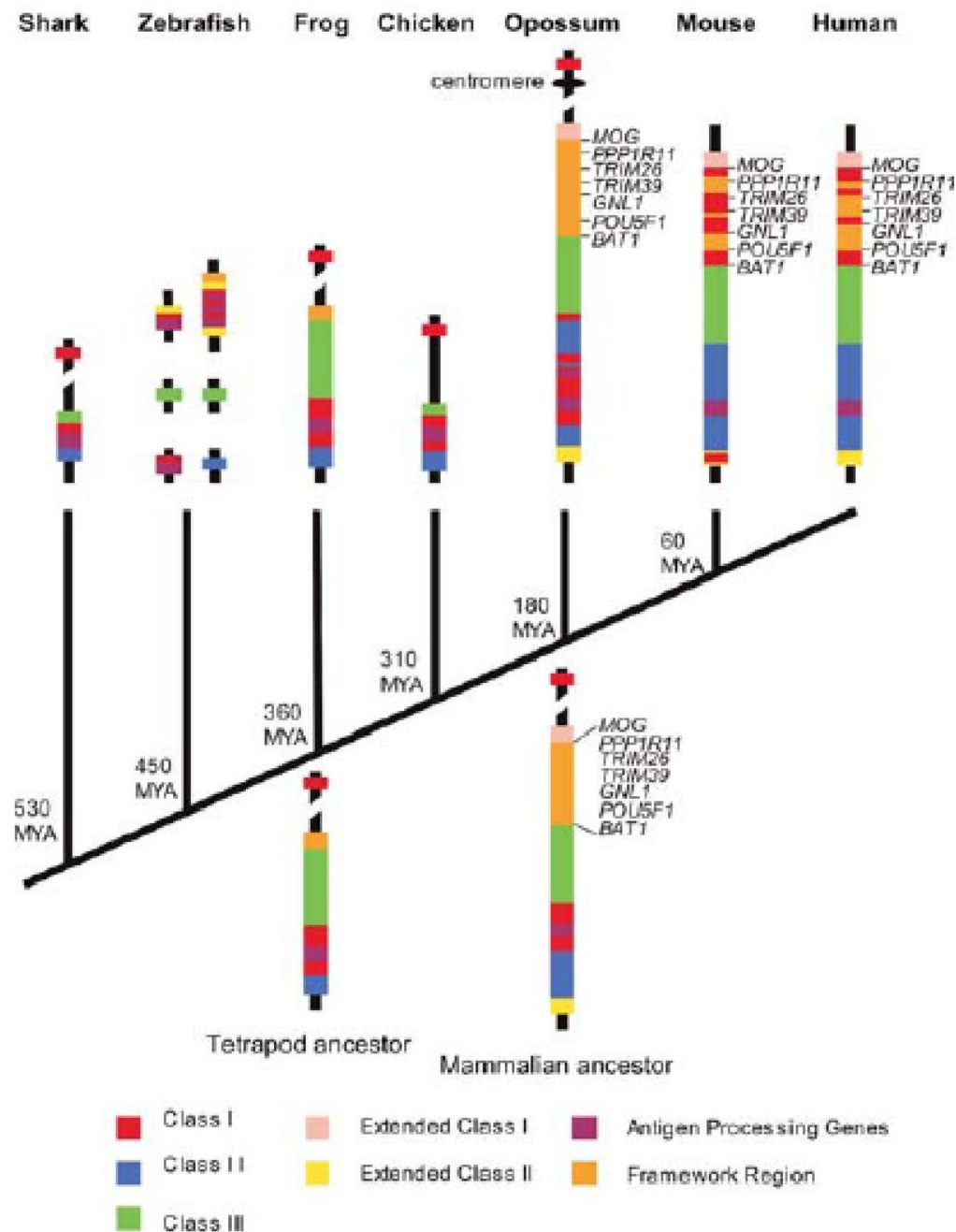
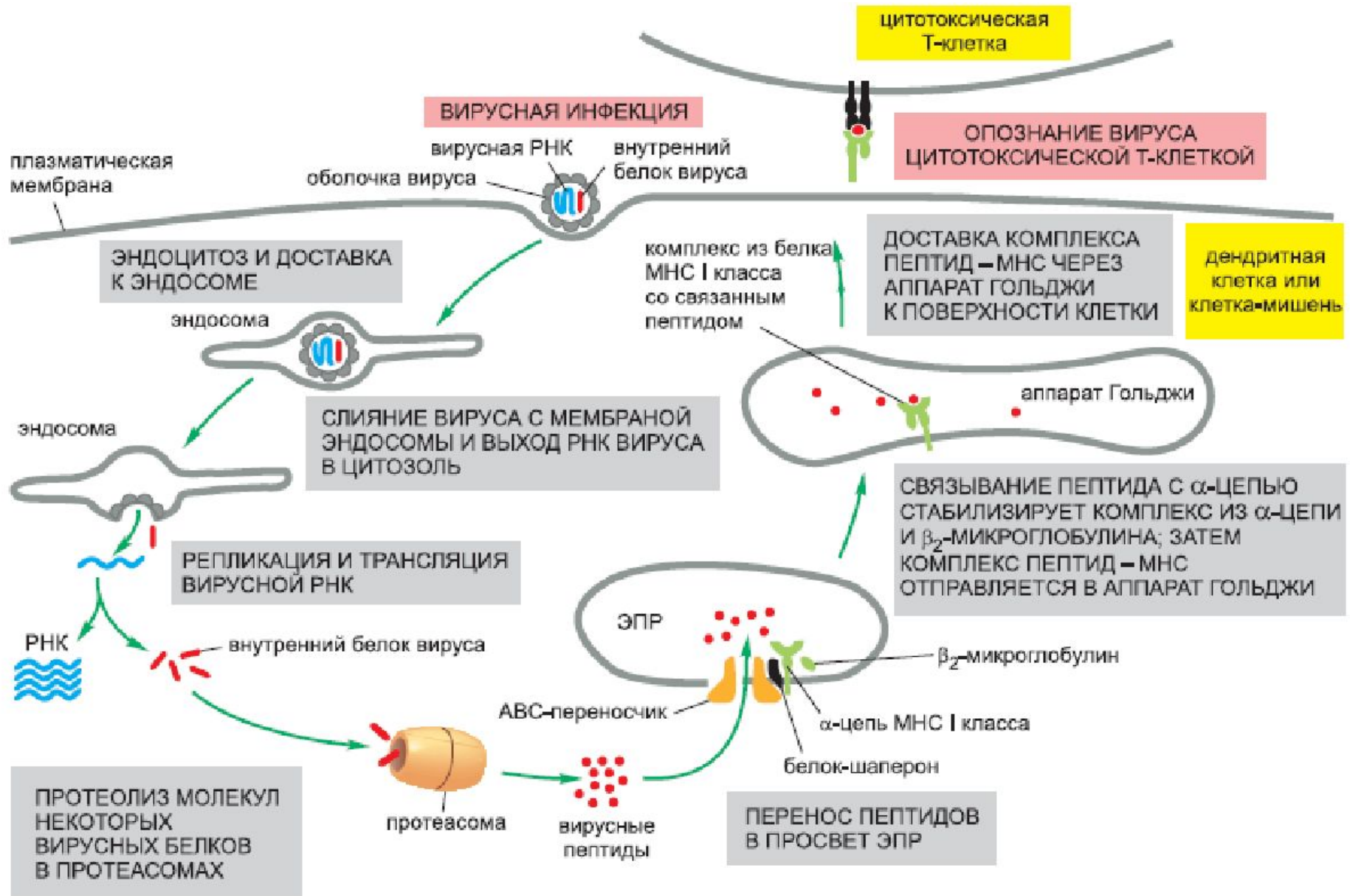
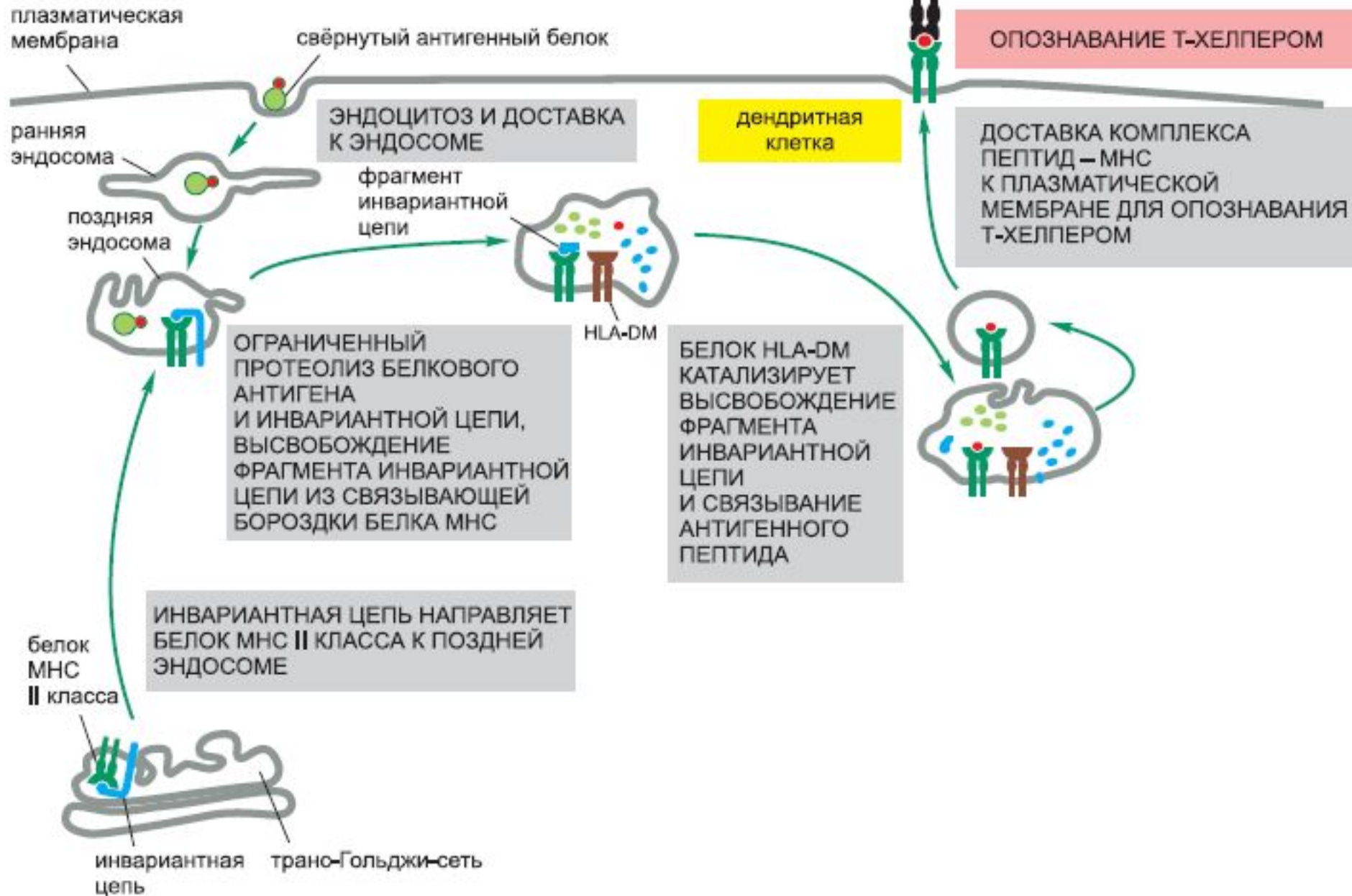


Figure 4. A Model of the Evolution of the Mammalian MHC

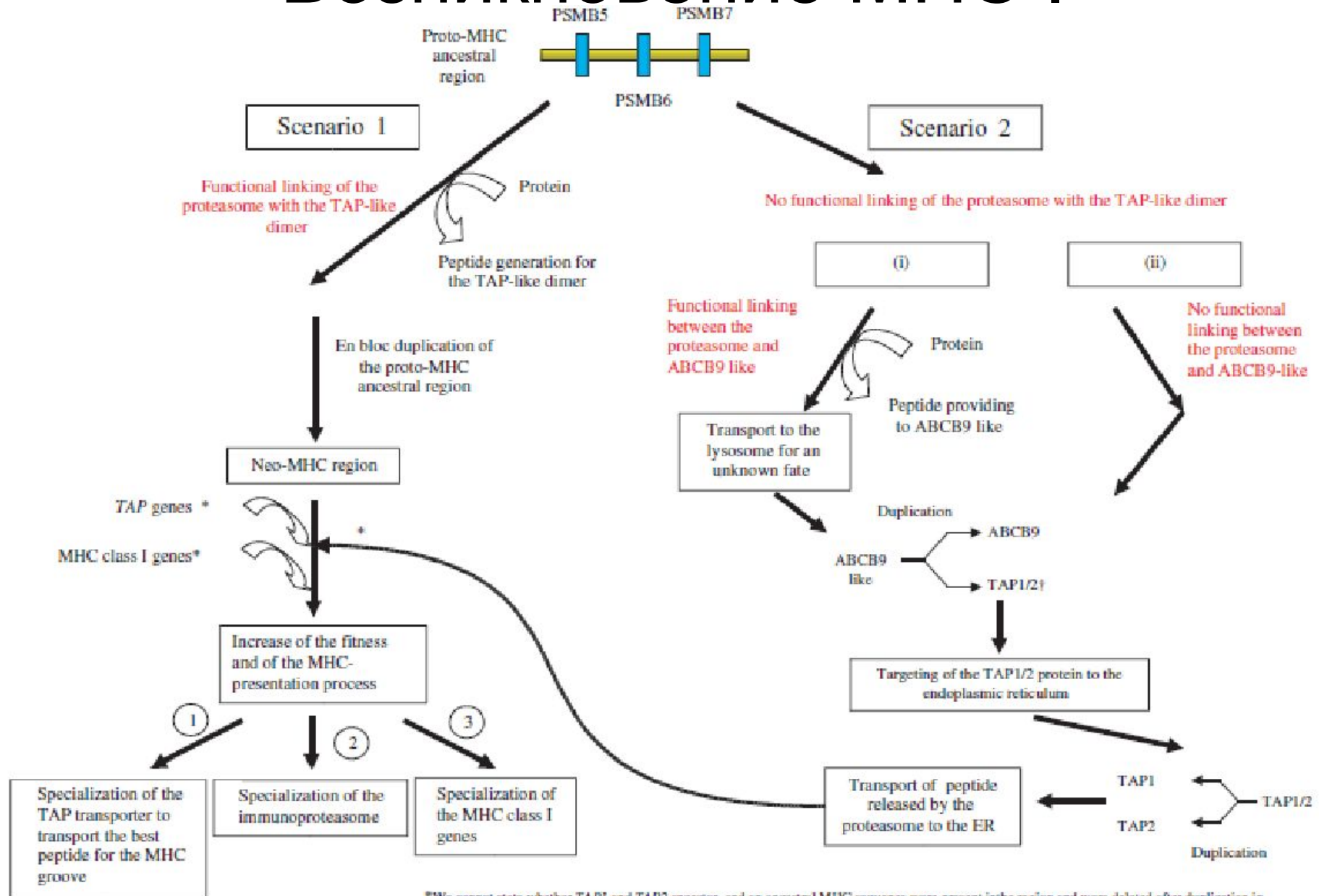
Функции МНС I



Функции МНС II

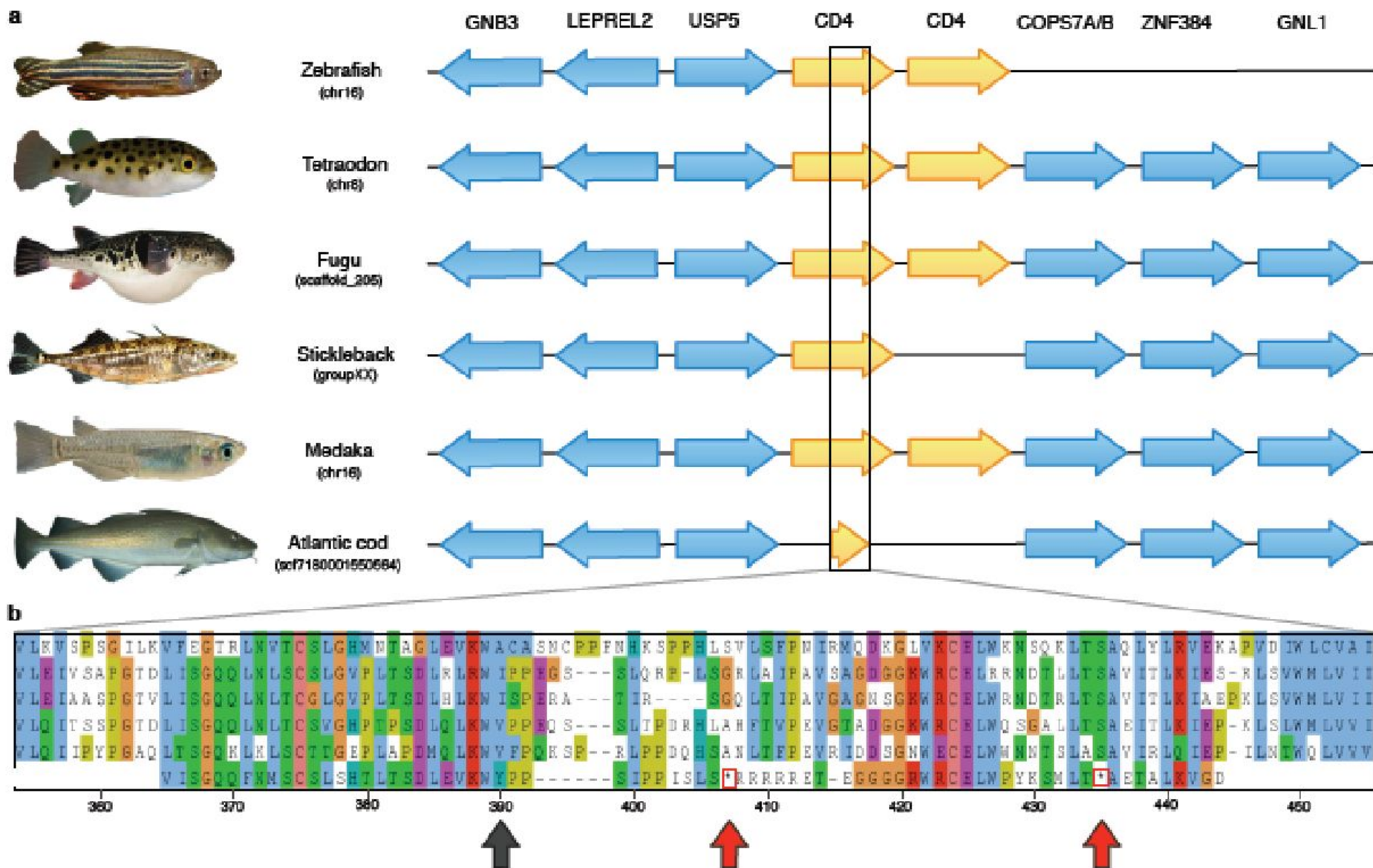


Возникновение МНС I

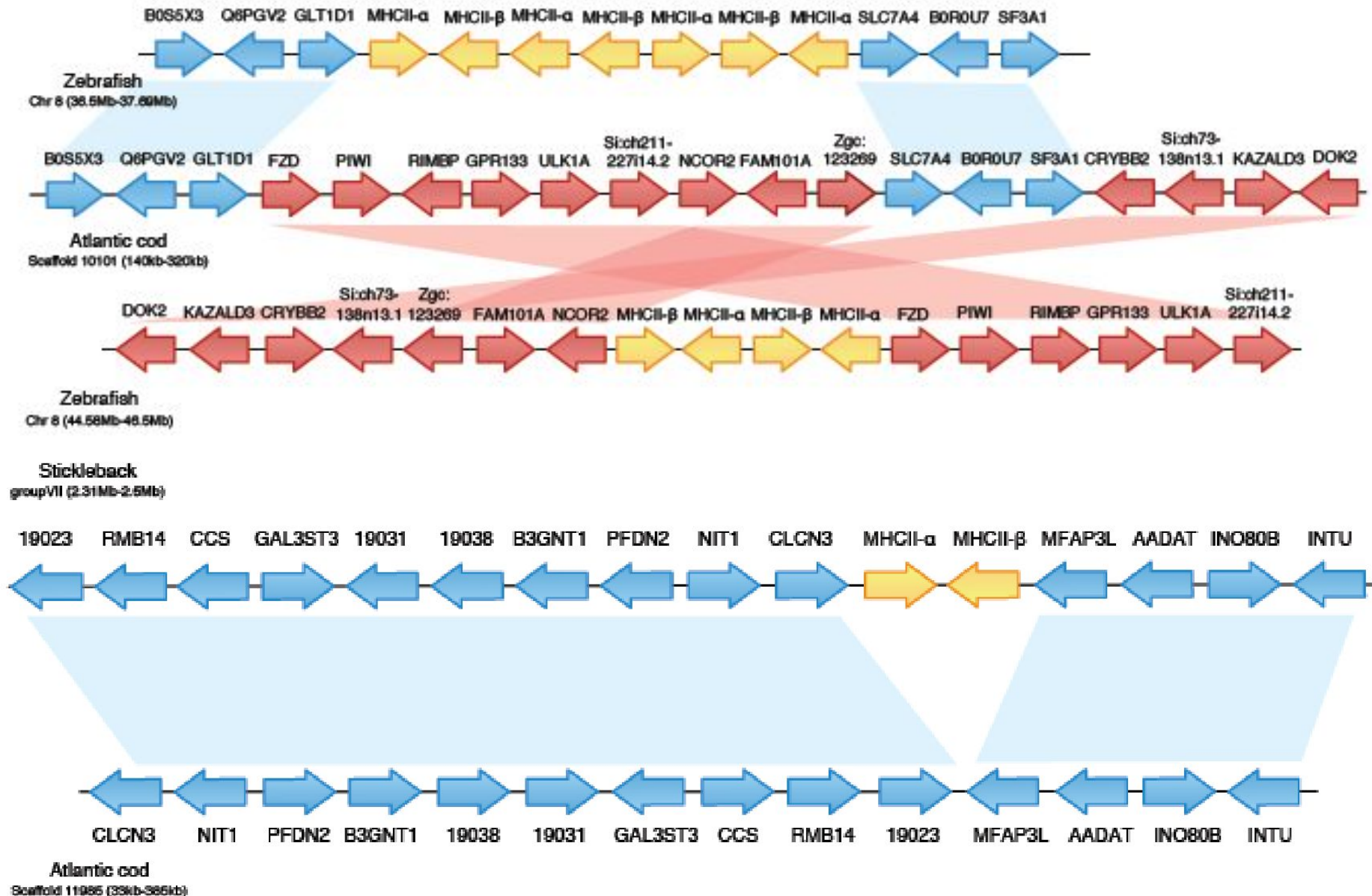


*We cannot state whether TAP1 and TAP2 ancestor, and an ancestral MHC sequence were present in the region and were deleted after duplication in the MHC sister regions or if the TAP-like and the MHC-like ancestral sequences were translocated into the neo-MHC genomic region
 †In scenario 2 (ii), TAP1/2 underwent mutations that allowed the acquisition of the peptide transport function.

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



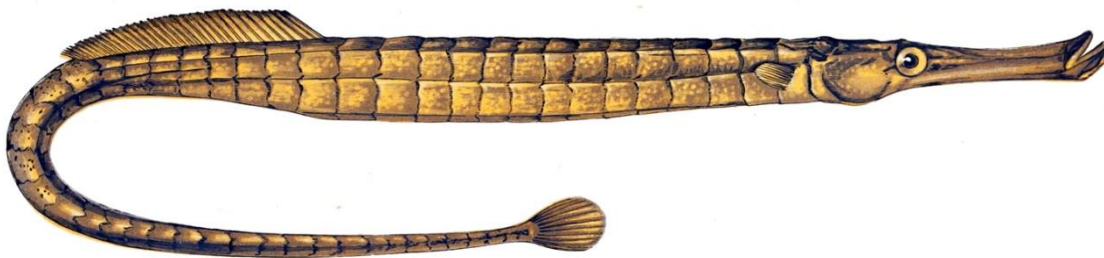
Это является результатом цепочки хромосомных перестроек, затрагивающих локус МНС



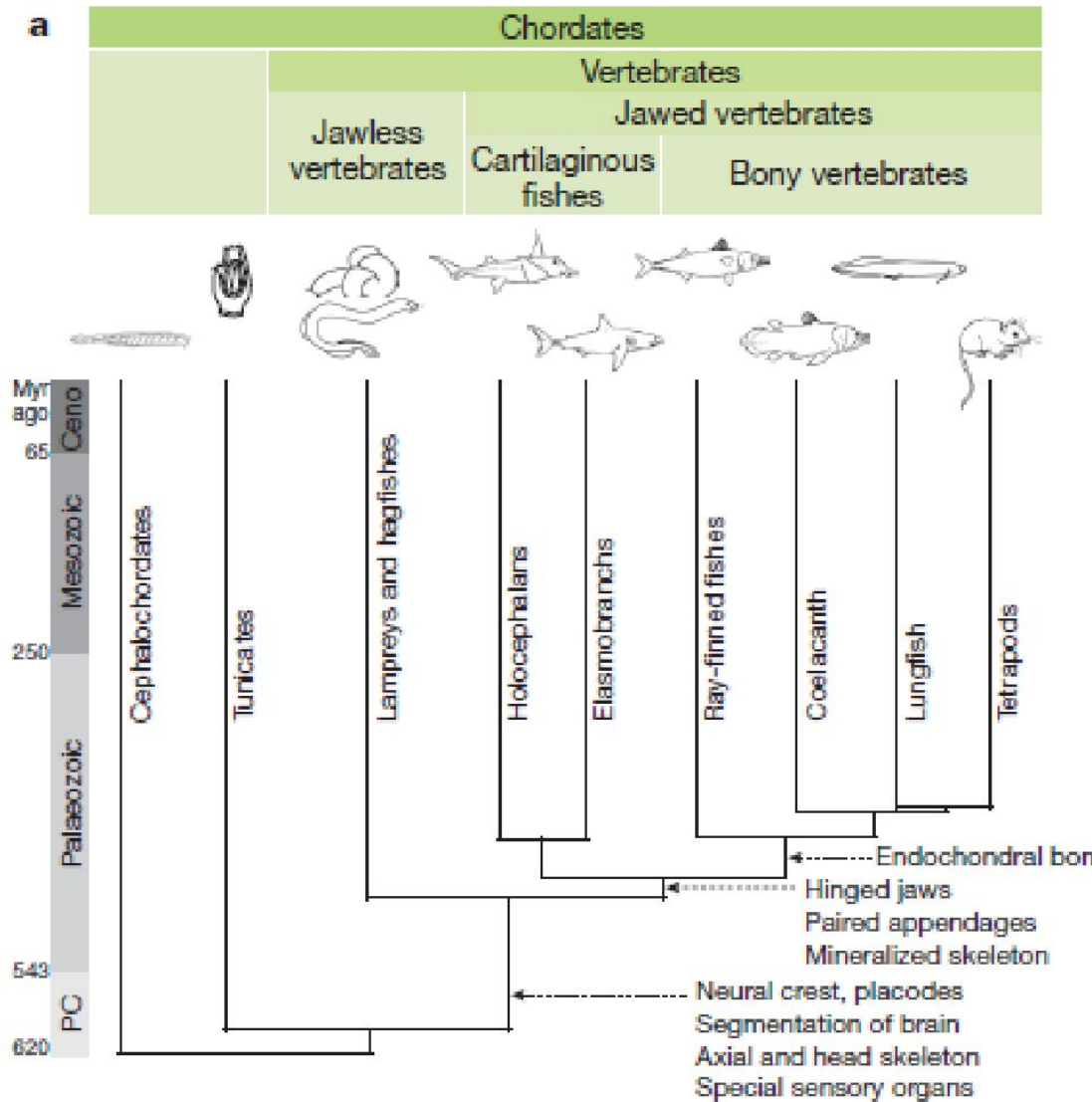
Рыбы, экономящие на Т-хелперной ветви

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

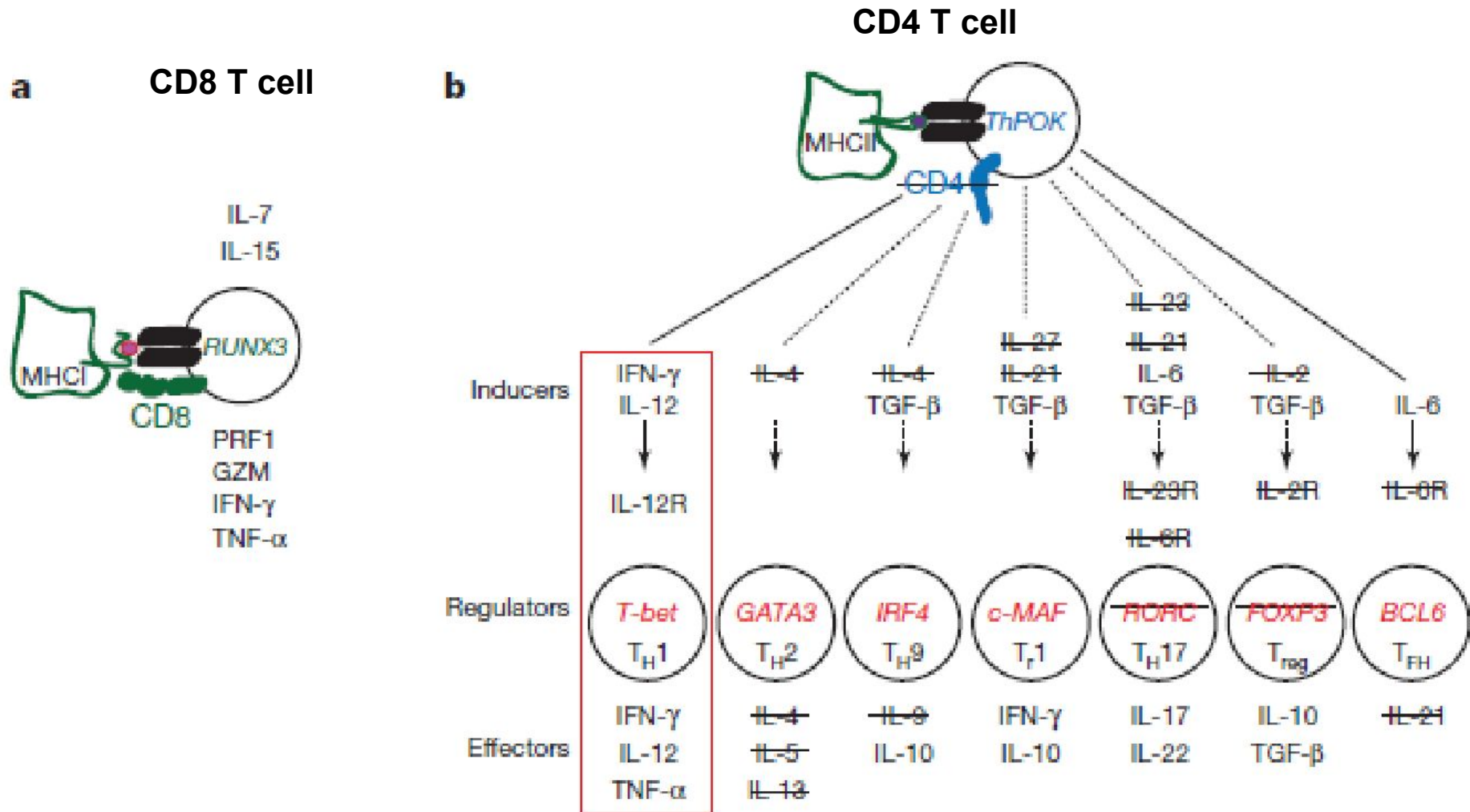
Scientific name	Common name	MHCII a and b chain genes	CD4	CD74	Compensatory mechanism
<i>Gadus morhua</i>	Atlantic cod	Absent	Pseudogene	Absent	Expansion of MHC I, TLR and other innate-immunity related gene families Possibly same as in cod
Other Gadoidei	European hake, haddock, whiting, burbot, etc.	Absent or not expressed	Absent or not expressed	Absent or not expressed	Possibly same as in cod
<i>Syngnathus typhle</i>	Broadnosed pipefish	Absent	Absent	Present, but possibly not functional	Unknown
<i>Hippocampus abdominalis</i>	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 *Callorhynchus milii* утратила CD4...

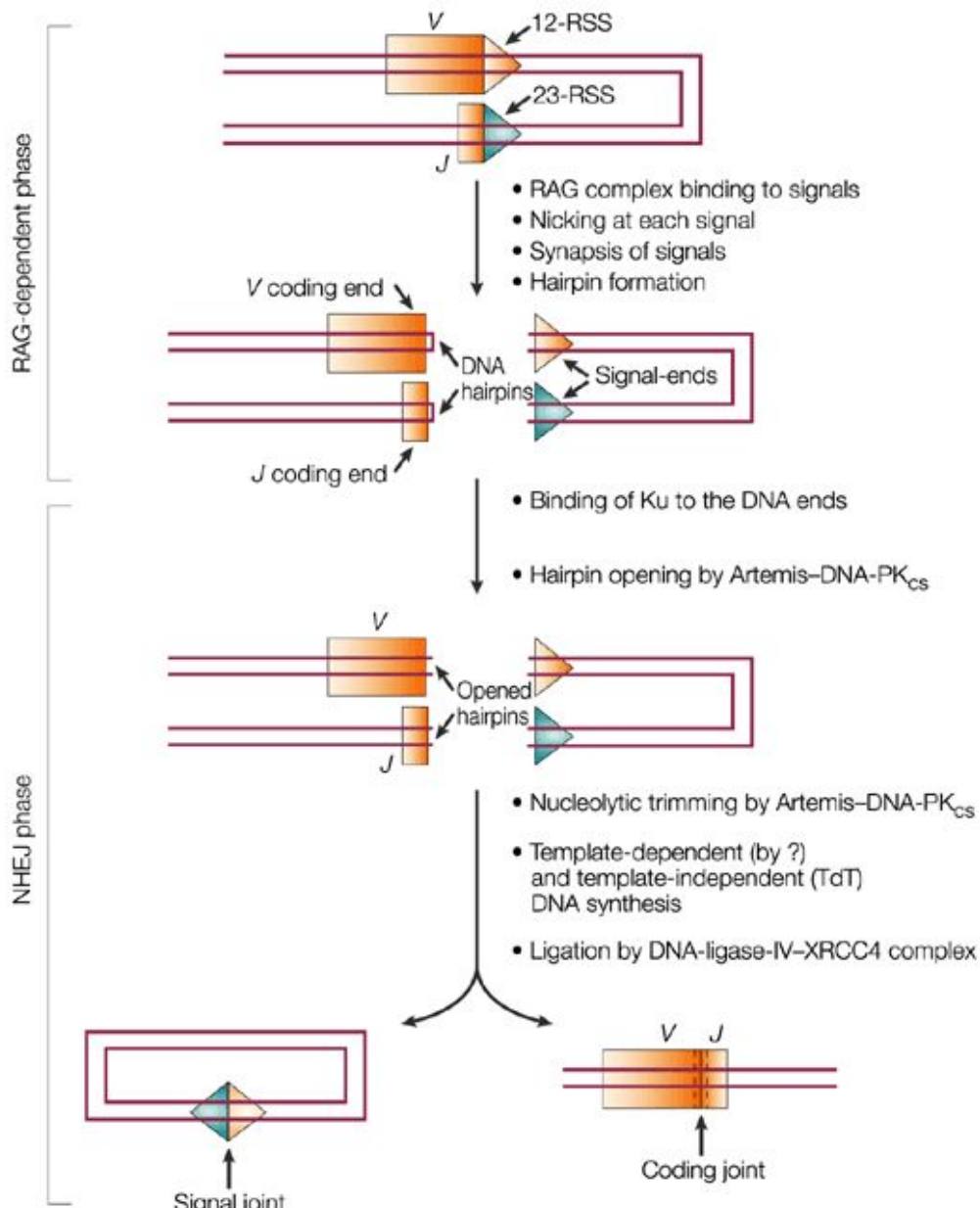


... и несколько цитокинов и транскрипционных факторов



(Venkatesh et al, Nature, 2014)

Роль рекомбиназ RAG



David Schatz,
клонировал предска-
занные Сакано и
Тонегавой рекомбиназы

Возникновение RAG генов



John Marchalonis
1941-2007

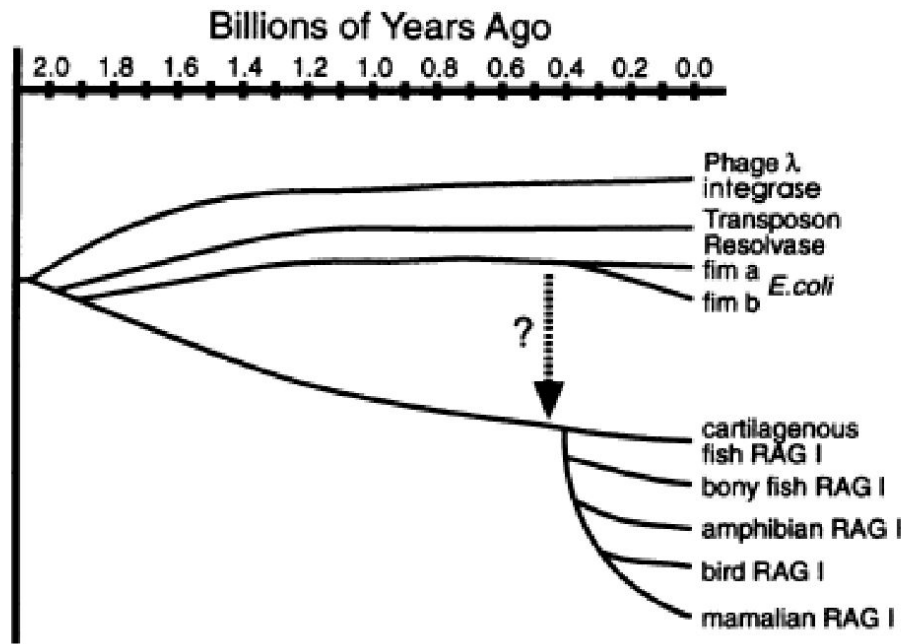
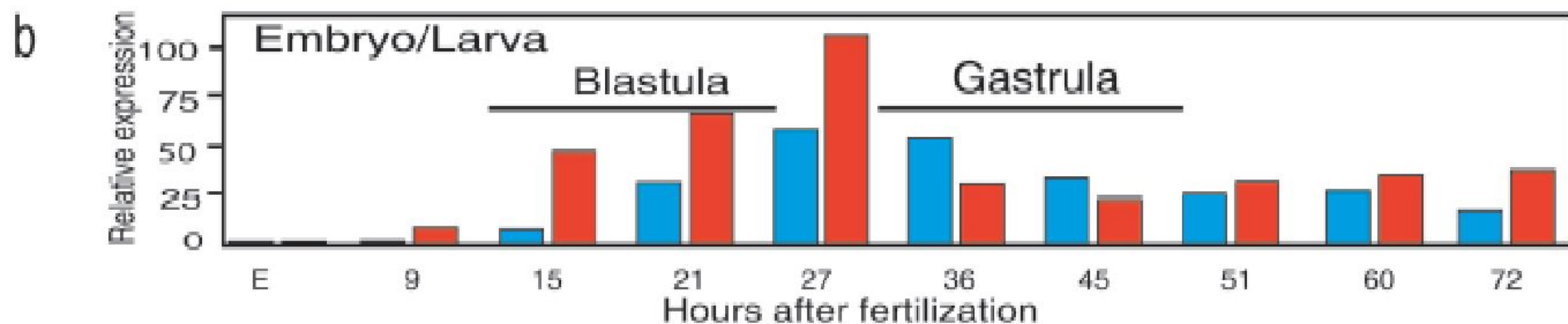
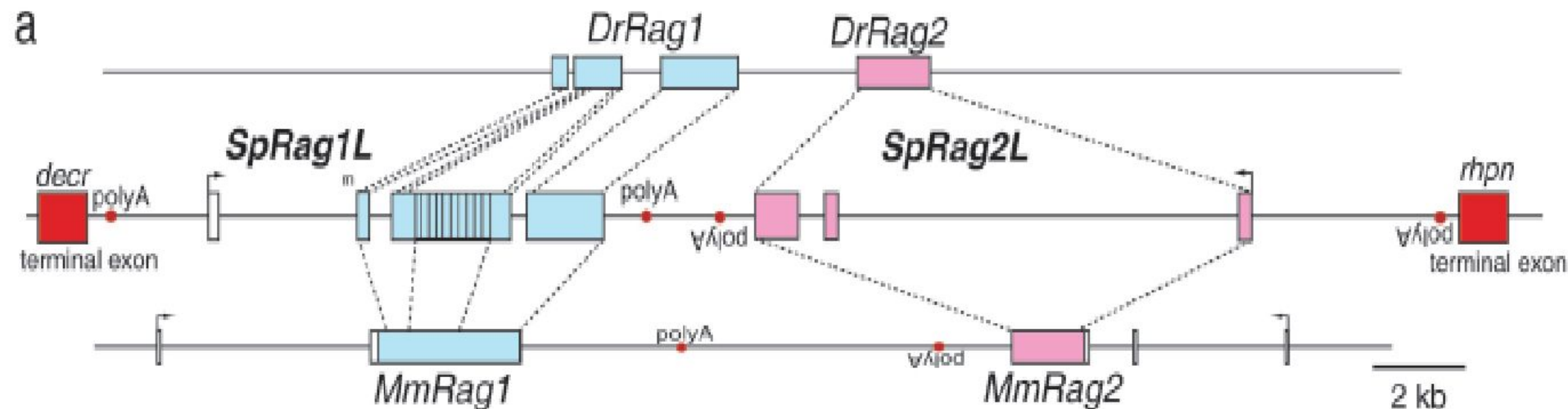


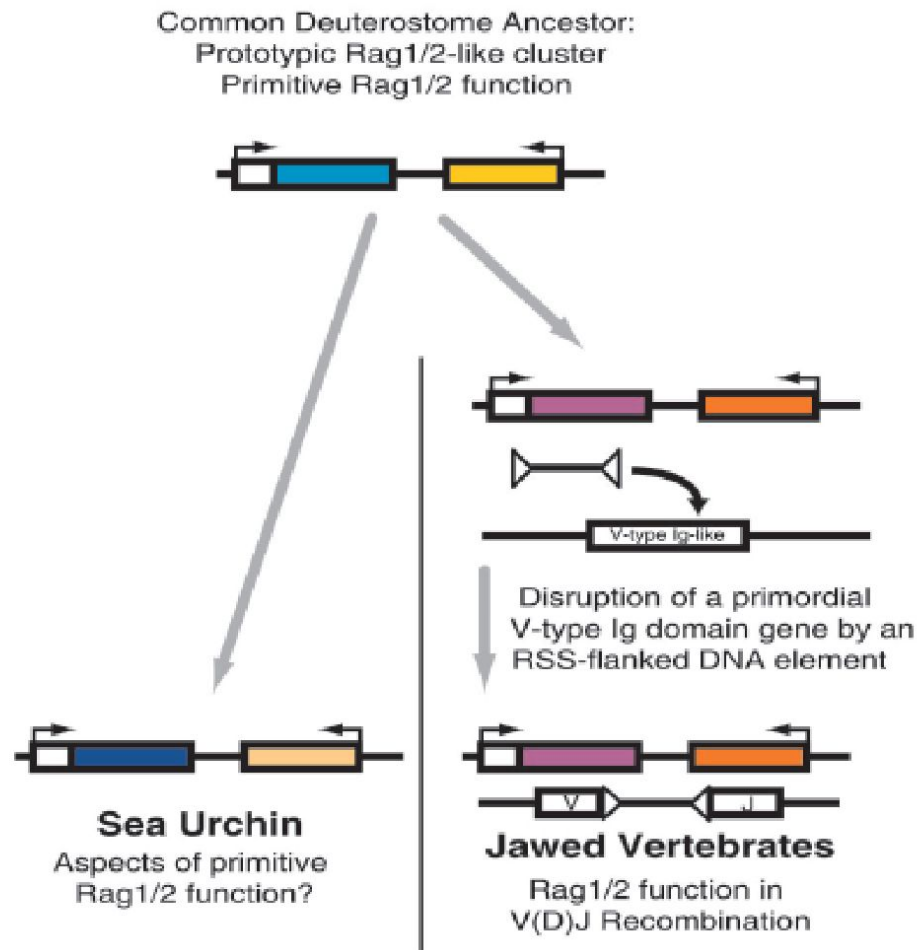
FIG. 5. A phylogenetic tree depicting the evolutionary relationship between members of the INT family of site-specific recombinases. The RAG I INT motif is shown to have diverged prior to 1.8 billion years ago from a common ancestor with the bacterial INT family recombinases. The alternative possibility 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 некоторыми 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

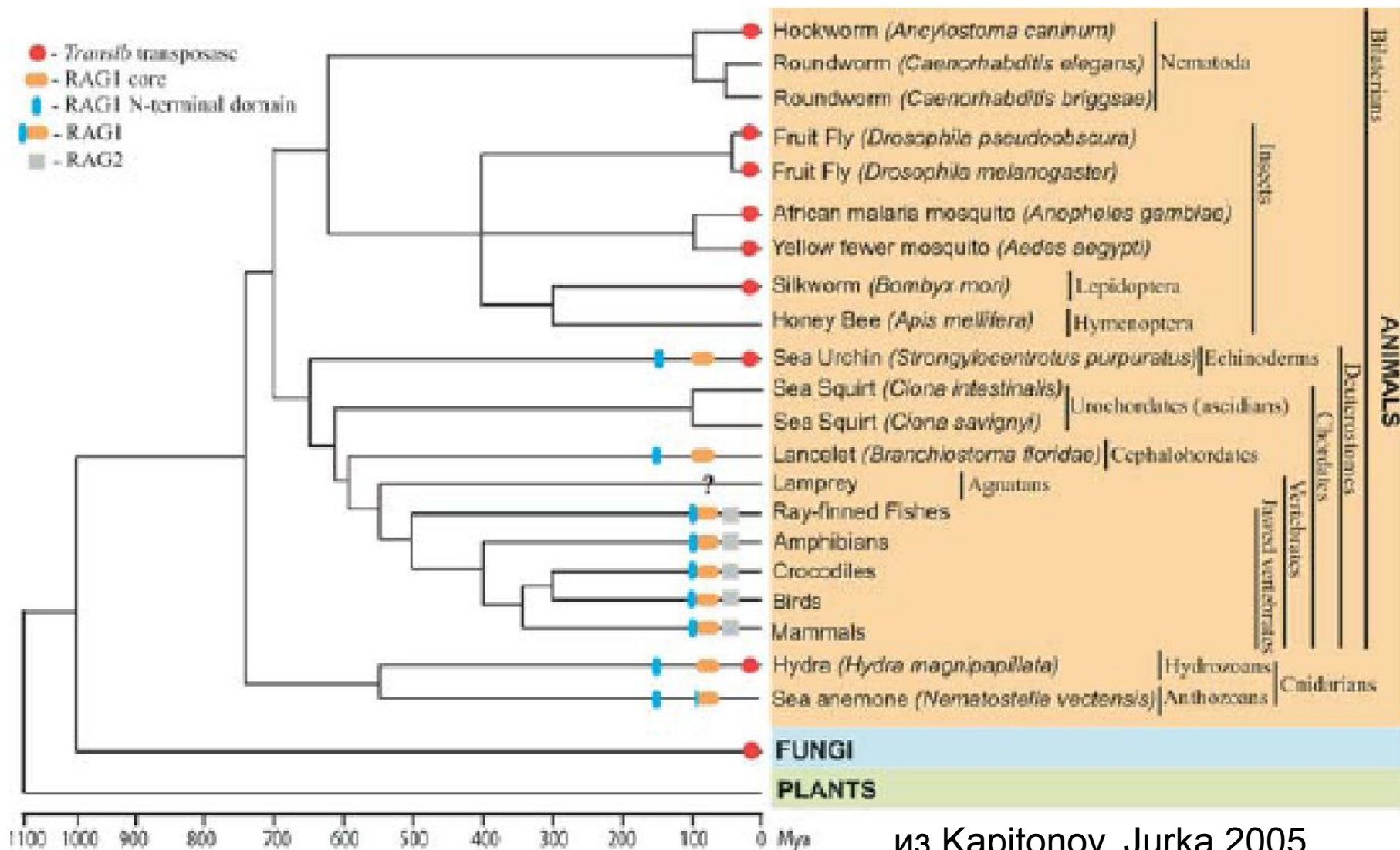


Возникновение RAG генов у общего предка вторичноротых заложило основы для развития адаптивного иммунного ответа

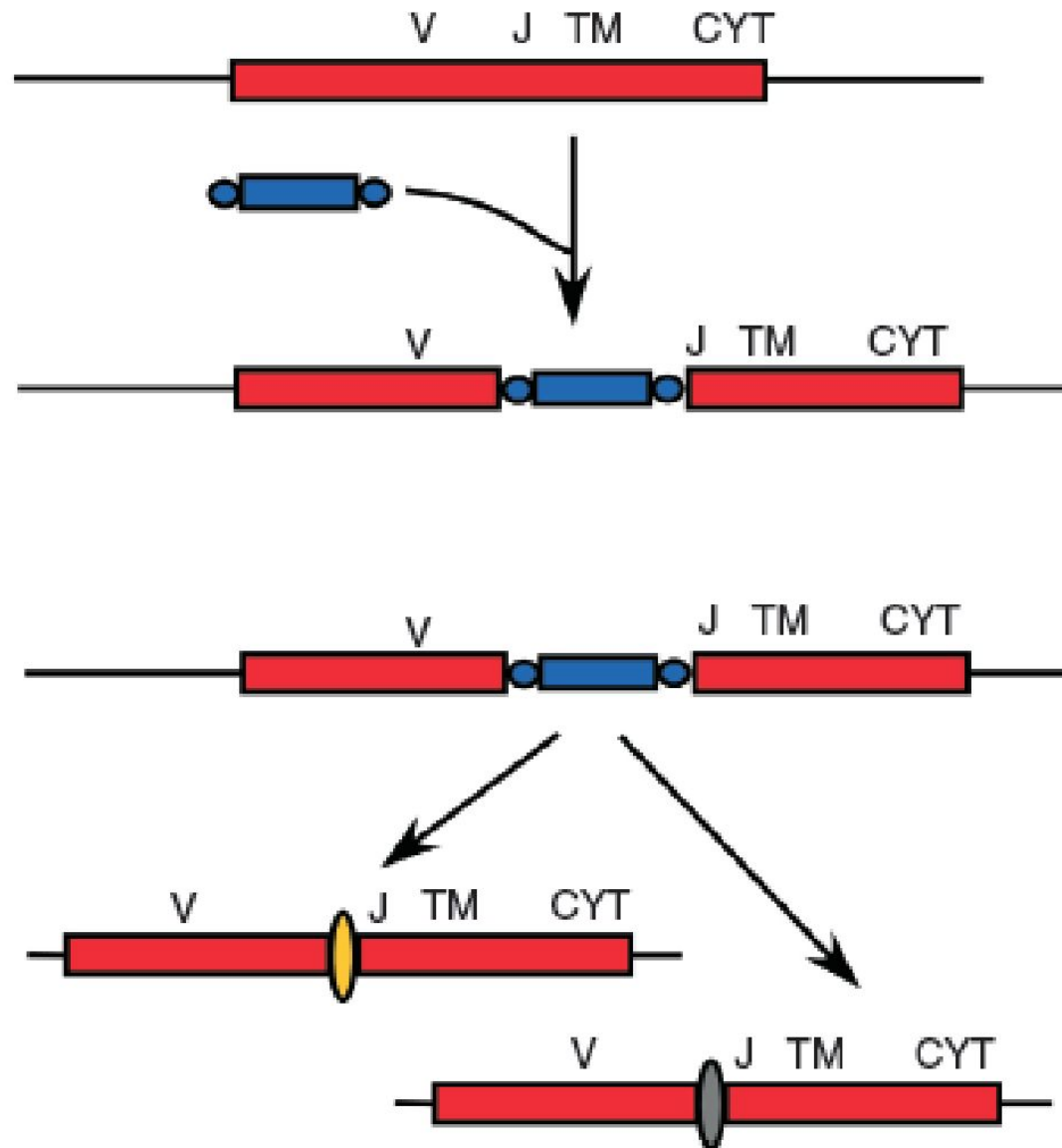


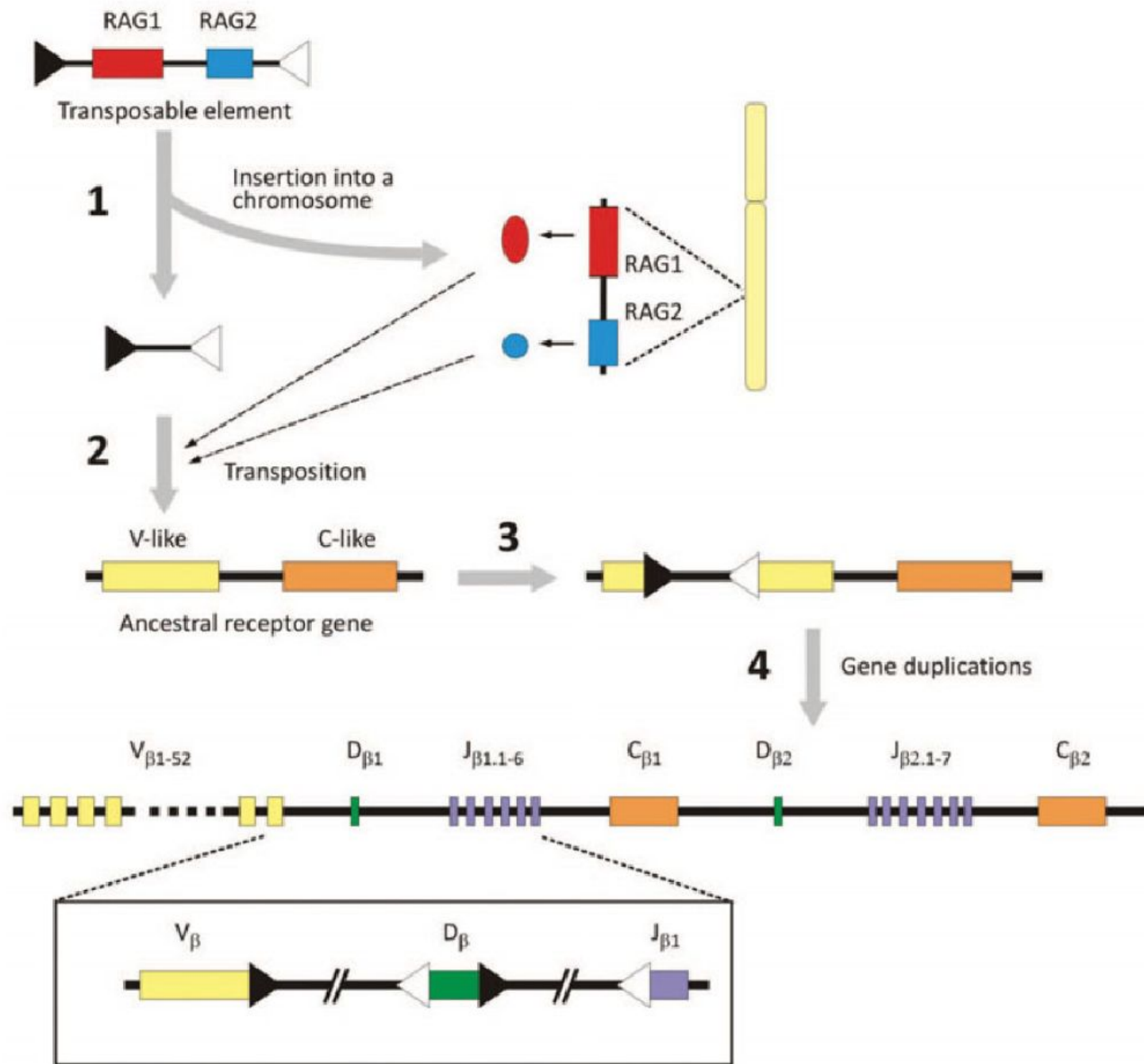
Выяснилось, что гомологи RAG генов есть даже в геноме морского ежа *Strongylocentrotus*, однако отсутствуют во вчетверо меньшем геноме асцидии *Cyopa*. Поскольку у морских ежей нет антител и механизма соматической рекомбинации, очевидно, что их рекомбиназы имеют какую-либо другую функцию.

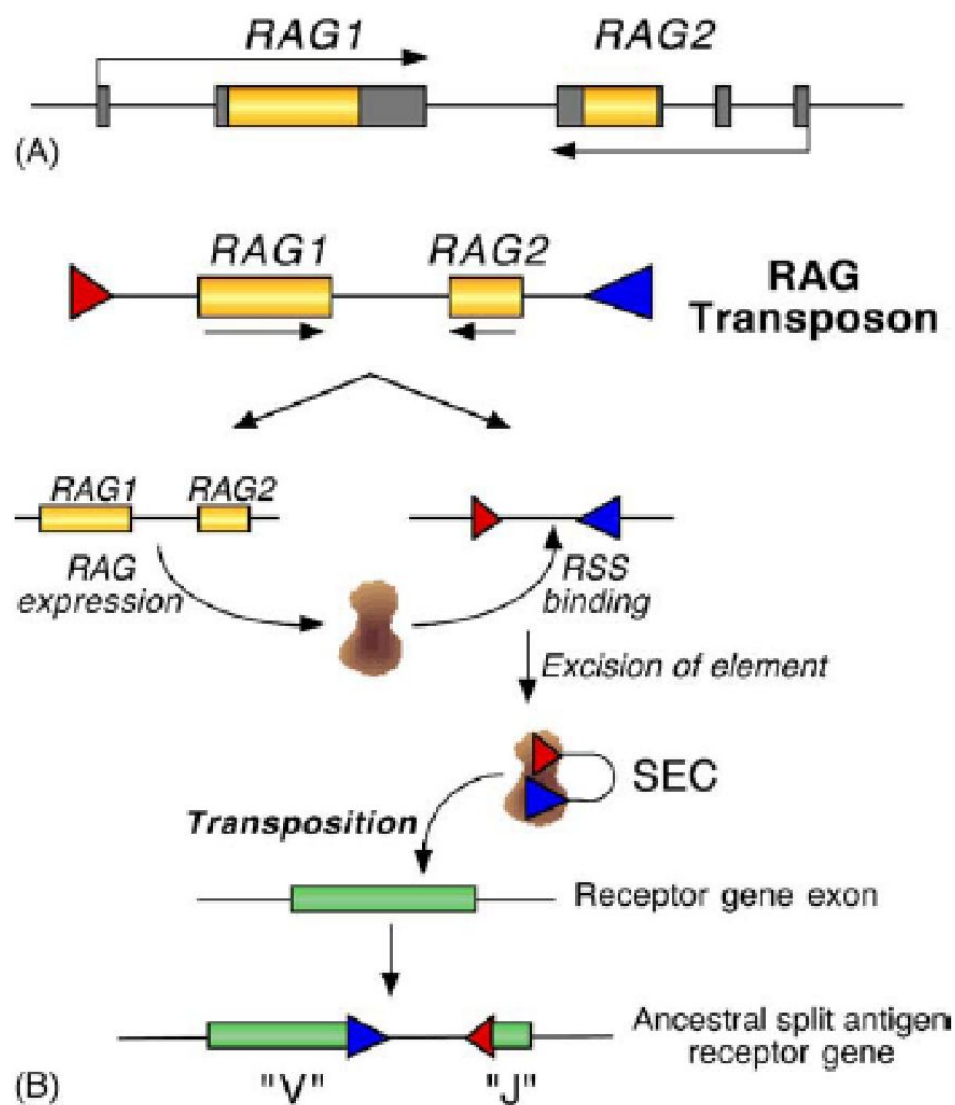
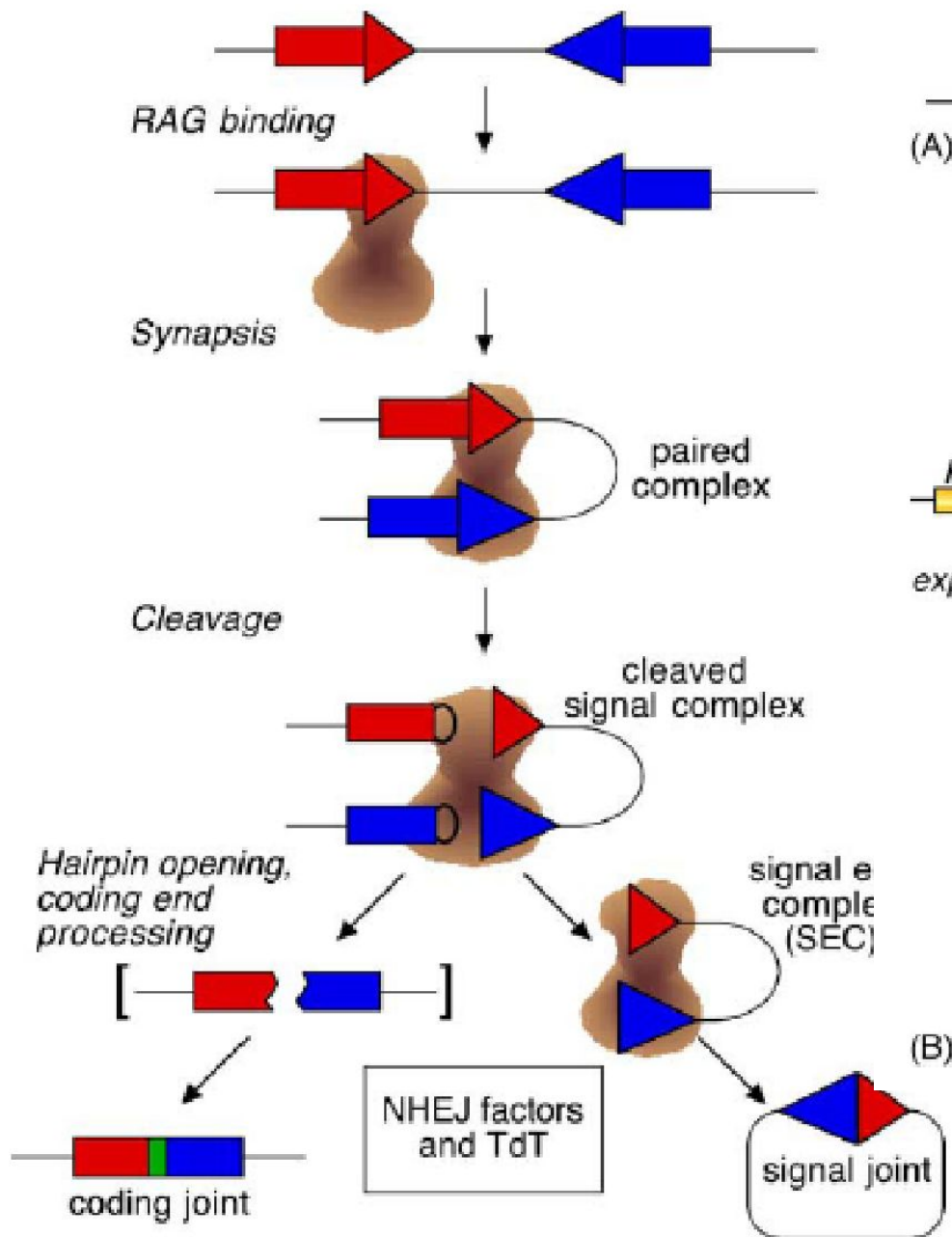
RAG1 сходен с транспозазой Transib

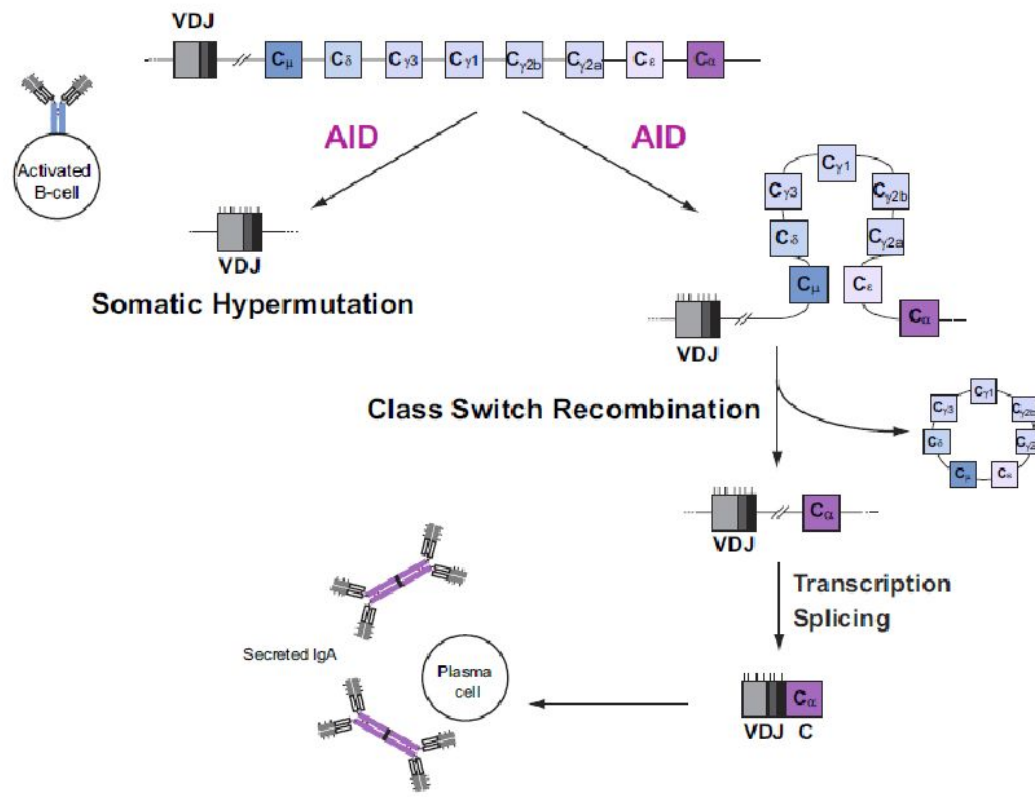
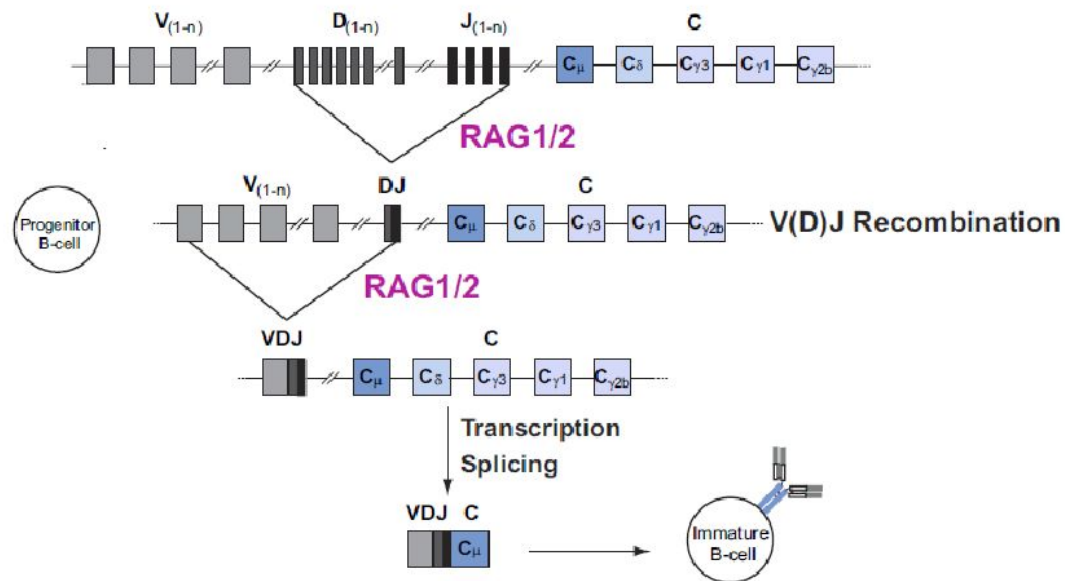


Использование транспозона «в мирных целях»



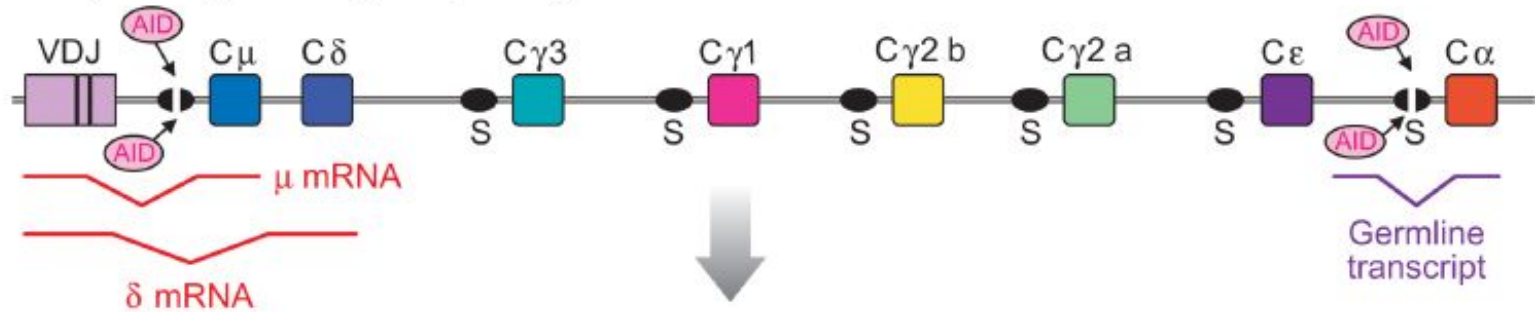




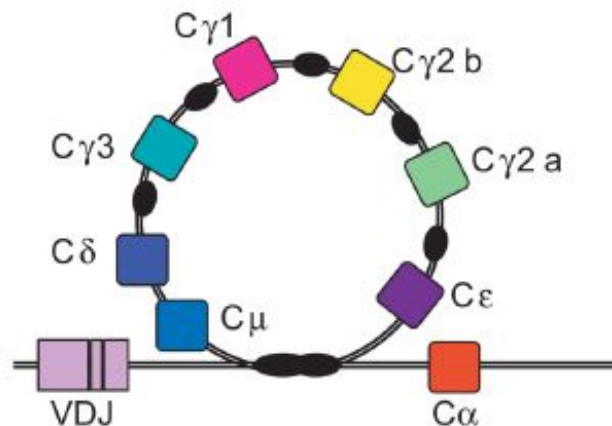


Механизм переключения классов антител

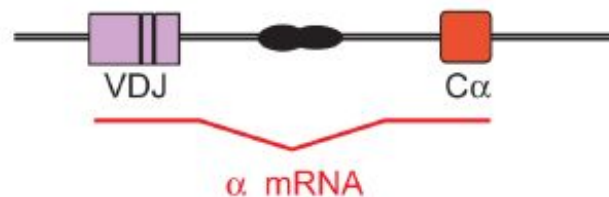
Heavy chain genes in IgM-expressing cells



Switch recombination
(requires DSBs)



Heavy chain genes
in IgA-expressing cell



Рецепторы врожденного иммунитета могли возникнуть из рецепторов NK-клеток

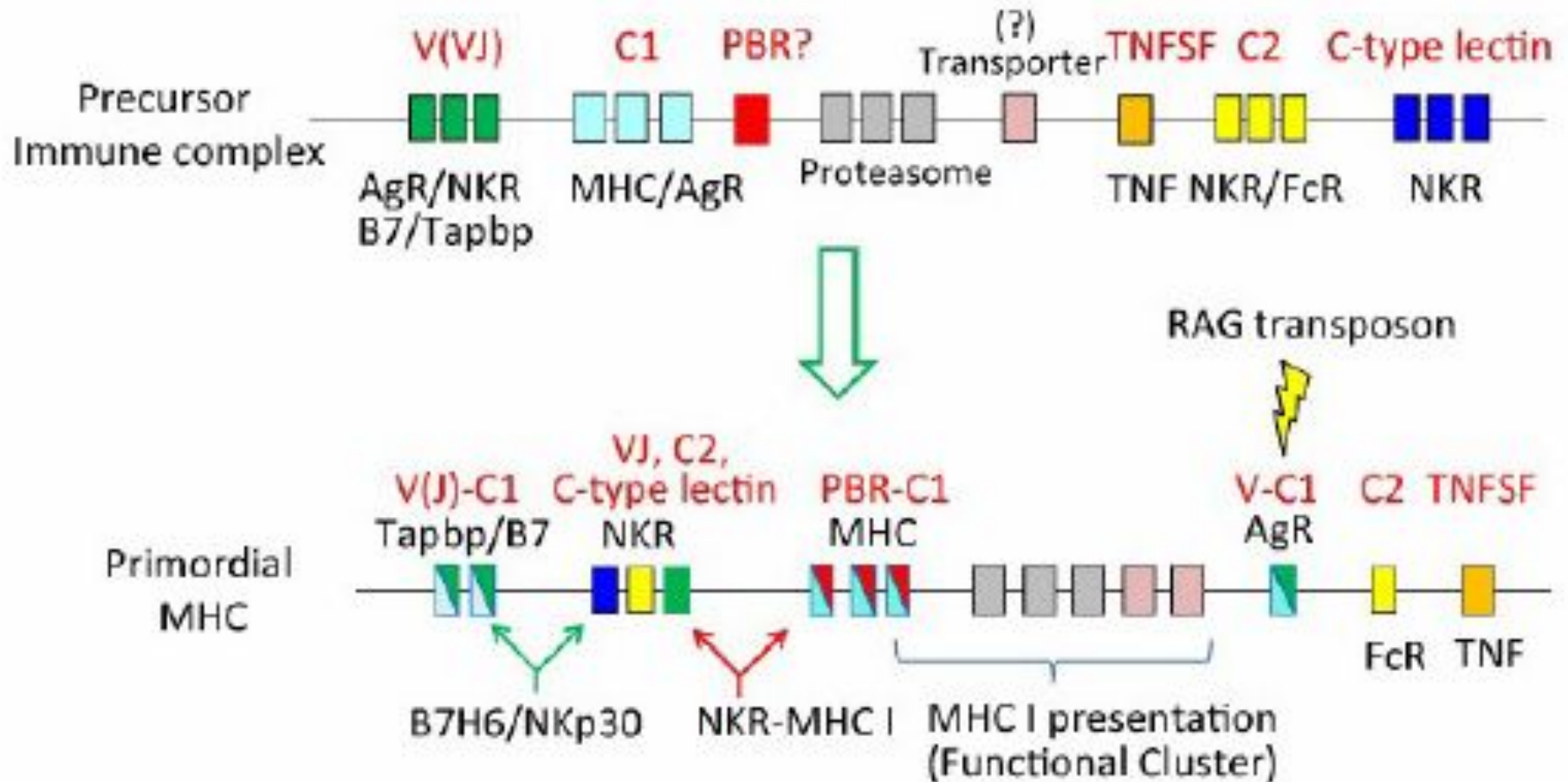


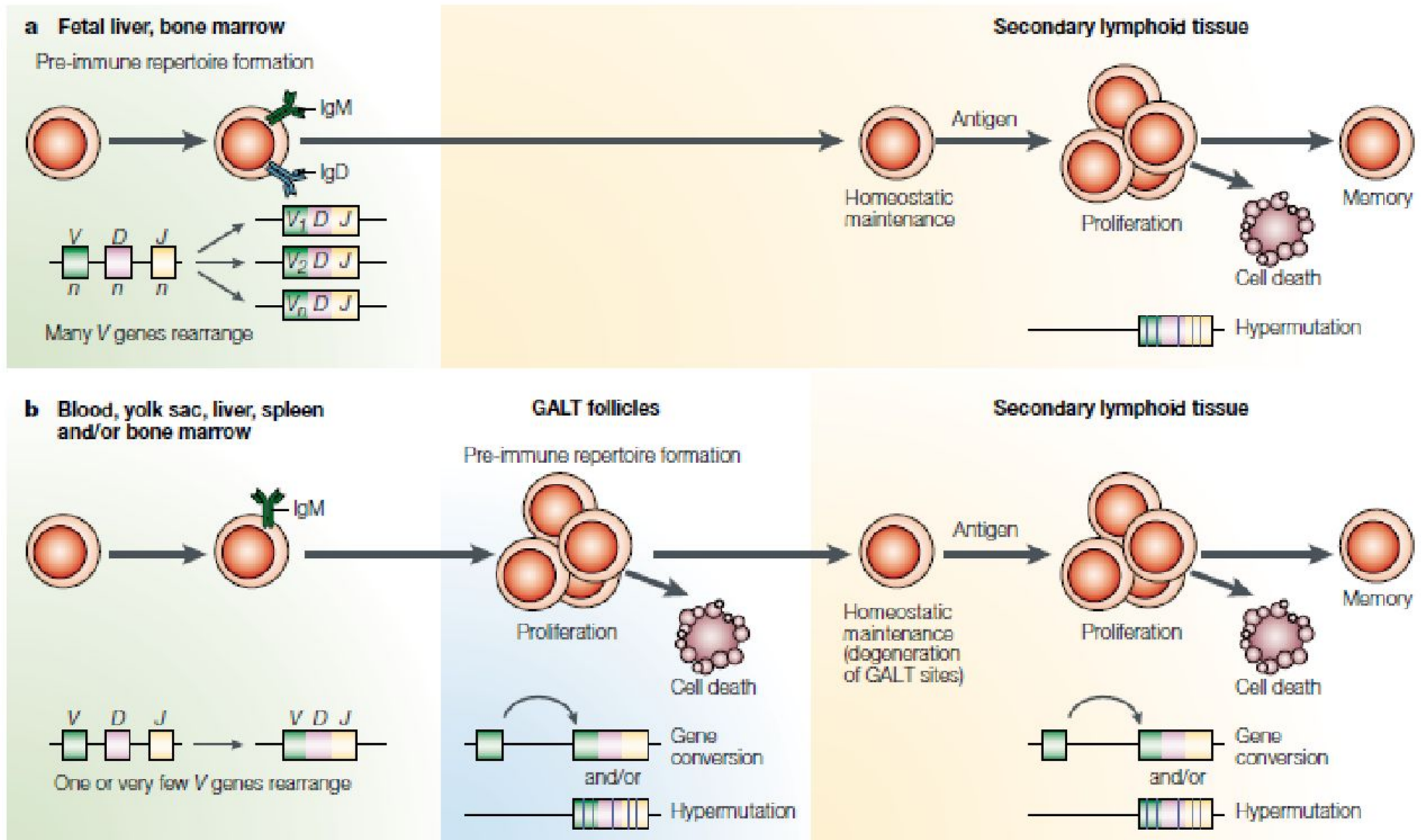
TABLE 1. Ig Gene Diversification System of Mammalian Species and Chicken

	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	Ileal Peyer's patches
Swine	Gene conversion and somatic hypermutation	Ileal Peyer's patches
Horse	Gene conversion and somatic hypermutation	Ileal Peyer's patches
Chicken	Gene conversion and somatic hypermutation	The bursa of Fabricius

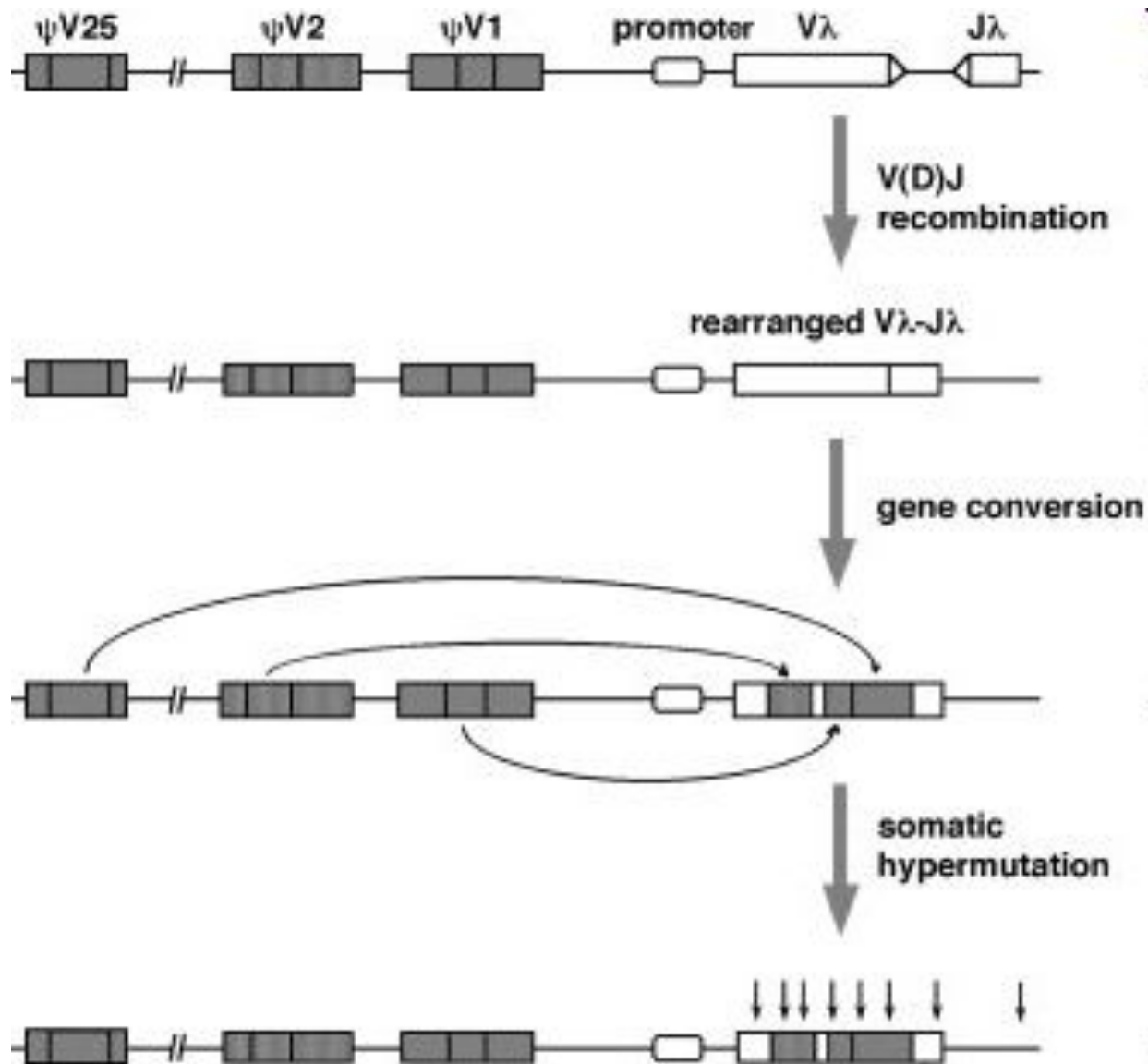
TABLE 2. DT40 Mutants Related to Gene Conversion and Somatic Hypermutation

	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 glycosylase (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

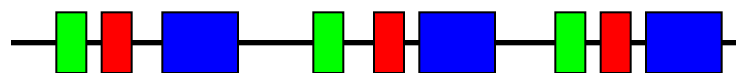
Rag-зависимая рекомбинация или конверсия генов?



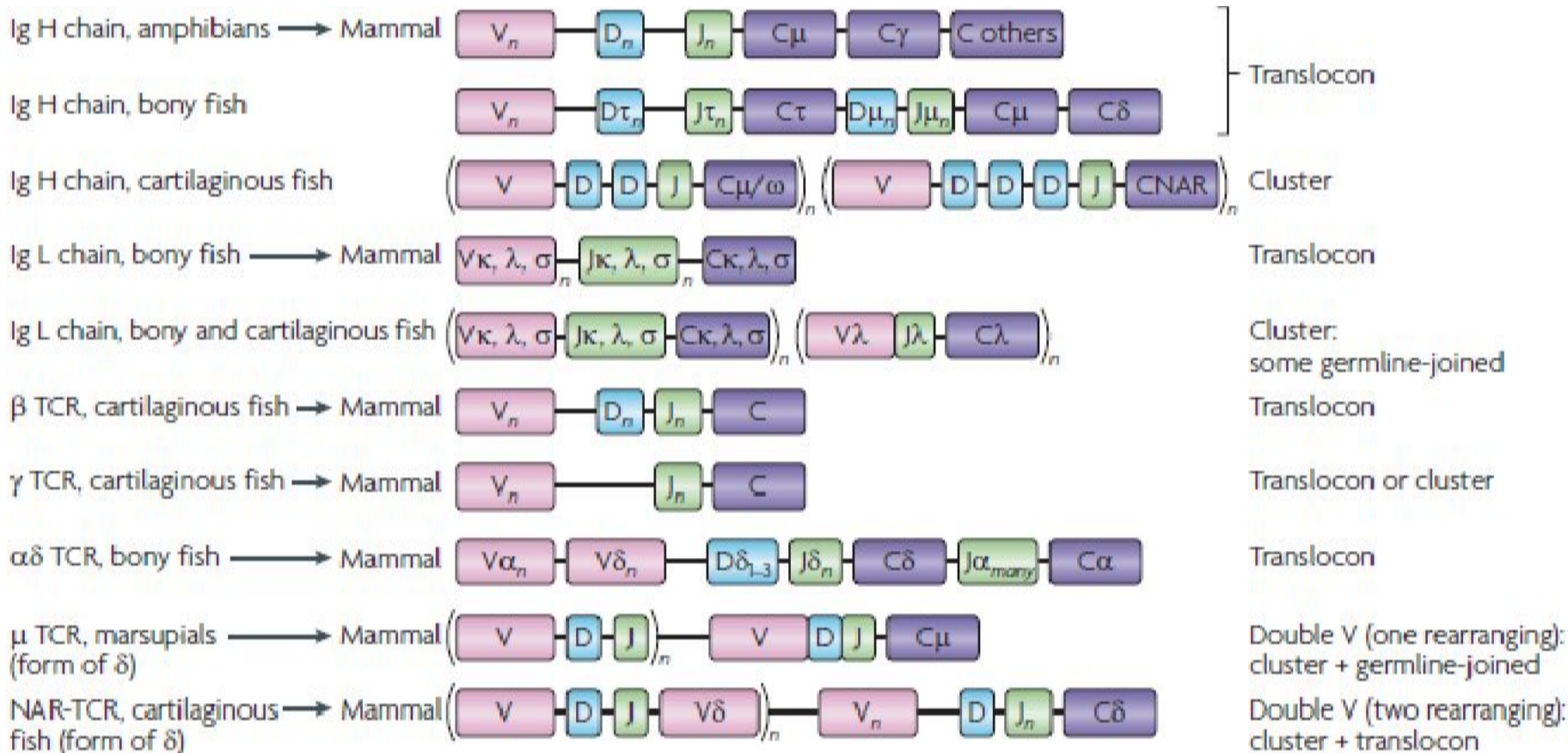
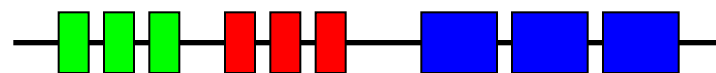
Общая схема конверсии



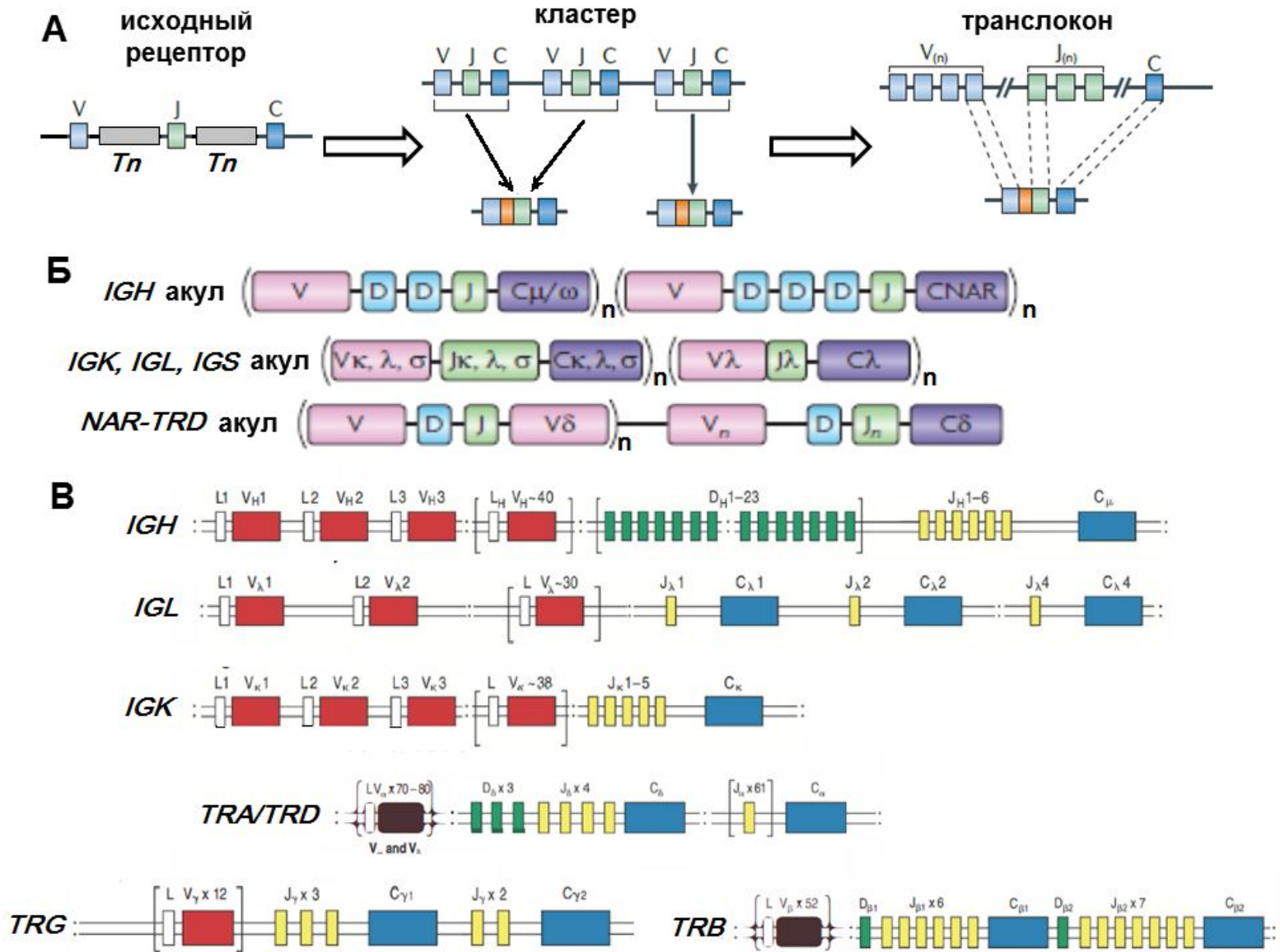
Организация генов в кластеры или транслоконы



или

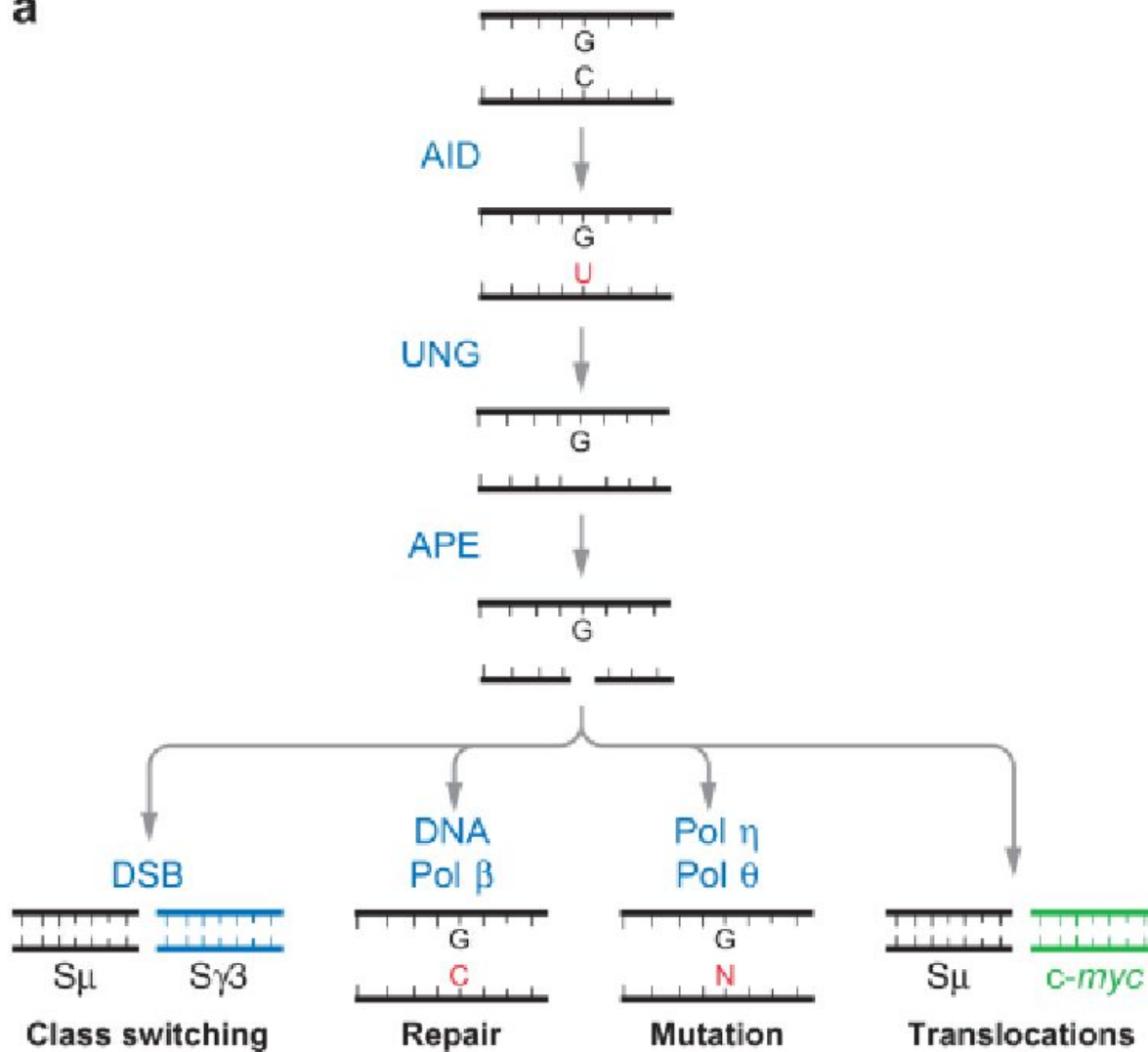


Организации генов в кластеры более примитивна

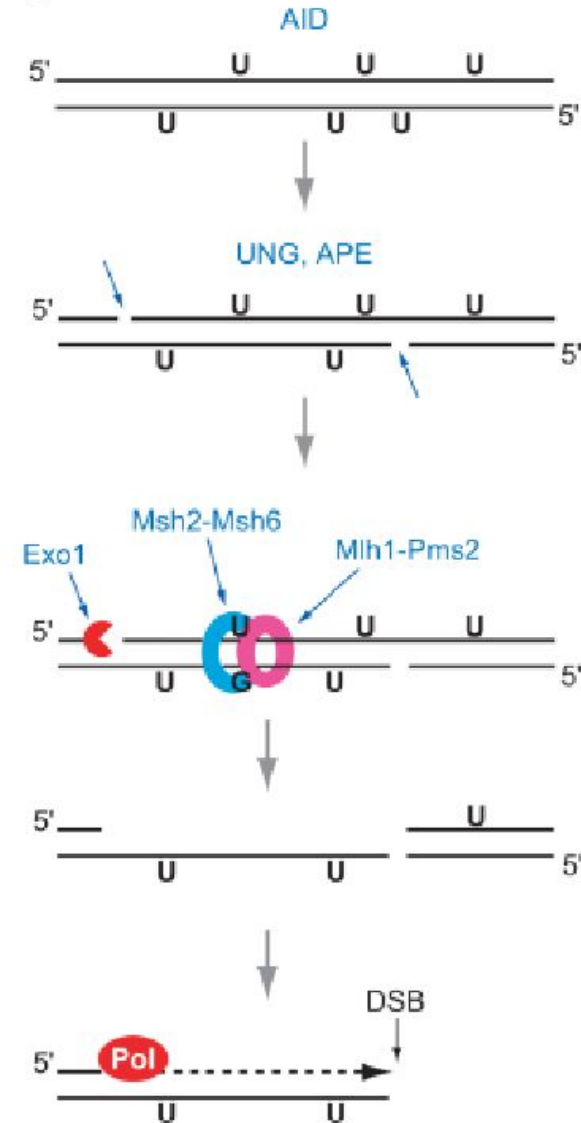


Для переключения классов снова важна цитидин-дезаминаза AID

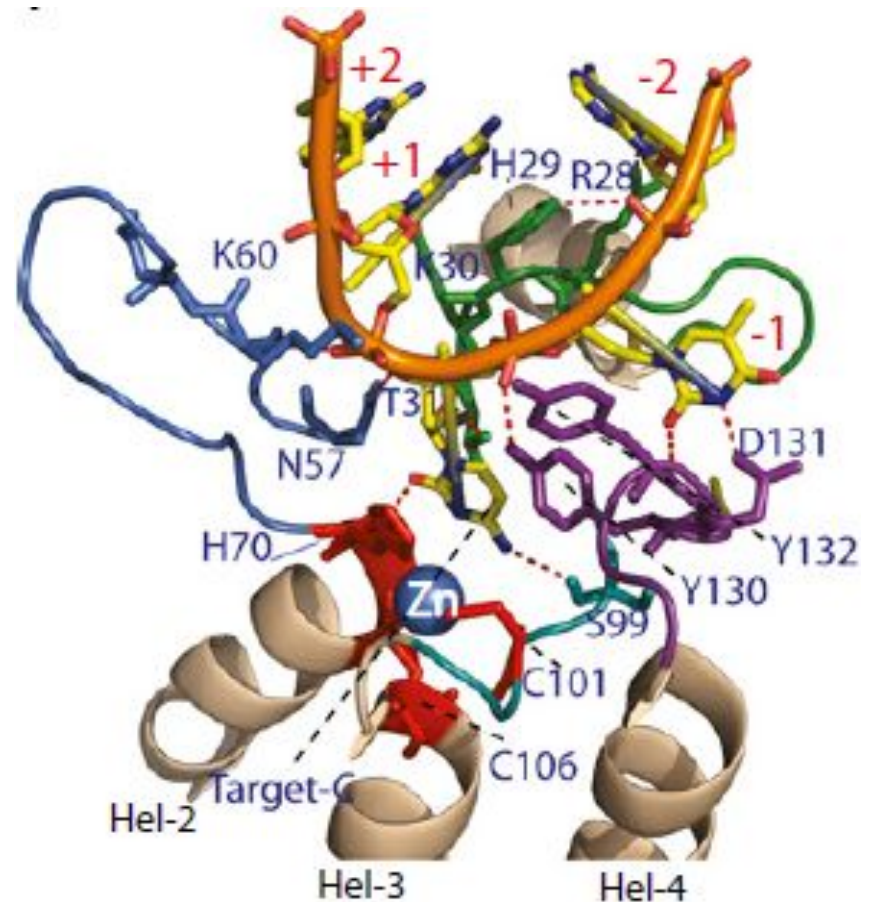
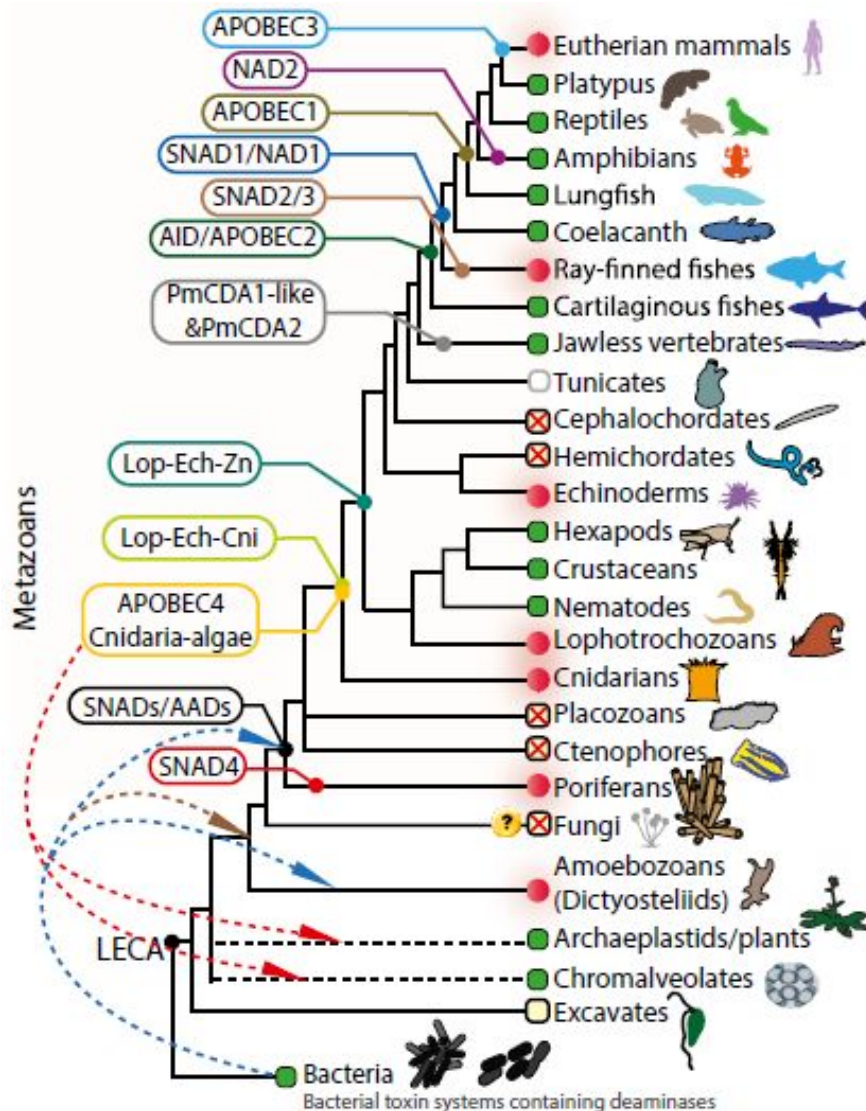
a



b



Эволюция семейств цитидиндезаминаз



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