VIVEKANANDA COLLEGE THAKURPUKUR

KOLKATA-700063

NAAC ACCREDITED 'A' GRADE

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NAME OF THE DEPARTMENT	**: DEPARTMENT OF ZOOLOGY [UG & PG]**

SEX DETERMINATION

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REFERENCE

1. iGENETICS-RUSSELL
2. GENETICS-KLUG & CUMMINS

SEX DETERMINATION OF DROSOPHILA

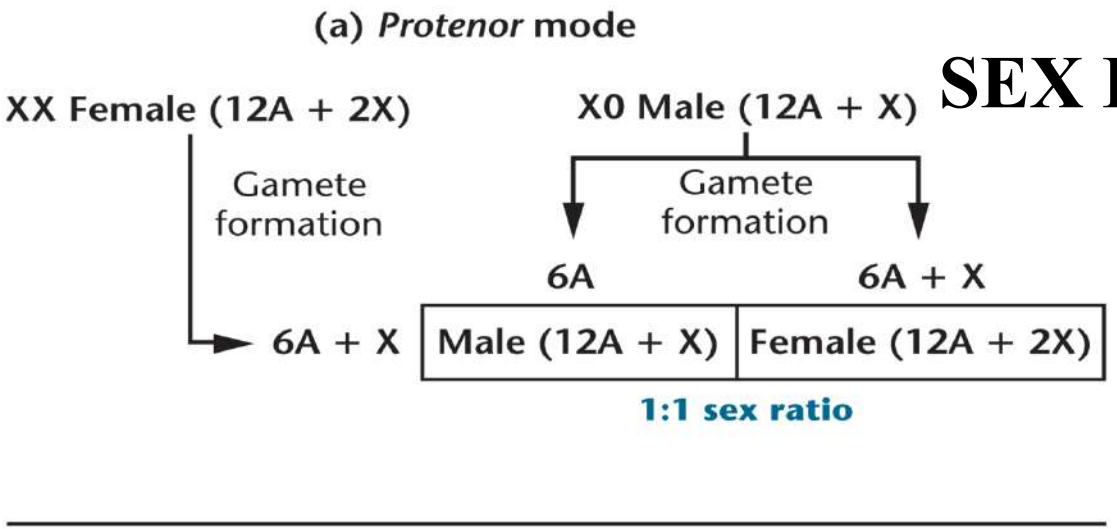
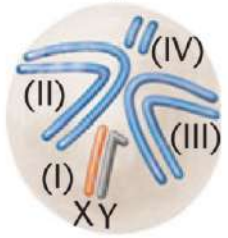


FIGURE 7–4 (a) The *Protenor* mode of sex determination where the heterogametic sex (the male in this example) is X0 and produces gametes with or without the X chromosome; (b) the *Lygaeus* mode of sex determination, where the heterogametic sex (again, the male in this example) is XY and produces gametes with either an X or a Y chromosome. In both cases, the chromosome composition of the offspring determines its sex.

Normal diploid male

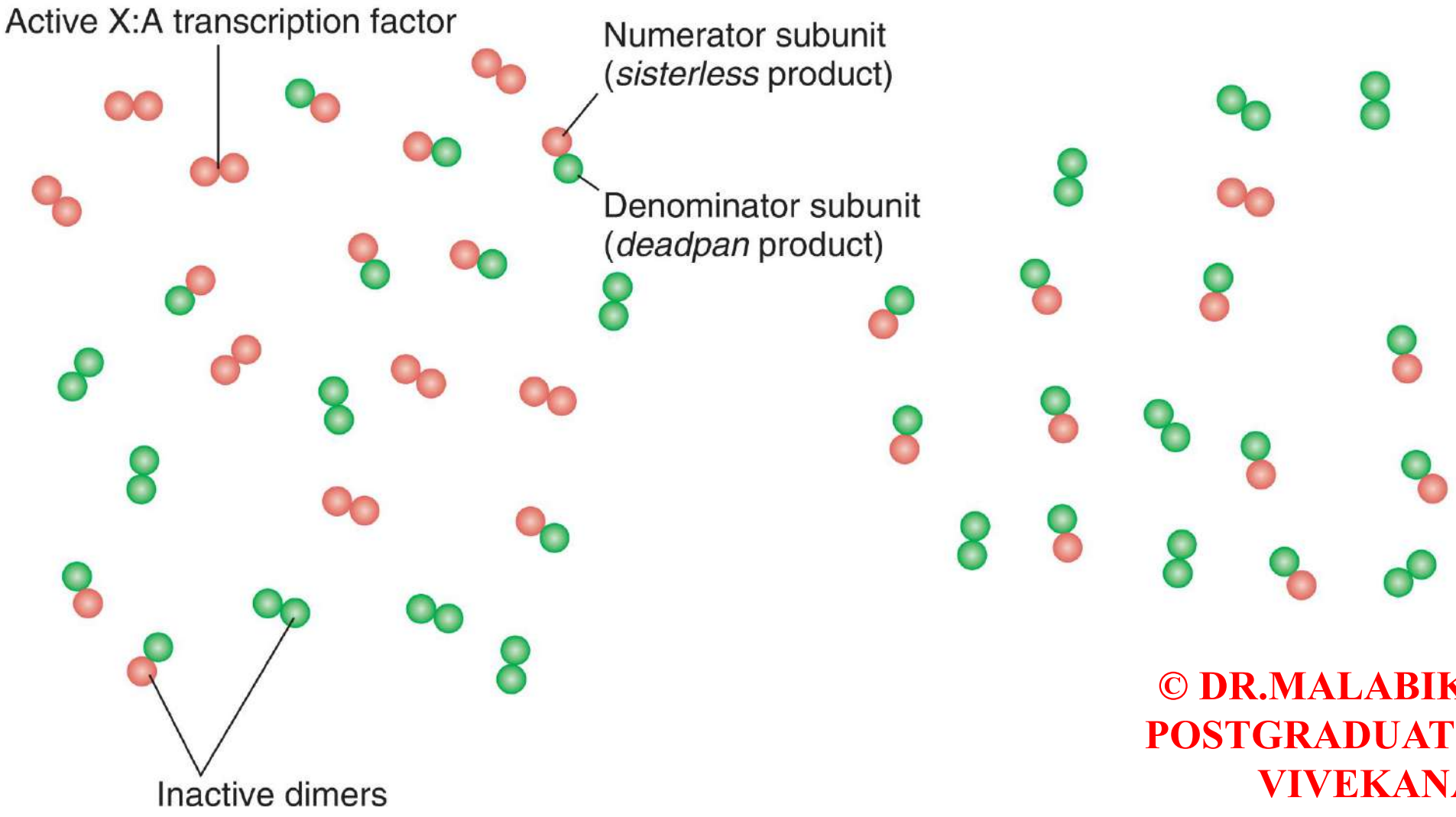


2 sets of autosomes
+
X Y

Chromosome formulation	Ratio of X chromosomes to autosome sets	Sexual morphology
$^{3X}/_{2A}$	1.5	Metafemale
$^{3X}/_{3A}$	1.0	Female
$^{2X}/_{2A}$	1.0	Female
$^{3X}/_{4A}$	0.75	Intersex
$^{2X}/_{3A}$	0.67	Intersex
$^{X}/_{2A}$	0.50	Male
$^{XY}/_{2A}$	0.50	Male
$^{XY}/_{3A}$	0.33	Metamale

♀ X:A = 1 (XX AA)

♂ X:A = 0.5 (XY AA)



Excess *sisterless* product

sisterless product bound with *deadpan* product

Detection of X: A ratio & Sex determination cascade

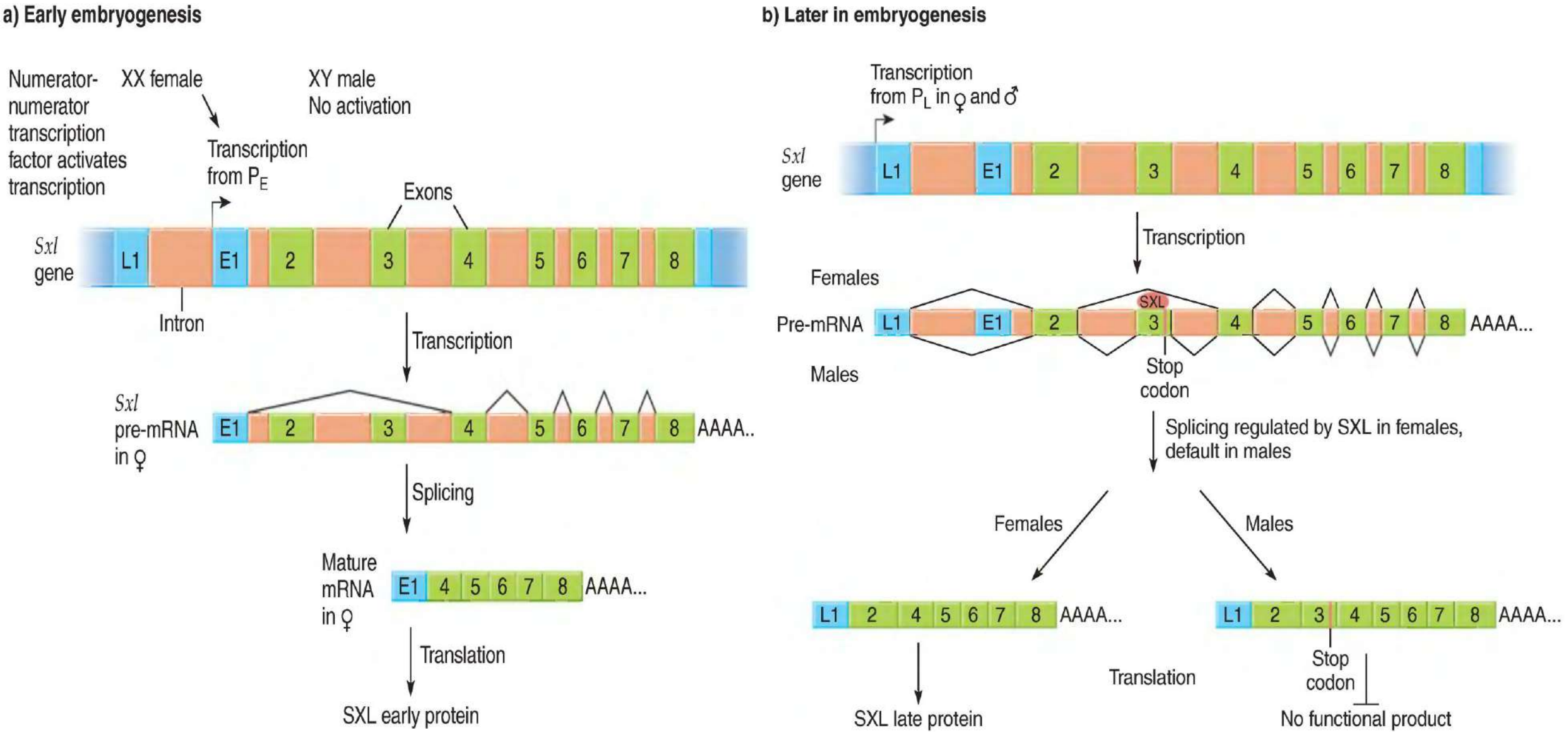
- On the **X chromosome** are the **sisterless numerator genes *sis-a*, *sis-b*, *and sis-c***, and on an **autosome** is the **deadpan (dpn) denominator gene**.

- The numerator genes are expressed to produce protein subunits that can form either homodimers or heterodimers with the subunit encoded by the denominator gene.

- In females, an excess of numerator subunits versus denominator subunits results from expression of the two copies of each numerator gene, so there are many numerator homodimers formed. These **numerator homodimers are transcription factors that activate Sxl expression.**

Detection of X: A ratio and Sex determination cascade continued

- In males, there is only one copy of each numerator gene, so most expressed numerator subunits are found in heterodimers with denominator subunits. As a result, **there are no (or insufficient) numerator homodimers for activating Sxl expression.**

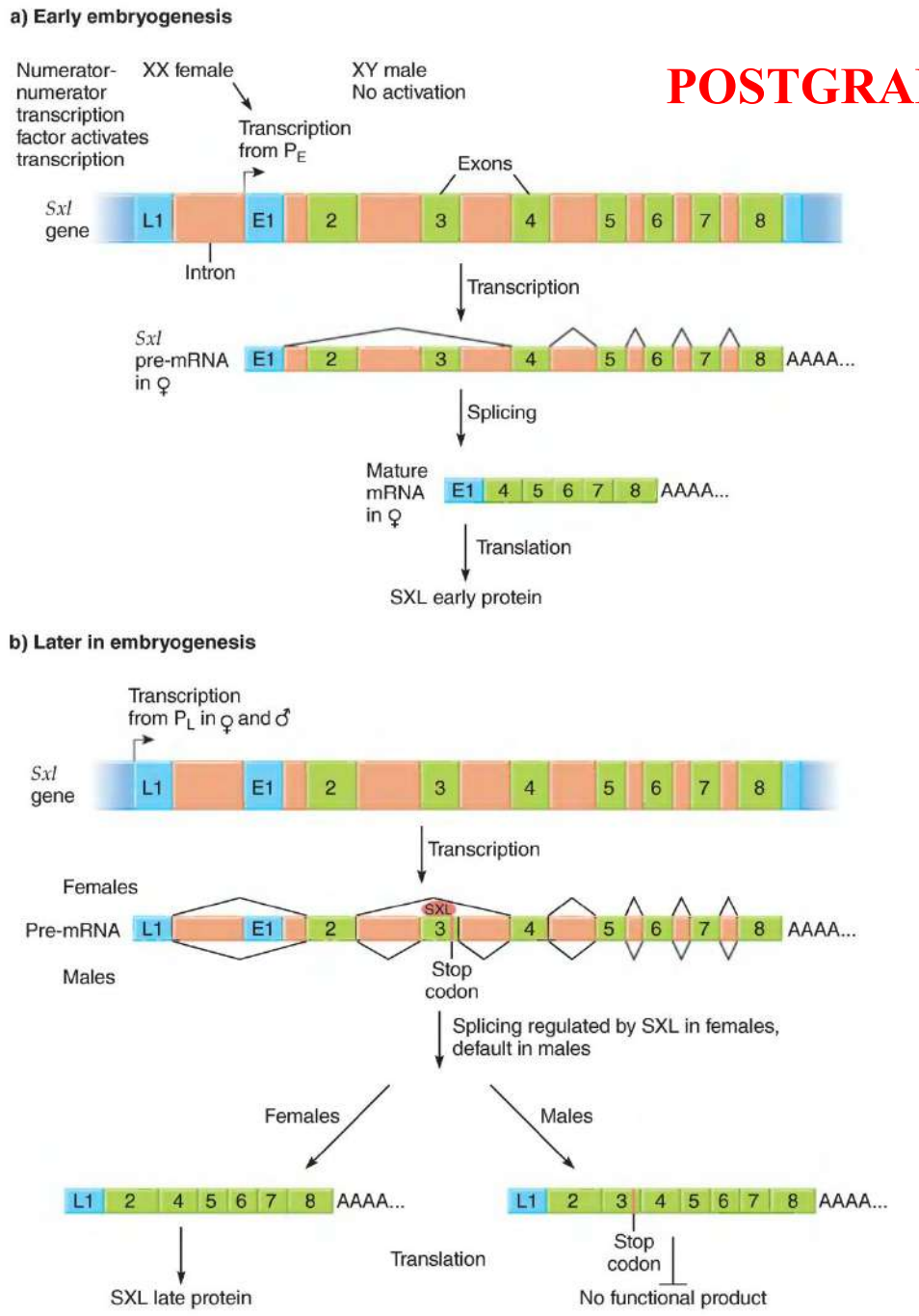


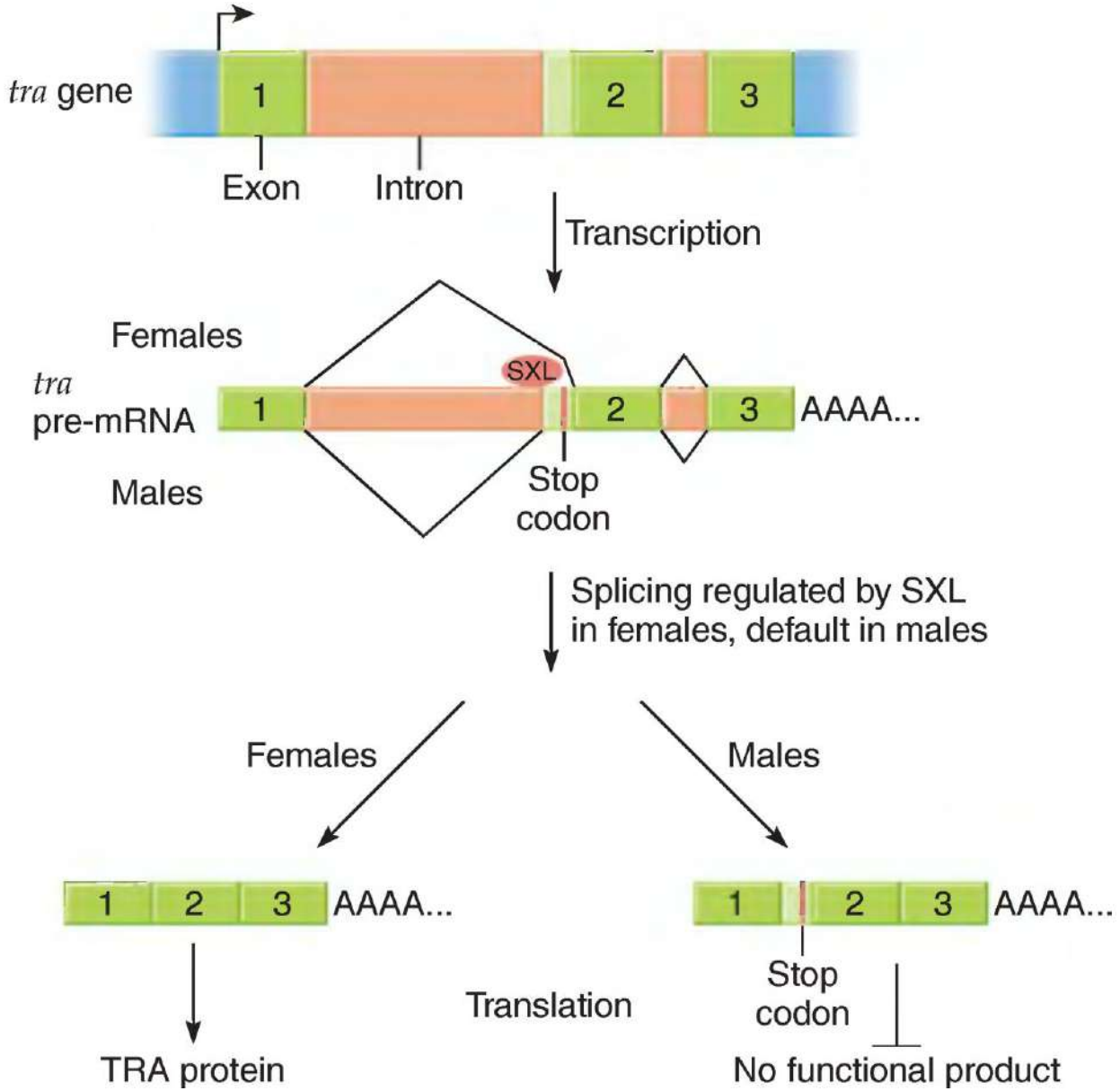
- **Early in embryogenesis** in the female, **the numerator-numerator dimer transcription factor** activates transcription of the Sxl gene from **P_E (promoter early)**, *one of two promoters for this gene, the other being a more upstream promoter, P_L (promoter late)*.

- The pre-mRNA transcribed from PE has **eight exons**; **exons 2** and **3** are skipped to produce the mature mRNA consisting of **exons El, 4, 5, 6, 7, and 8.** Translation of this mRNA produces the SXL early protein.

- In males, Sxl expression from P_E does not occur because sufficient numerator- transcription factors are absent: **No SXL protein is produced in males.**

- **Later in embryogenesis** (after gastrulation), **Sxl is transcribed constitutively from the late promoter, P_L**, in all cells, regardless of the X:A ratio. This transcription does not depend on the numerator transcription factors.
- The **pre-mRNA produced is longer than the transcript from P_E** and is subject to alternative depending on the presence or absence of SXL early protein.
- In females, the SXL early protein binds to the Sxl pre-mRNA and causes regulated splicing : exons **El** and **3** are skipped, resulting in a mature mRNA with exons **LI, 2, 4, 5, 6, 7,** and **8**. Translation of this mRNA produces **the SXL late protein.** In males, the absence of SXL early protein results in default splicing of the pre-mRNA and a mature mRNA is produced that includes exon 3.
- **Exon 3 has a stop codon** in frame with the start codon at the beginning of exon 2, so **no functional SXL late protein is produced in males.**



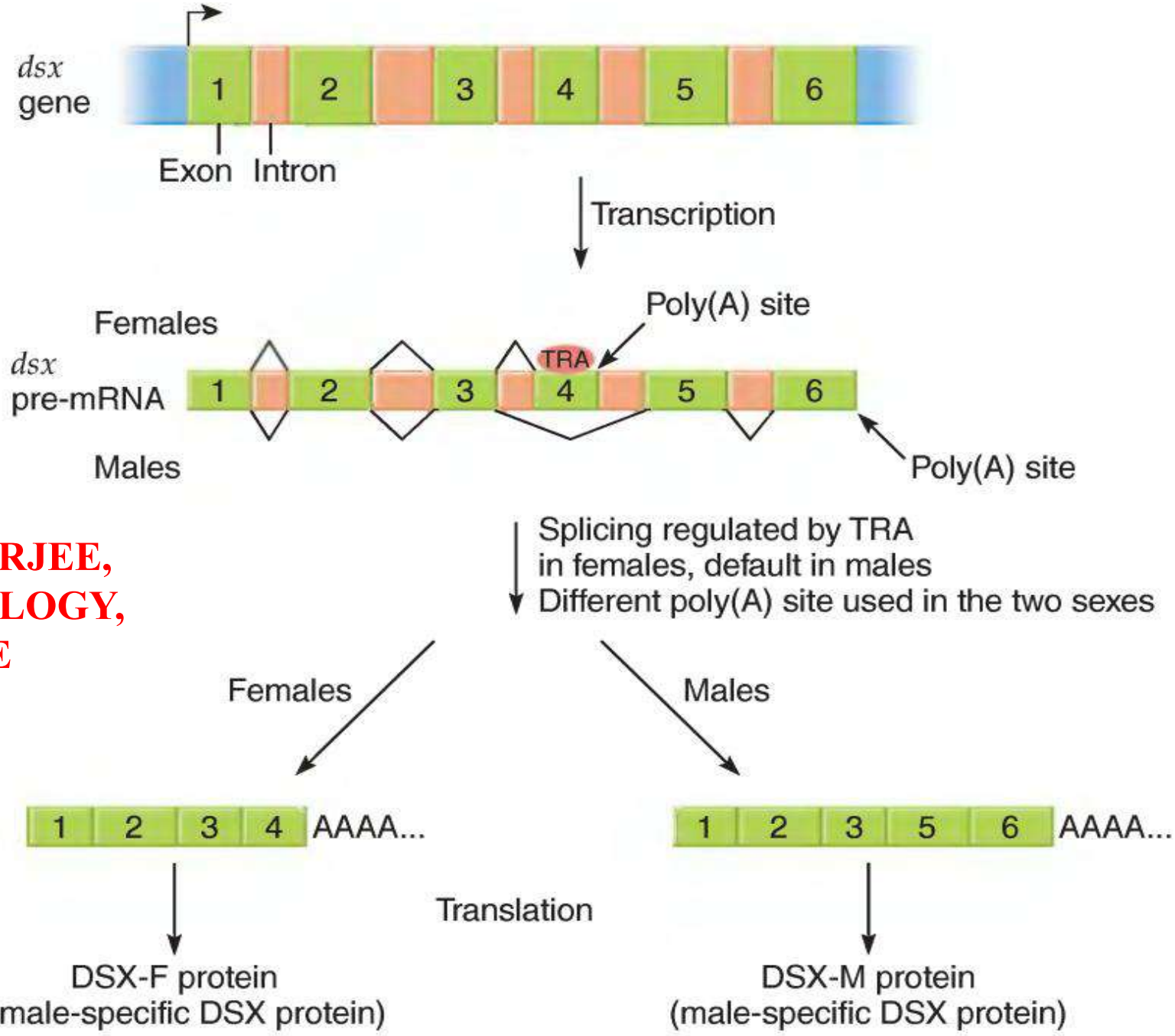


- In the female embryo, SXL late protein regulates splicing of transformer (tra) pre-mRNA.

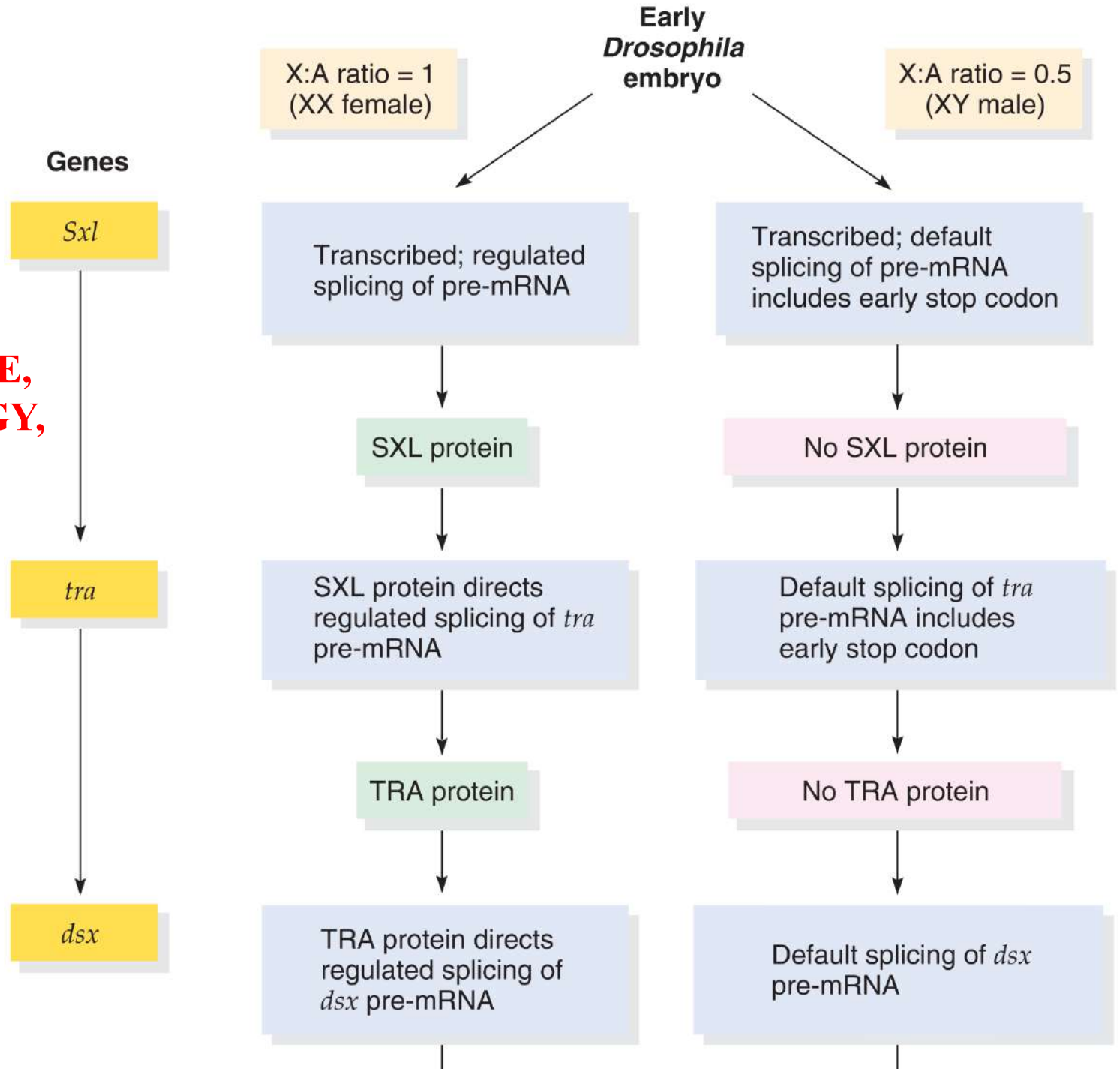
- In this case, a **stop codon-containing exon segment upstream of and contiguous with exon 2 is removed**, resulting in an mRNA with exons 1,2, and 3. Translation of this mRNA produces the **active TRA protein**.

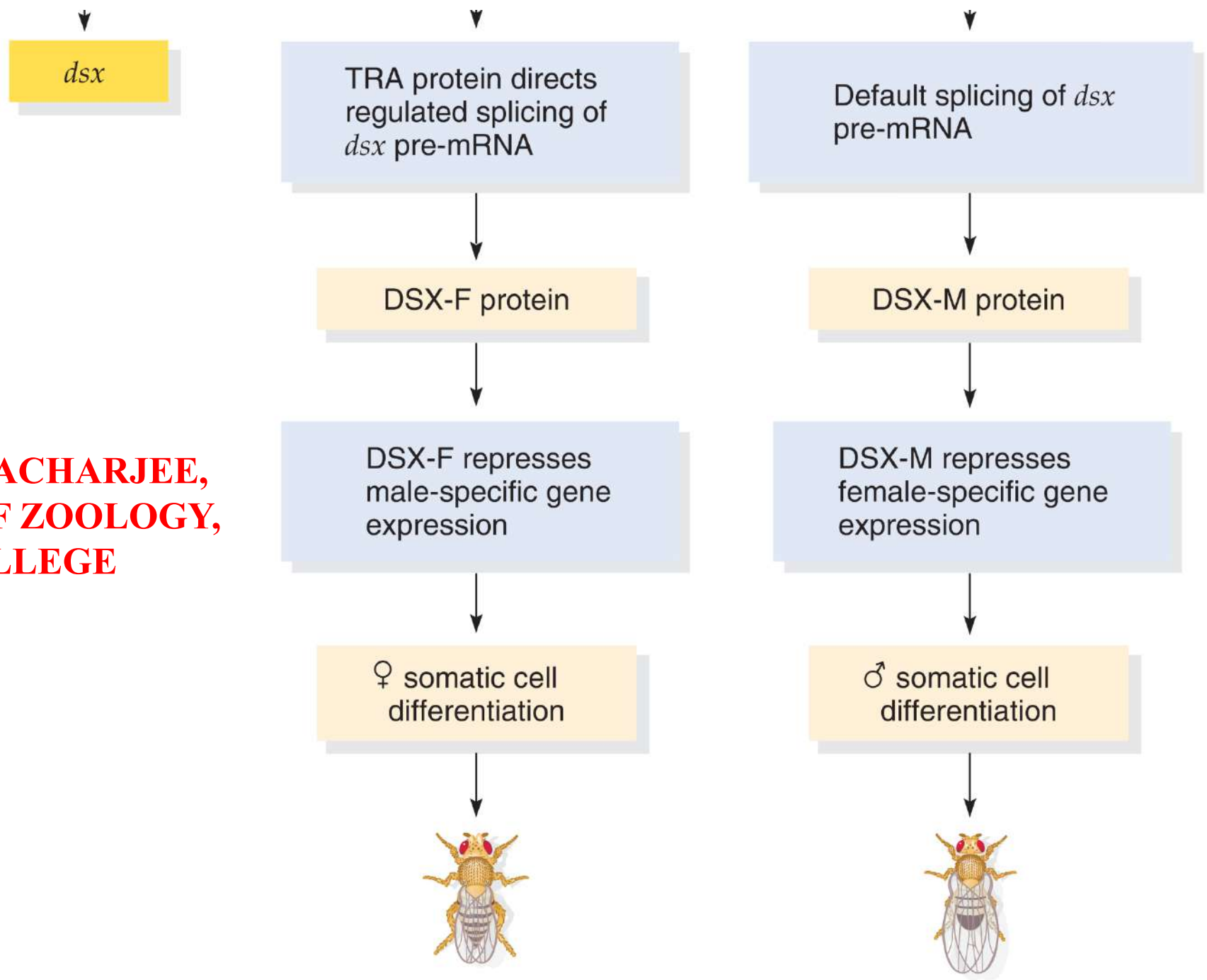
- In males, default splicing occurs as a result of the absence of SXL late protein.

- This means that the stop codon-containing segment is not removed. Translation of the resulting mRNA halts at the stop codon in that segment; **no functional TRA protein** is produced.



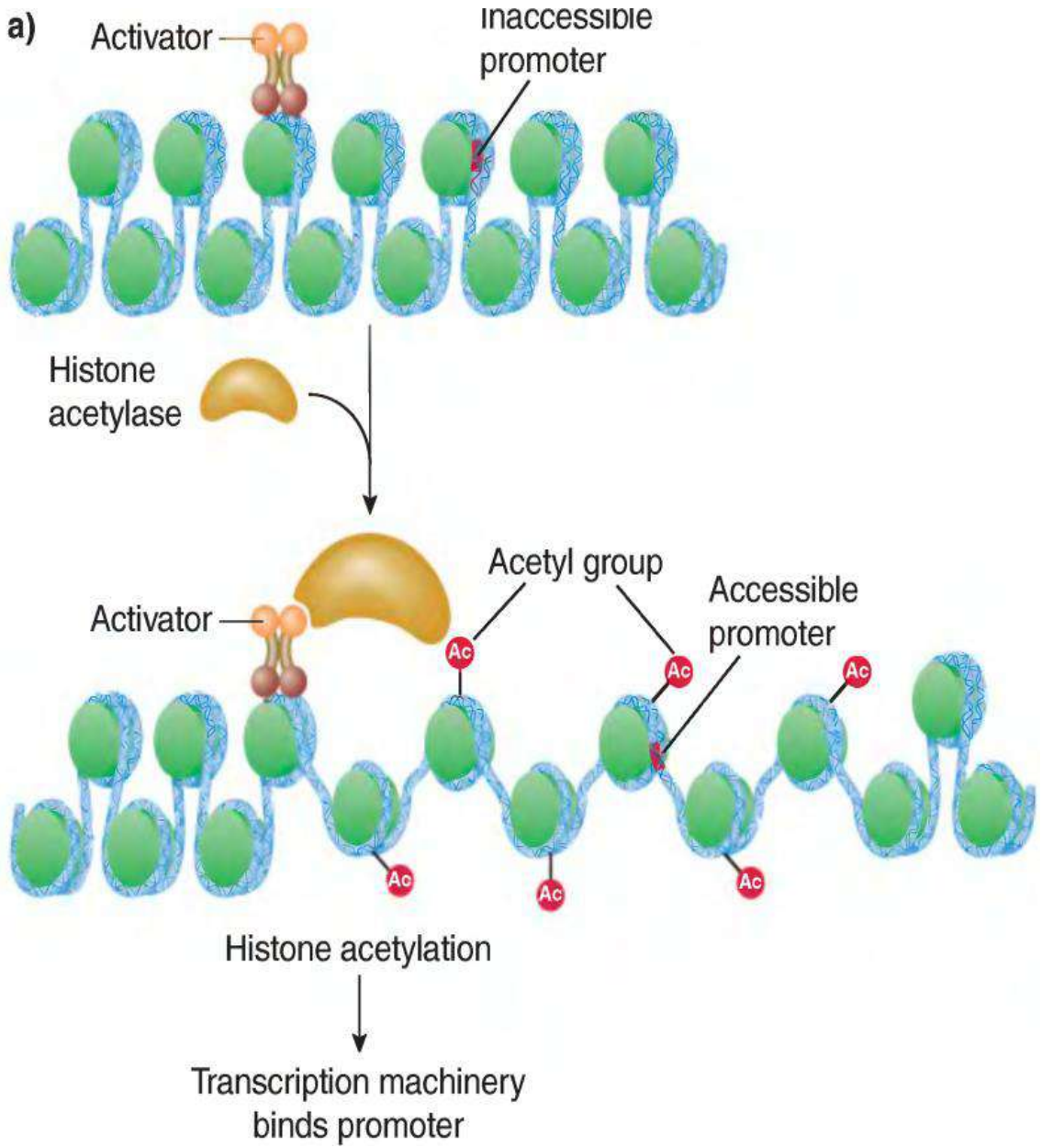
- **TRA protein** is also an RNA splicing regulator. The target is the pre-mRNA of the **doublesex (dsx) gene**.
- In females, TRA-regulated splicing gives rise to **female dsx mRNA**.
- This mRNA encodes the DSX-F (F for female) protein, a transcription factor that **represses male-specific gene expression** in all cells. As a result, female-specific somatic cell differentiation occurs.
- In males, the **absence** of functional TRA protein results in **default splicing** of the dsx pre-mRNA to produce **male dsx mRNA**.
- This mRNA encodes the **DSX-M (M for male) protein**, a transcription factor **that represses female- specific gene expression** in all cells. As a result, male- specific somatic cell differentiation occurs.





Dosage Compensation in *Drosophila*

1. Key male- specific lethal genes are mle (*maleness*), msl-1 (*male- specific lethal-1*), msl-2, msl-3, and mof (*males absent on the first*). The products of these genes are collectively called the **male-specific lethal (MSL)** proteins.
2. The SXL late protein plays a key role in dosage compensation.
3. **In females**, **the SXL late protein binds to the transcript of msl-2**, blocking its translation; **no MSL2 protein** is produced.
4. **In males**, the **msl-2 transcript can be translated because SXL late protein** is absent. **MSL2 forms a complex with the other MSL proteins, MLE, MSL1, MSL3, and MOF**.
5. This **MSL complex binds to about 35 chromatin entry sites (CES)** on the Drosophila **male X chromosome** and then MSL complexes spread from those sites in both directions into the flanking chromatin. The **MOF protein of the MSL complex is a histone acetyl transferase (HAT)**, and **its chromatin remodeling activity spreads along the X chromosome** and is responsible for the twofold higher level of transcription of X chromosome genes in males than in females.
6. In females, the MSL proteins other than MSL2 are produced. However, because MSL2 is essential for the binding of the MSL complex to the X chromosome, no chromatin remodeling can occur in XX females.



1. Histones are acetylated by **histone acetyl transferases (HATs), recently renamed lysine (K) acetyl transferases (KATs).**
2. Found in multiprotein complexes, KATs are recruited to the chromatin when activators bind to their DNA binding sites and acetylate lysines of the amino- terminal tails of particular core histones. **Acetylation neutralizes the positive charge of lysine residues.**
3. With **increasing acetylation, the positively charged histones slowly lose affinity for negatively charged DNA, and the 30-nm** chromatin fiber loses histone HI and changes conformation to a 10-nm chromatin fiber.
4. In this form, the promoter is more accessible for activation of transcription.