

Prof. **Giorgio DIECI**

Dipartimento di Bioscienze  
Università degli Studi di Parma

## Frontiere della Biologia Molecolare

Milano, 4 marzo 2016

# Central Dogma of Molecular Biology

NATURE VOL. 227 AUGUST 8 1970

by

FRANCIS CRICK

MRC Laboratory of Molecular Biology,  
Hills Road,  
Cambridge CB2 2QH

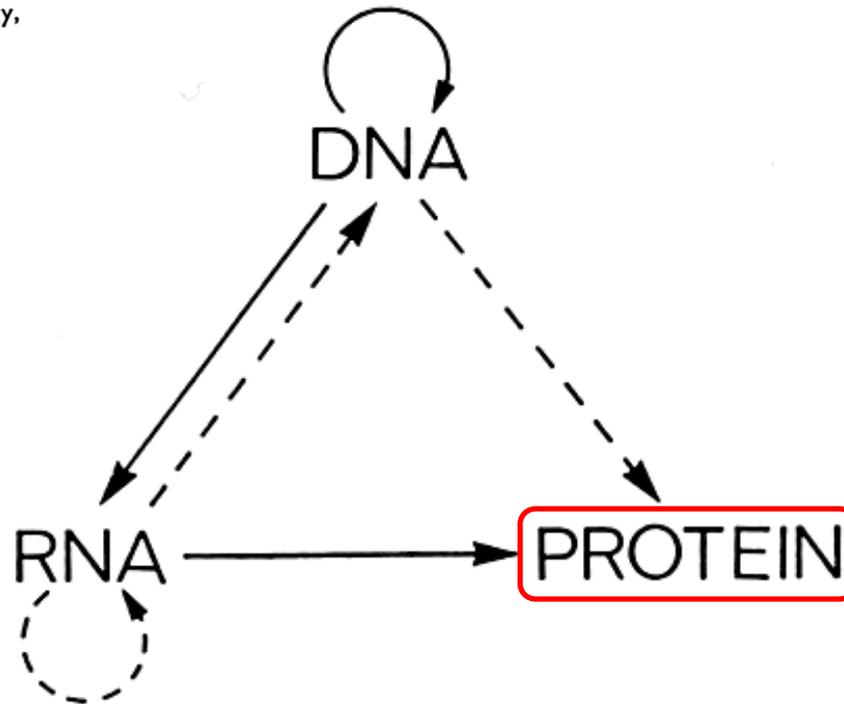
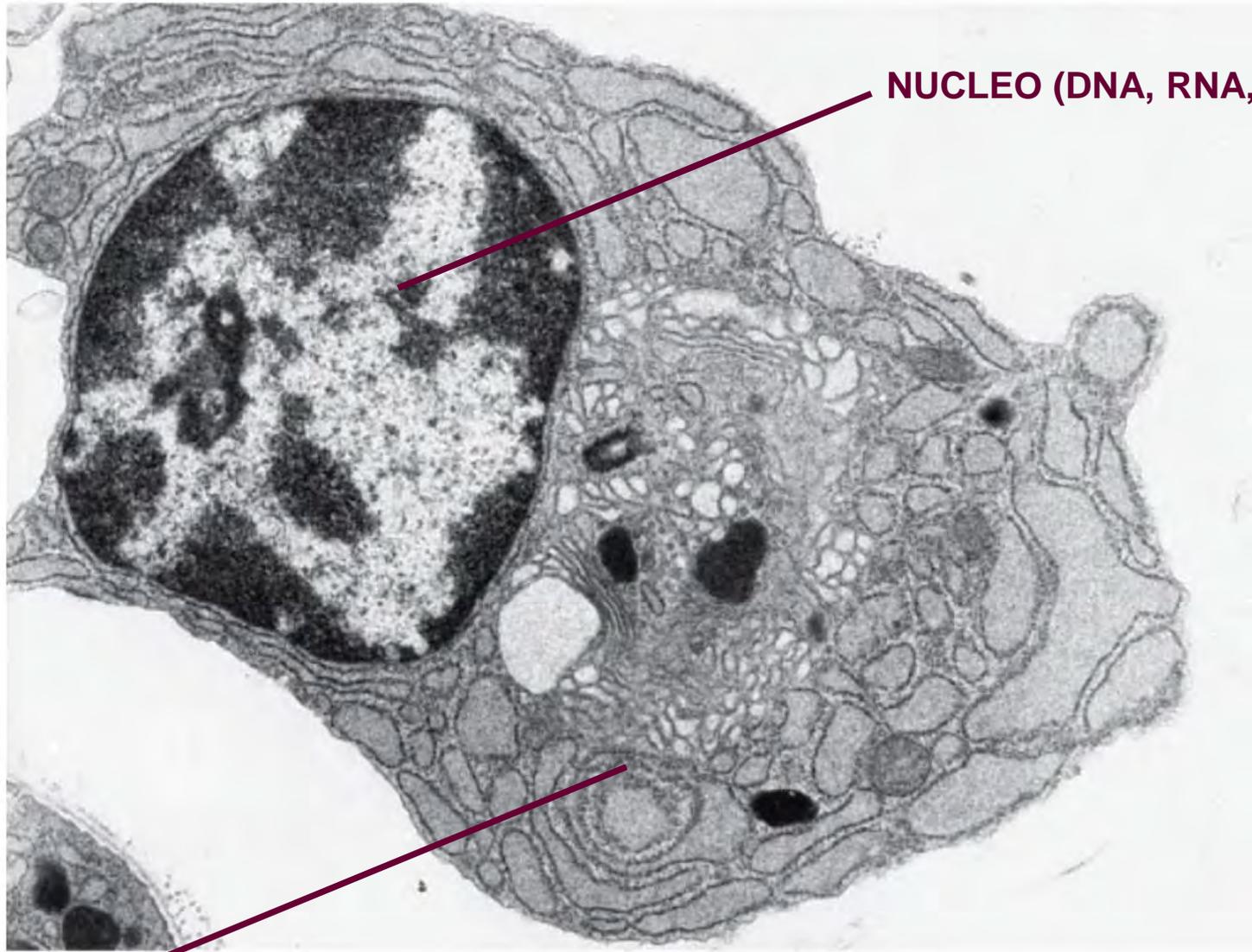


Fig. 3. A tentative classification for the present day. Solid arrows show general transfers; dotted arrows show special transfers. Again, the absent arrows are the undetected transfers specified by the central dogma.

# Fotografia al microscopio elettronico di una plasmacellula

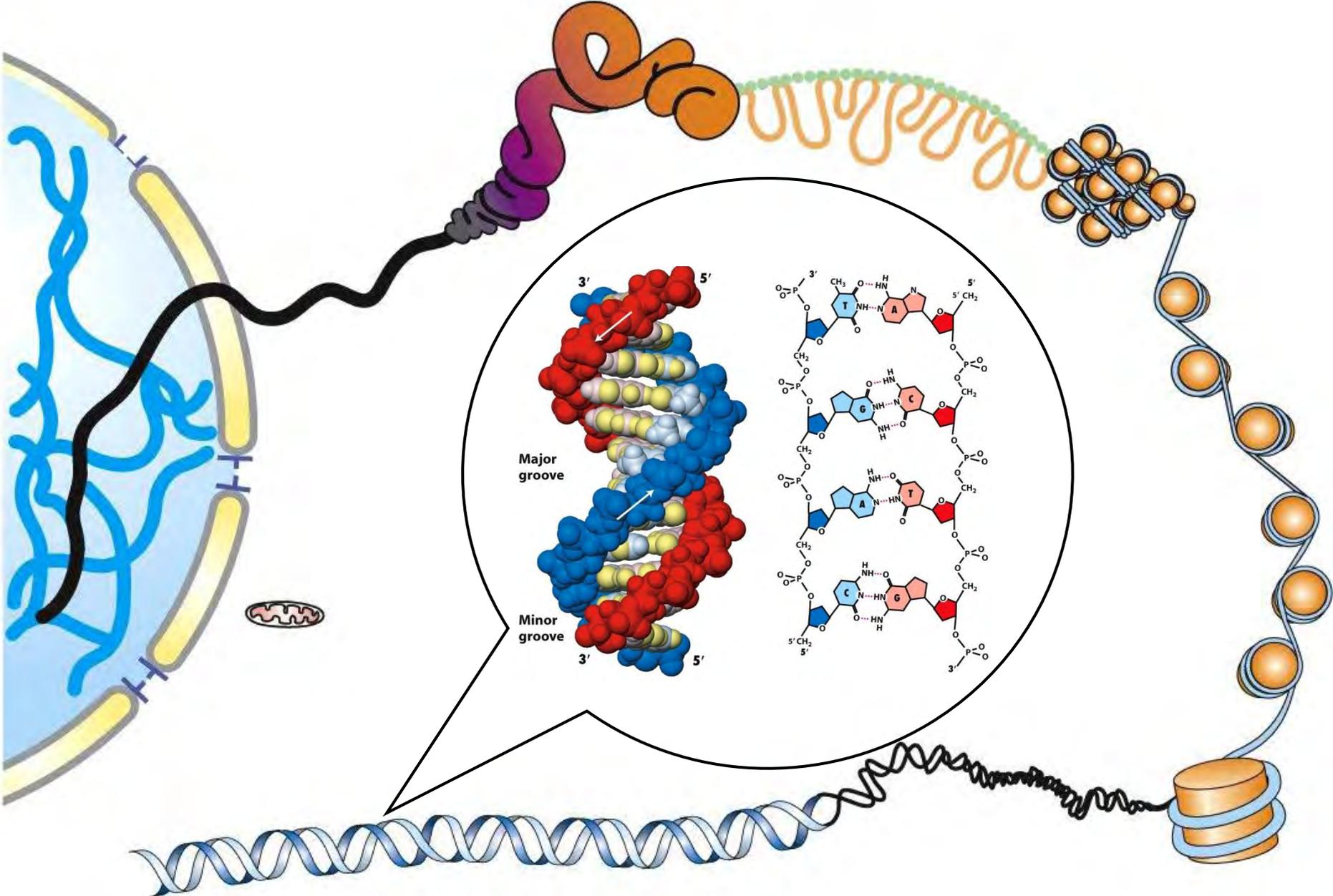


NUCLEO (DNA, RNA, proteine)

CITOPLASMA (RNA, proteine)

1  $\mu$ M

# DNA, cromatina e cromosomi



# Sintesi di RNA mediante trascrizione del DNA

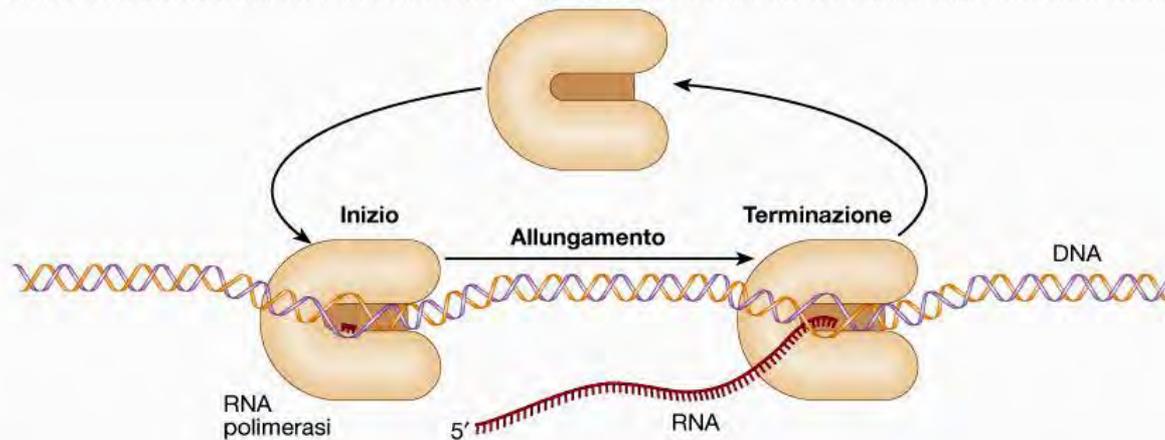
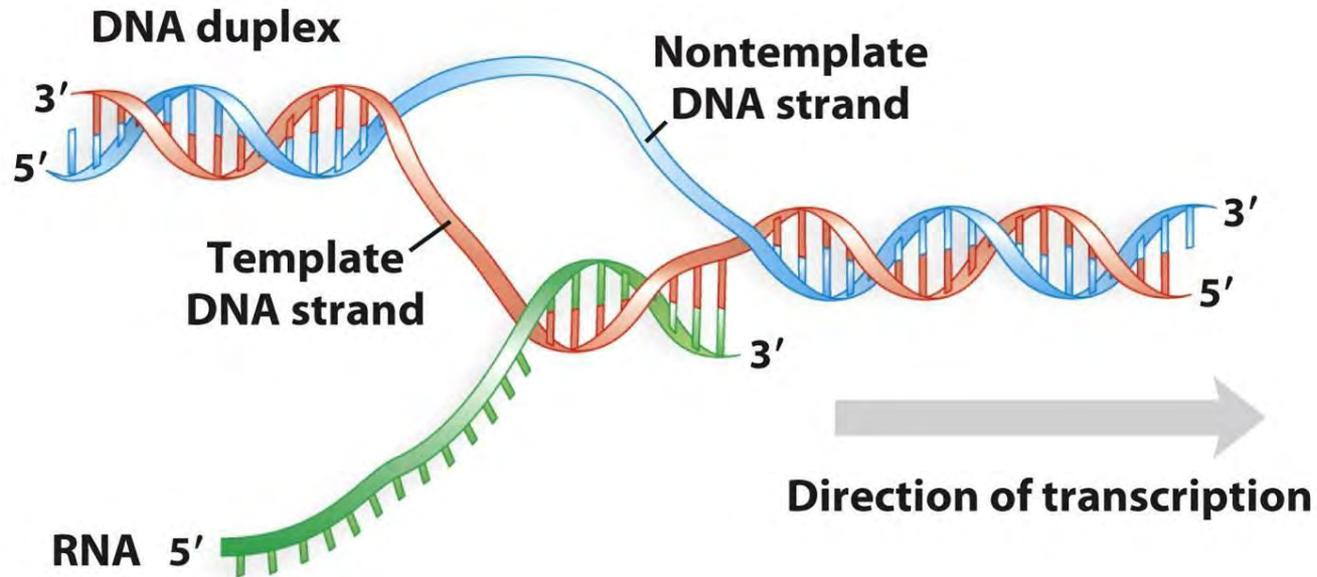


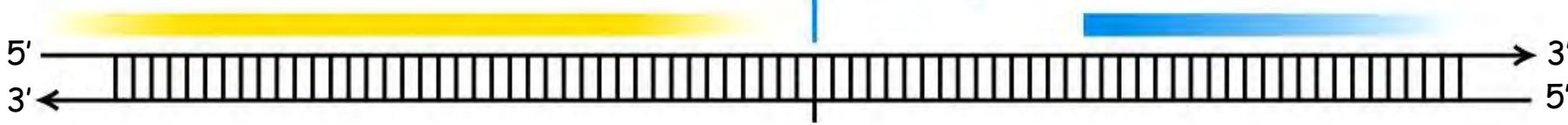
Figura 9.1 **Le tre fasi della trascrizione.** L'RNA polimerasi riconosce il promotore e inizia la trascrizione dal sito di inizio; estende poi il trascritto fino al sito di terminazione.

# Gene:

Regione di controllo

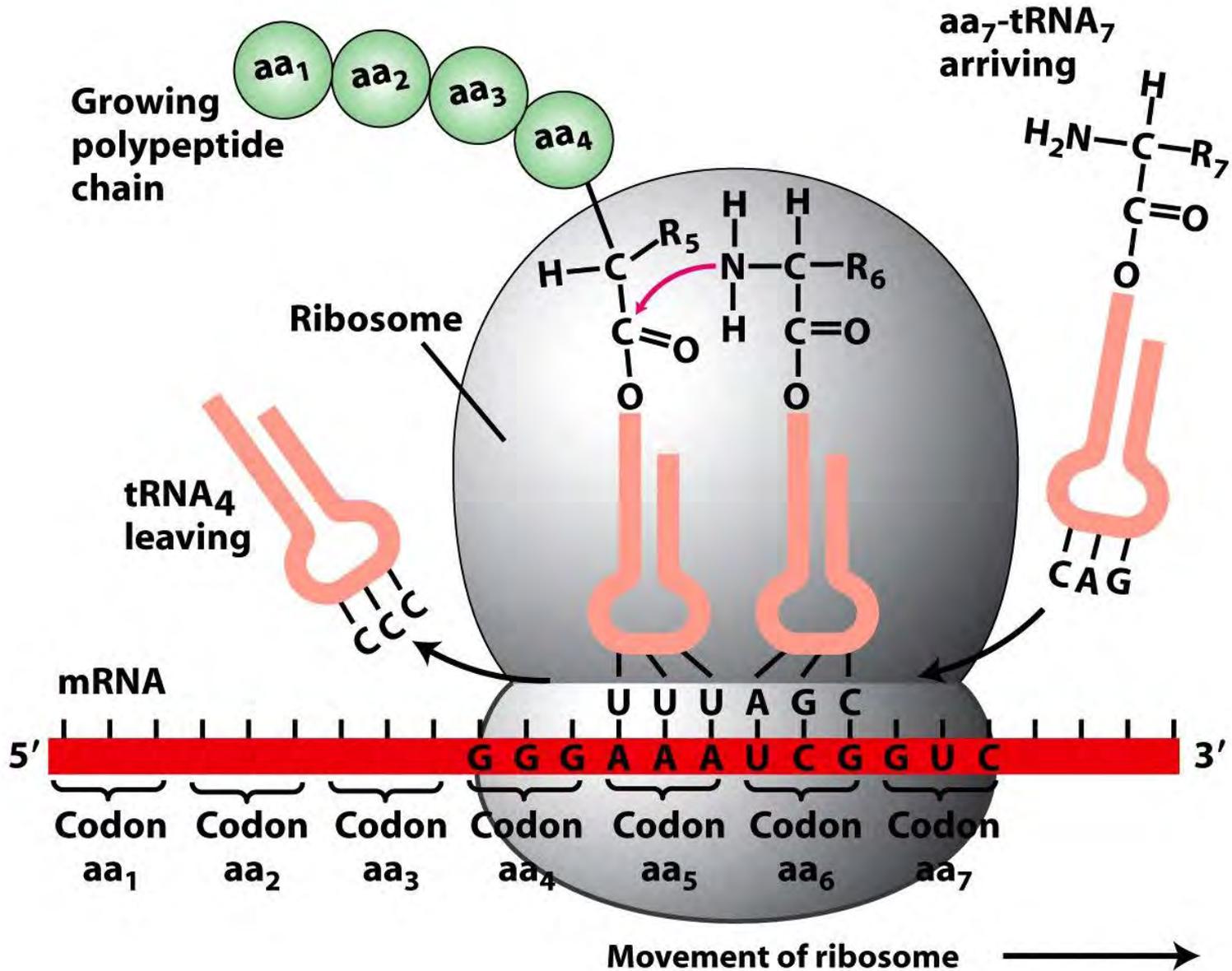
*Sito di inizio della trascrizione*

Regione trascritta

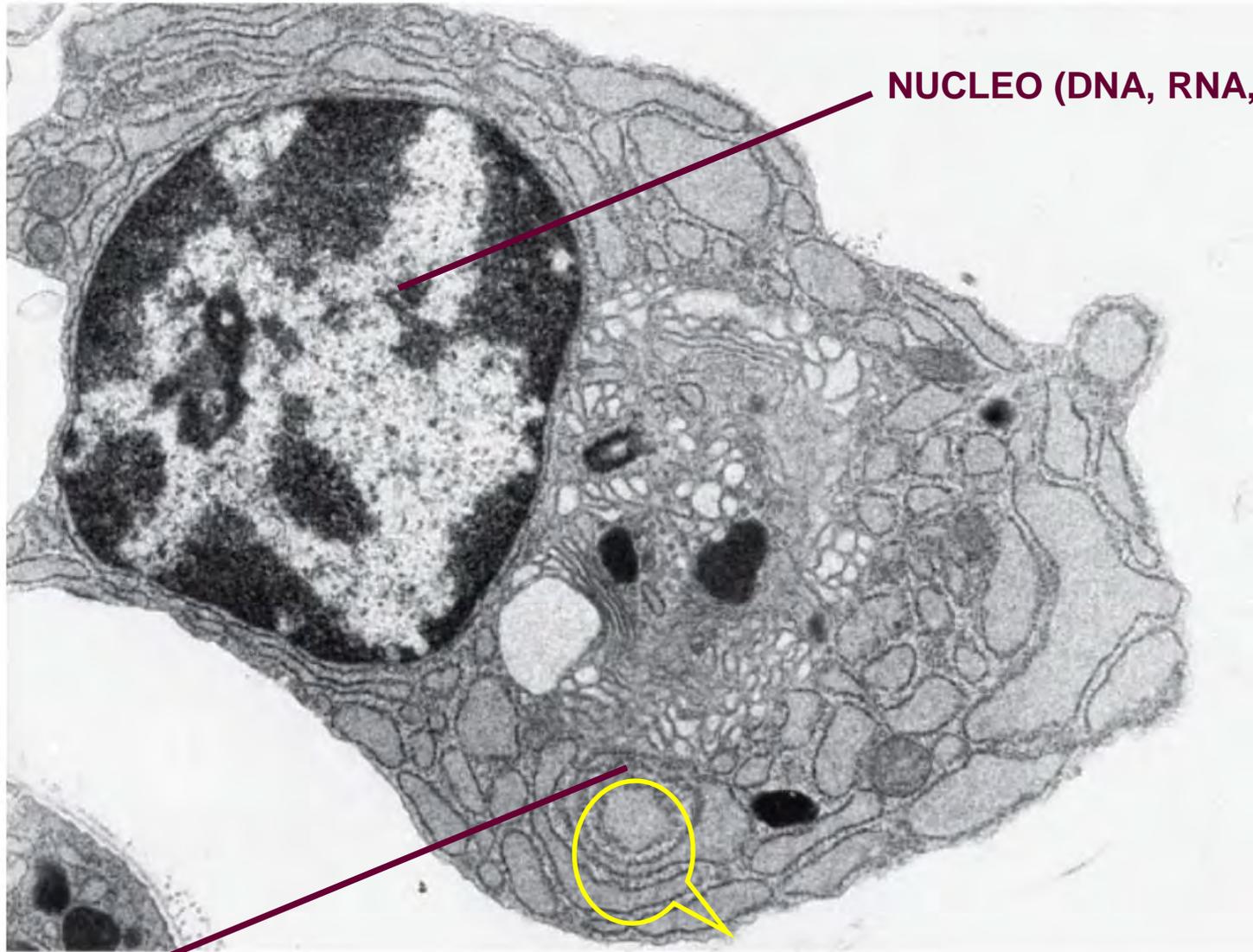


RNA (trascritto primario)

# Codice genetico e traduzione: biosintesi delle proteine



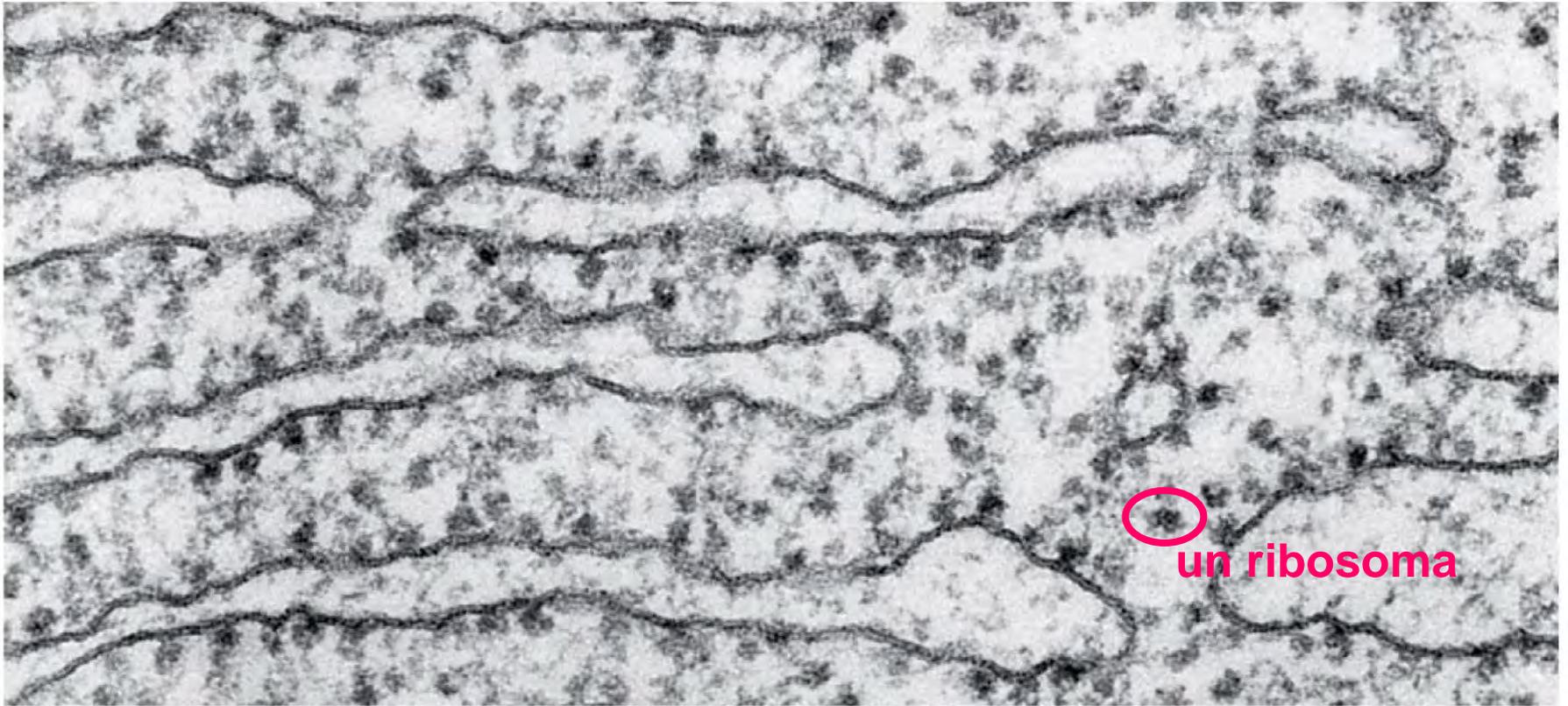
# Fotografia al microscopio elettronico di una plasmacellula



NUCLEO (DNA, RNA, proteine)

CITOPLASMA (RNA, proteine)

1  $\mu$ M

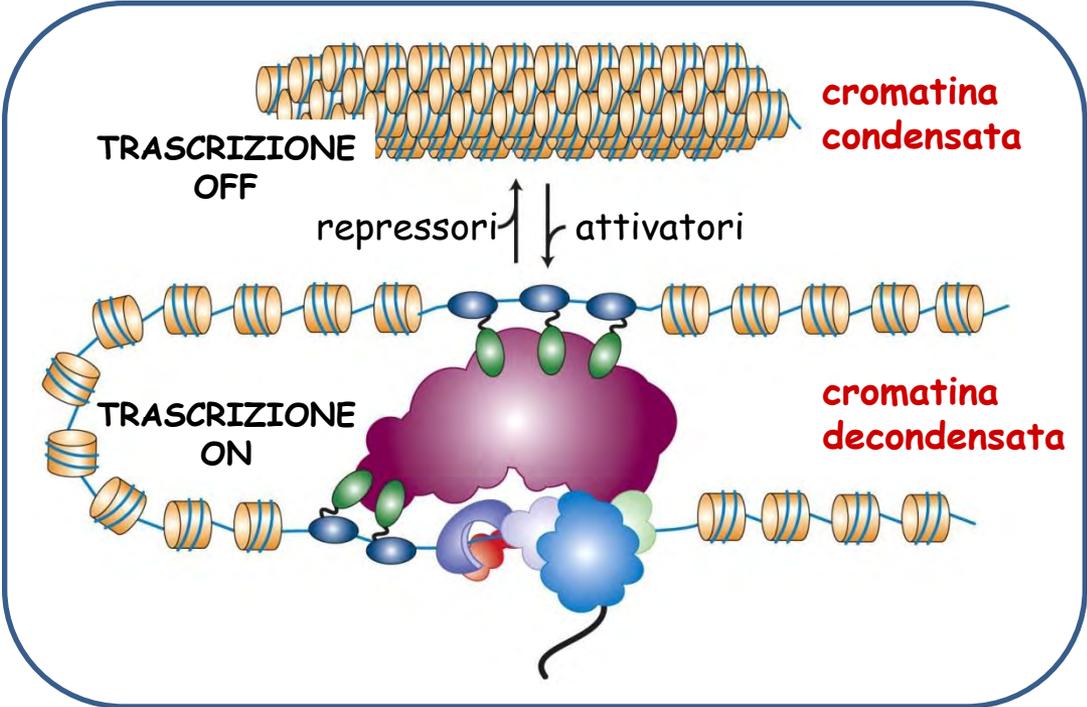
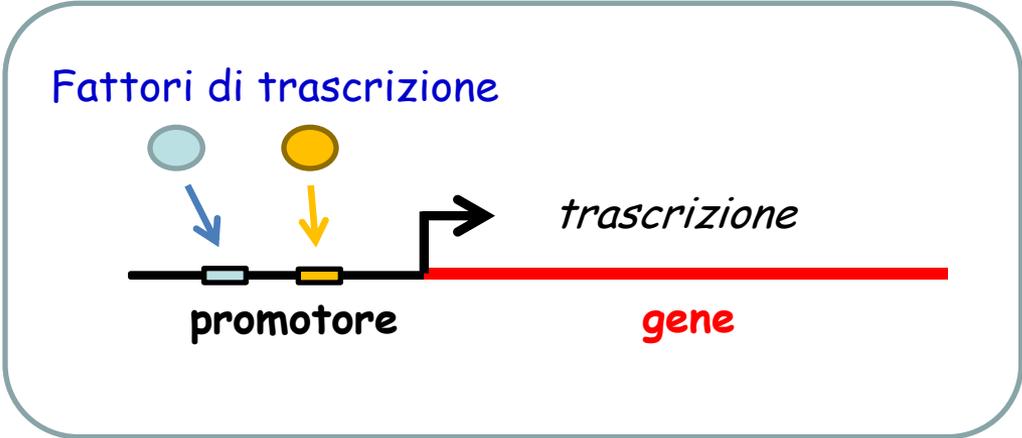
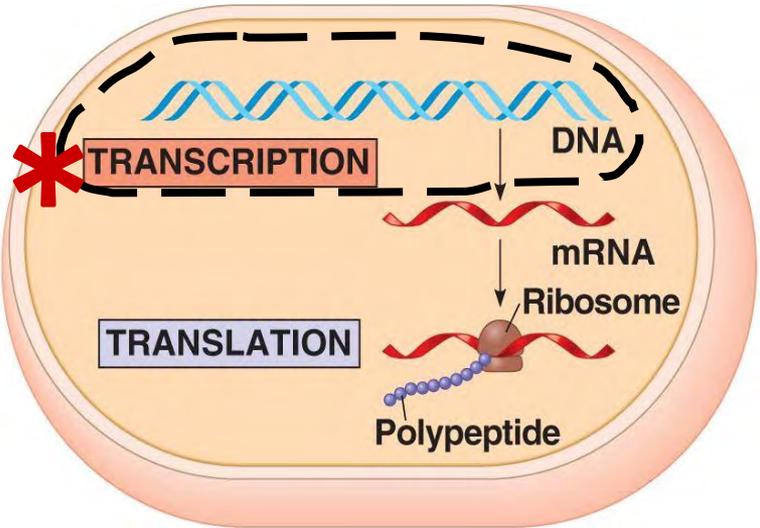


un ribosoma

0.5  $\mu$ M

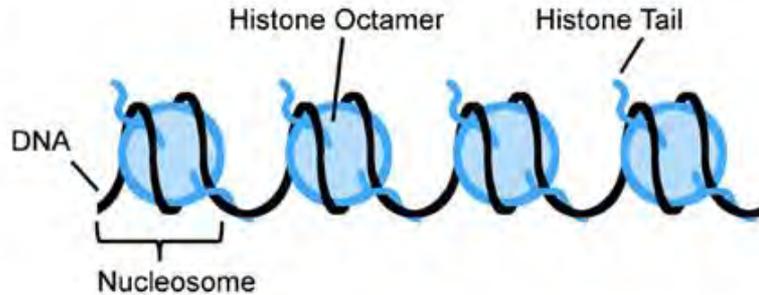
**Figure 13-2a**  
*Molecular Cell Biology, Sixth Edition*  
© 2008 W. H. Freeman and Company

# Regolazione genica trascrizionale\*



# Metilazione del DNA e acetilazione/metilazione degli istoni influenzano fortemente la trascrizione genica

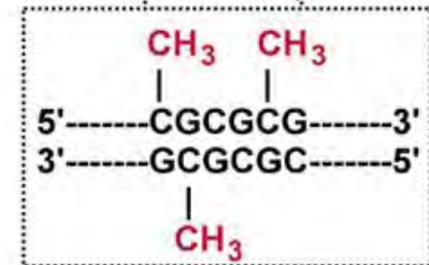
Chromatin



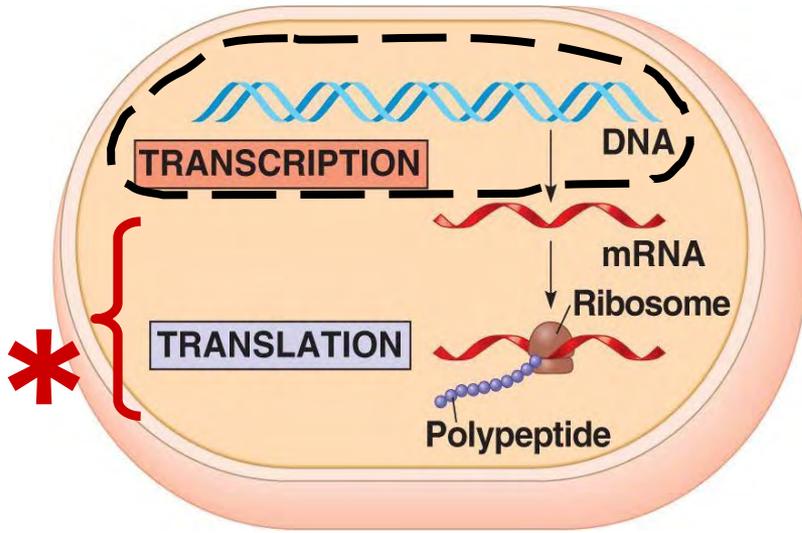
DNA Methylation  
Histone Methylation



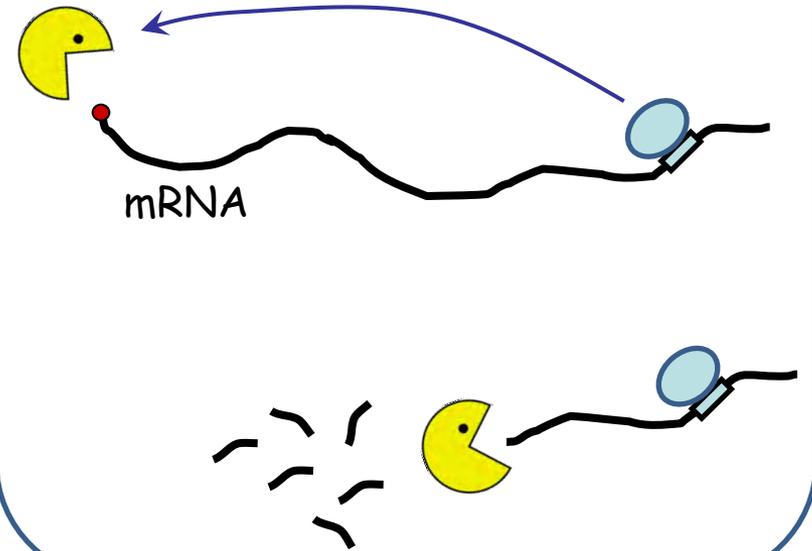
- ◆ Methyl group
- Histone methylation
- ▲ Histone acetylation / phosphorylation



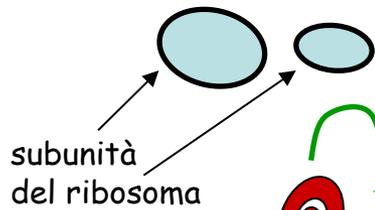
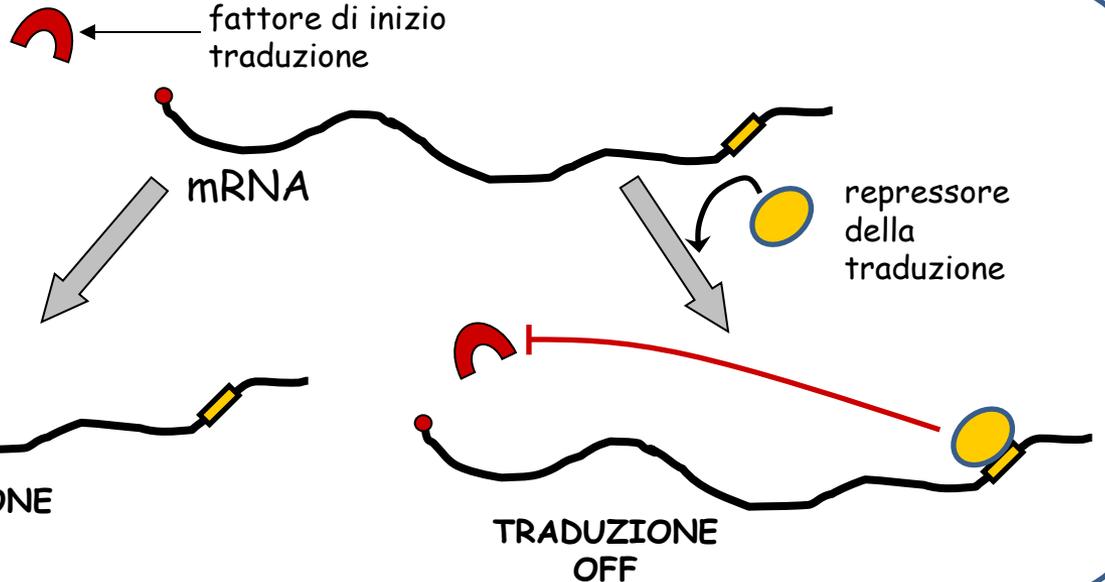
# Regolazione genica post-trascrizionale\*



## Regolazione della stabilità del mRNA



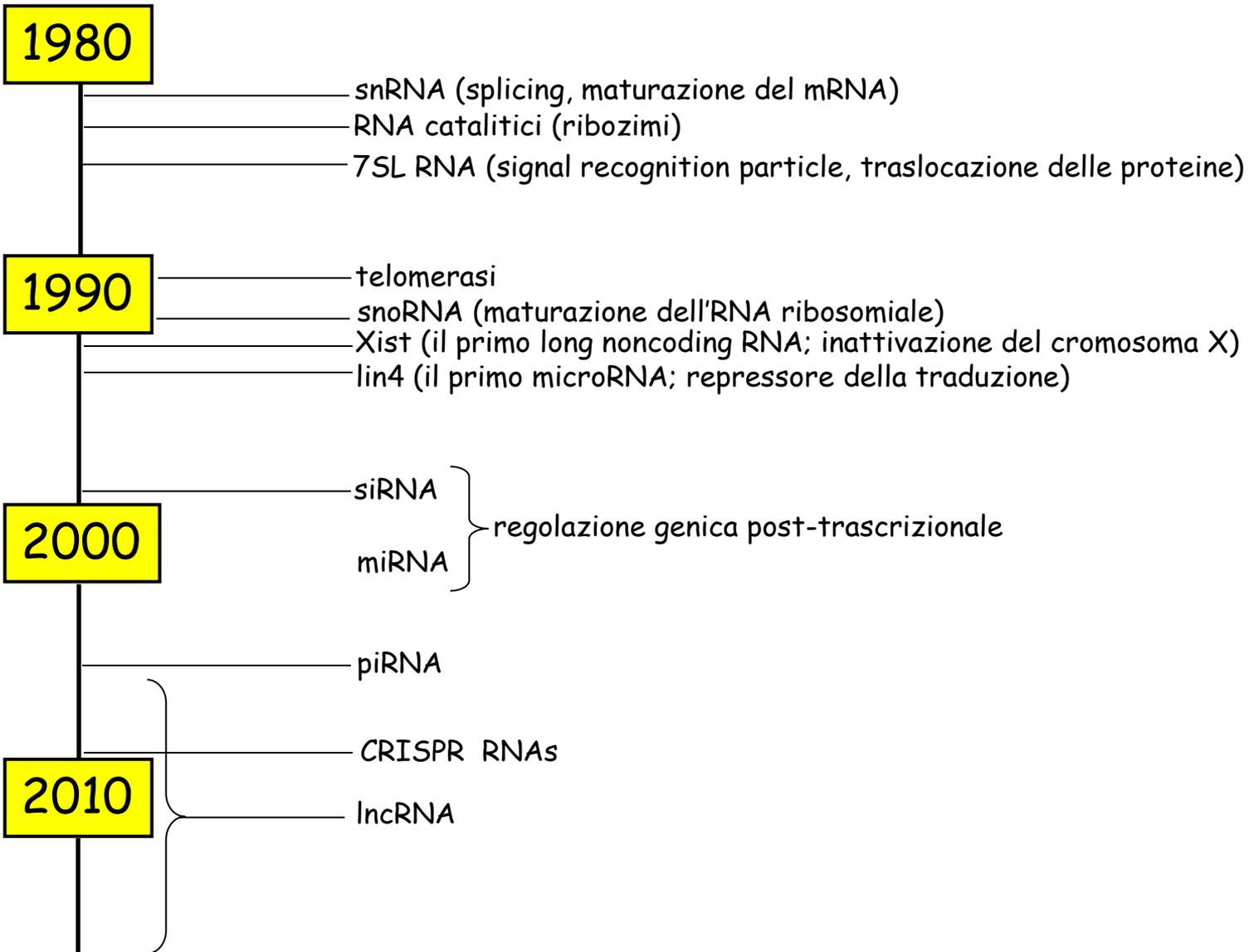
## Regolazione della traduzione



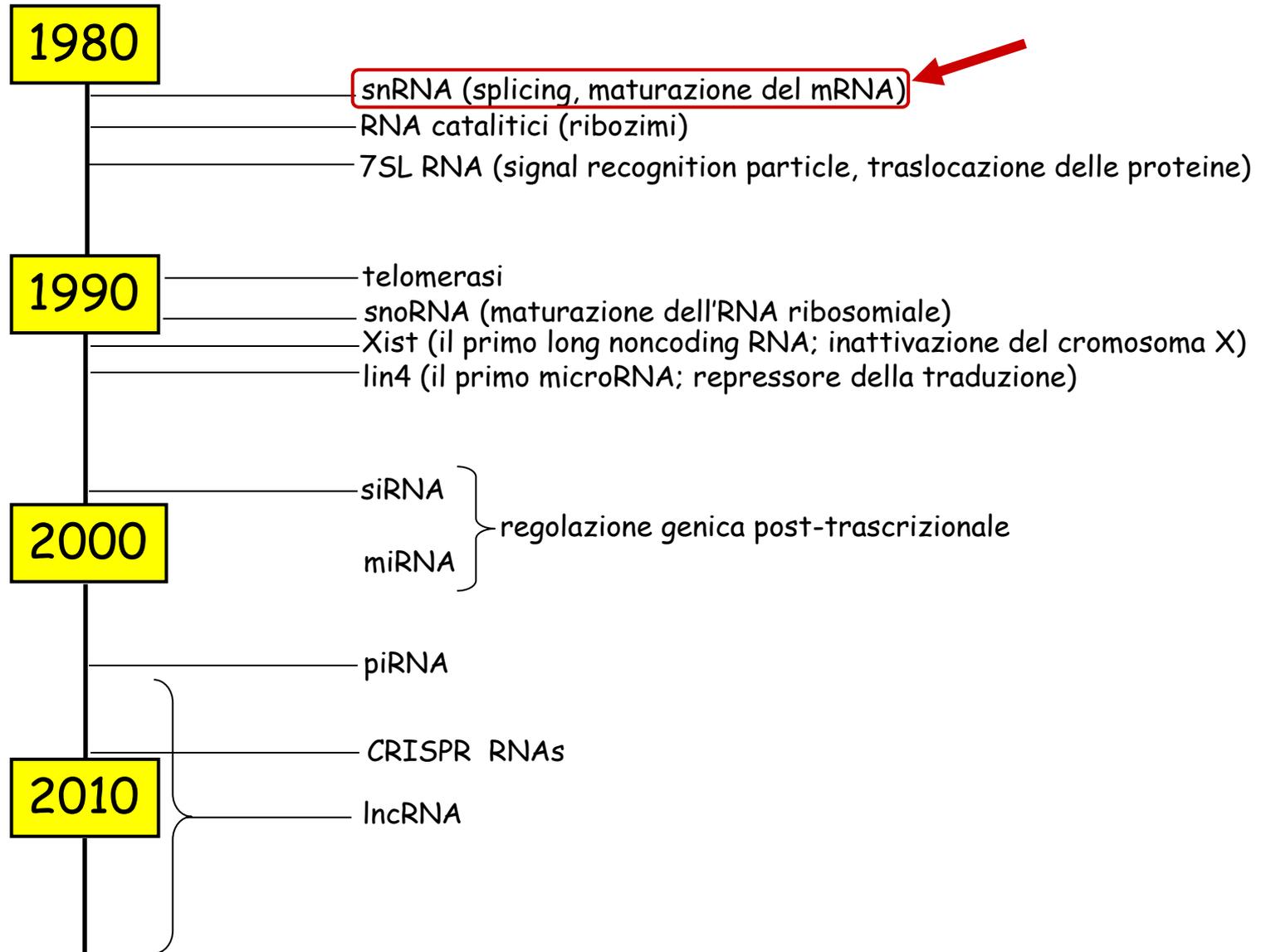
TRADUZIONE ON

TRADUZIONE OFF

# "The noncoding RNA revolution"



# "The noncoding RNA revolution"

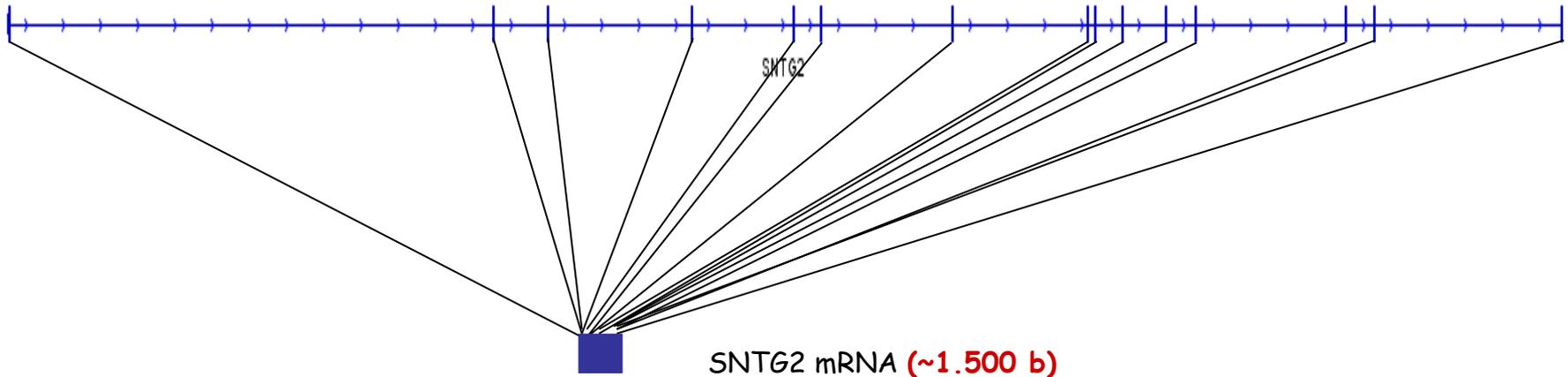


# Geni discontinui e splicing (RNA acrobatics)

Gene  
SNTG2  
(Syntrophin  $\gamma$ 2)

Coordinate  
chr2:944,554-1,373,384

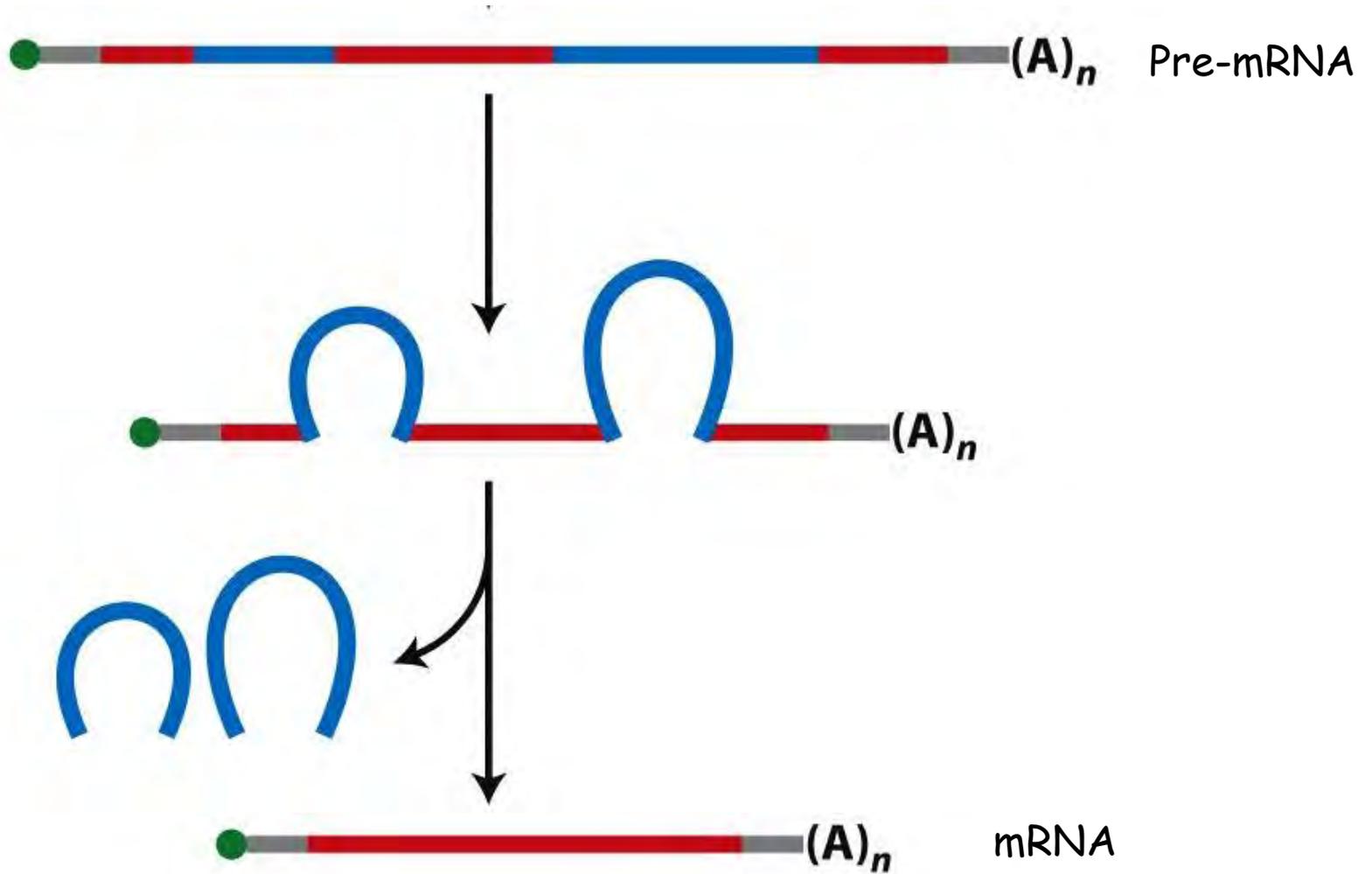
SNTG2 trascritto primario (~430.000 b)  
15 esoni e 14 introni



Lunghezza media degli introni nei geni umani: 3300 bp

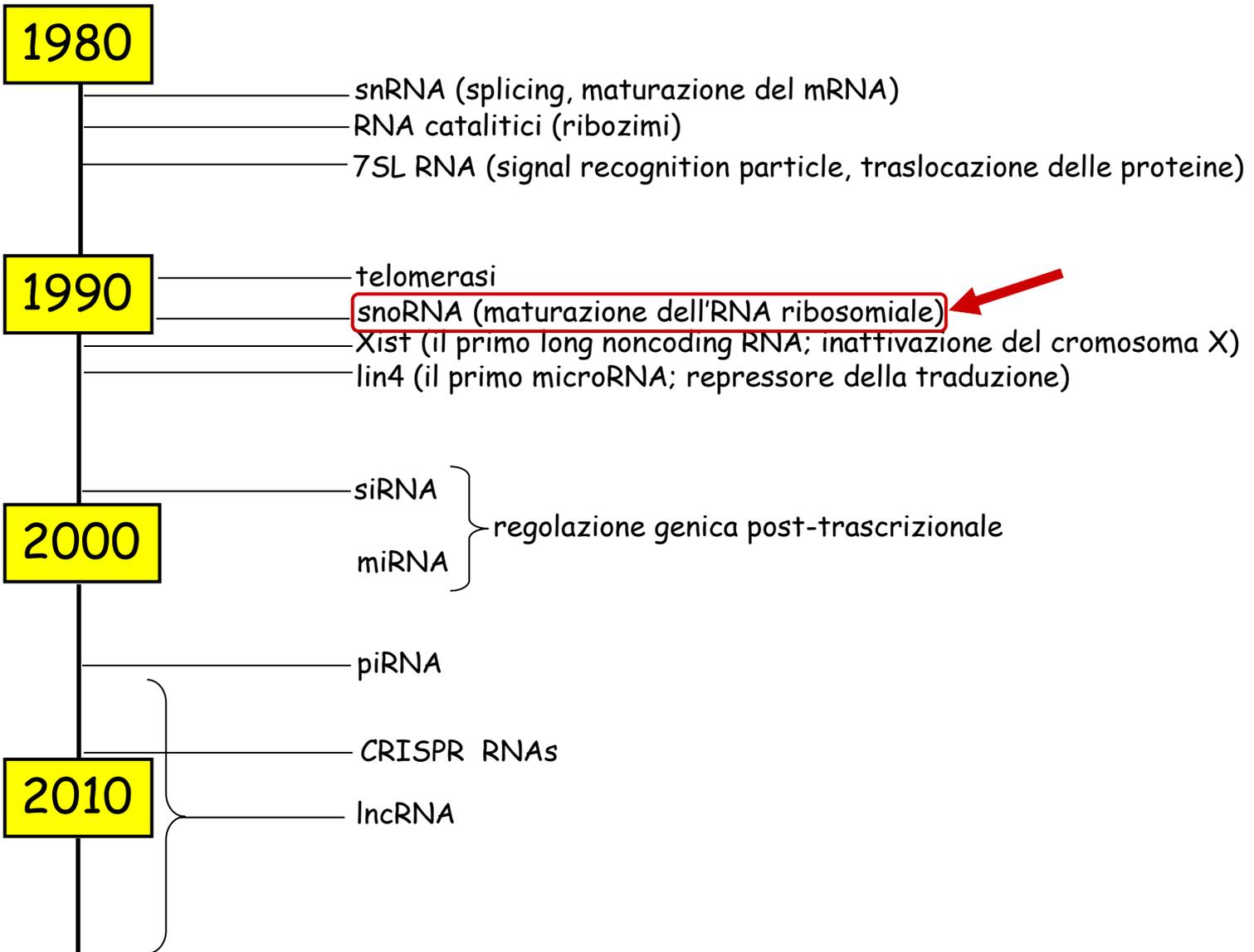
Lunghezza tipica degli esoni nei geni umani: 50-200 bp

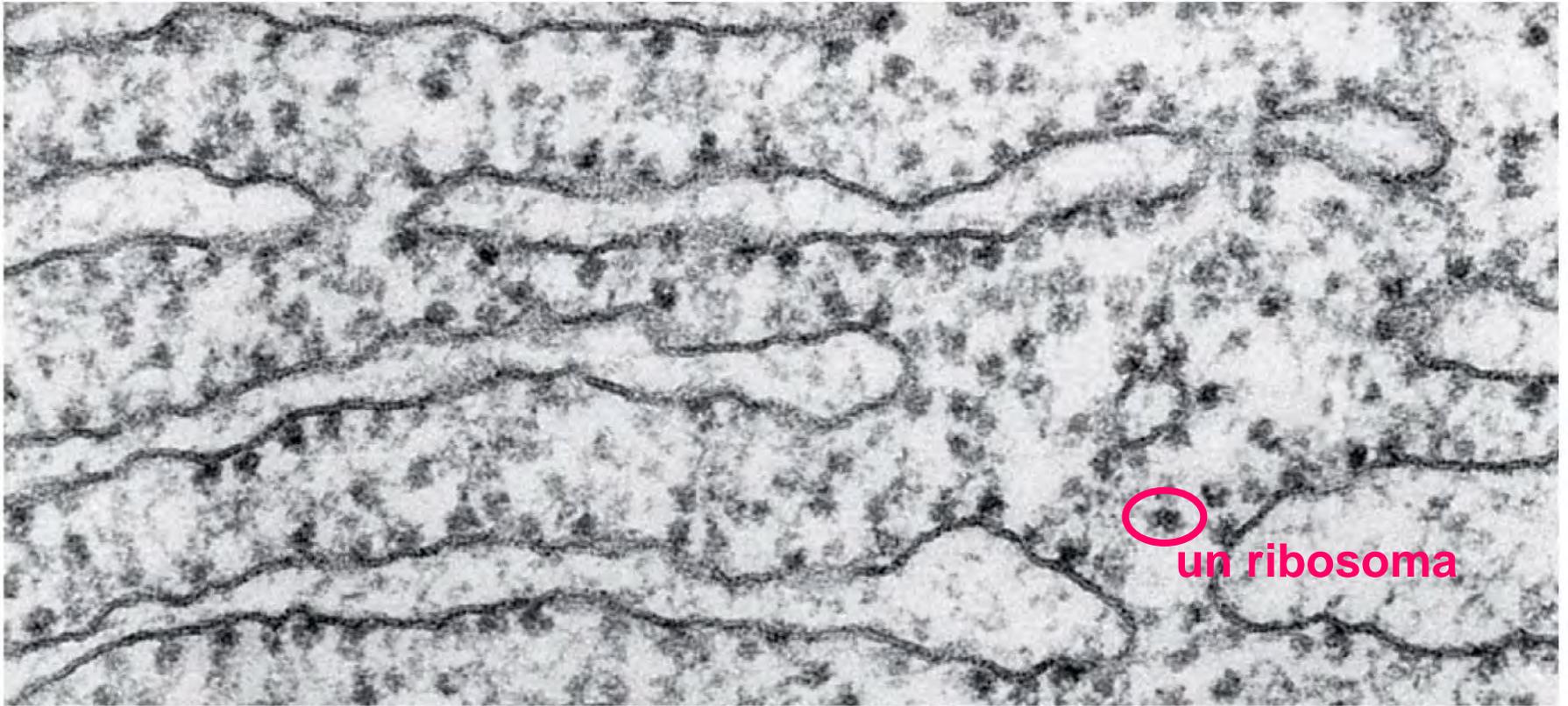
# mRNA splicing





# "The noncoding RNA revolution"



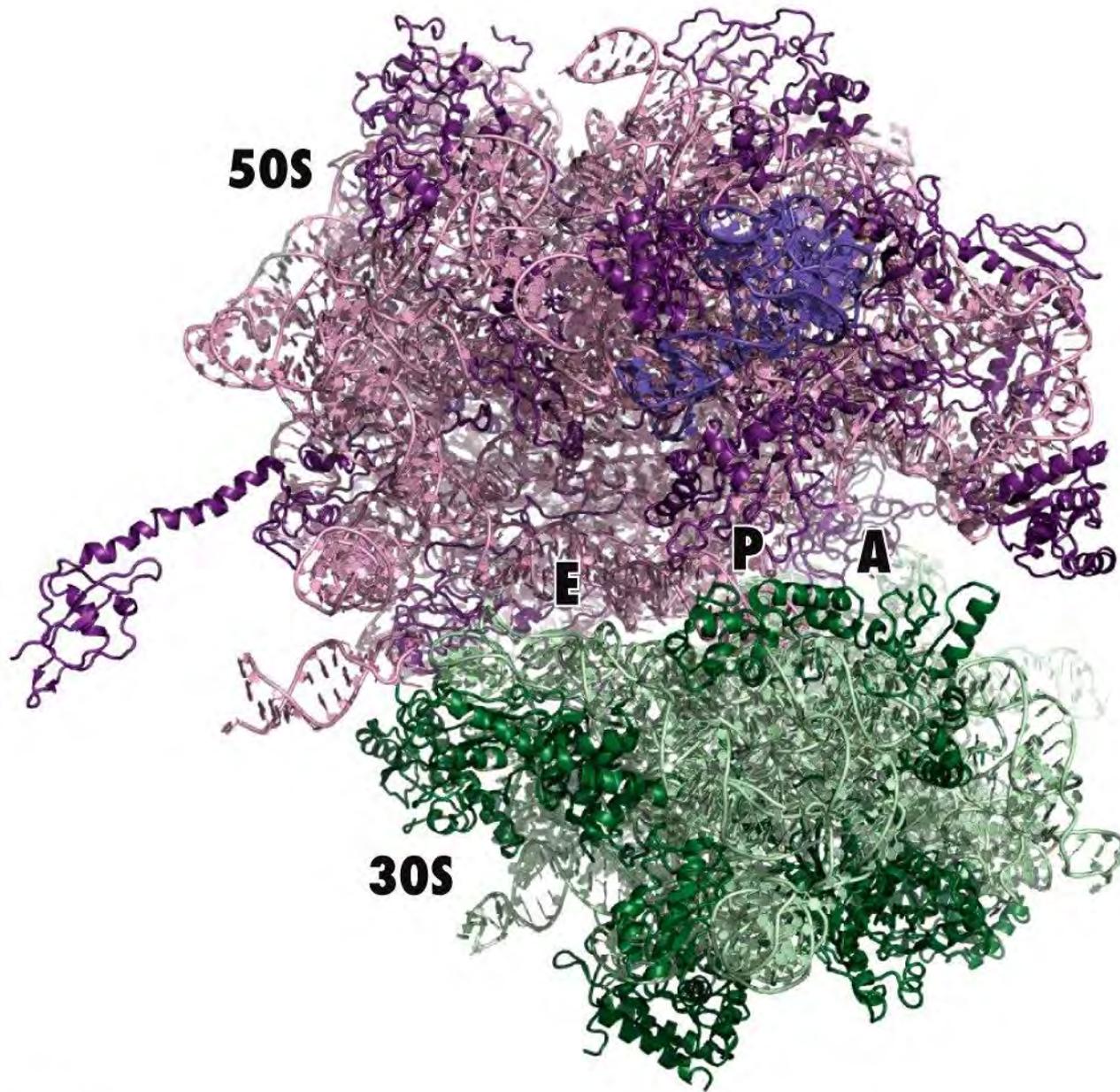


un ribosoma

0.5  $\mu$ M

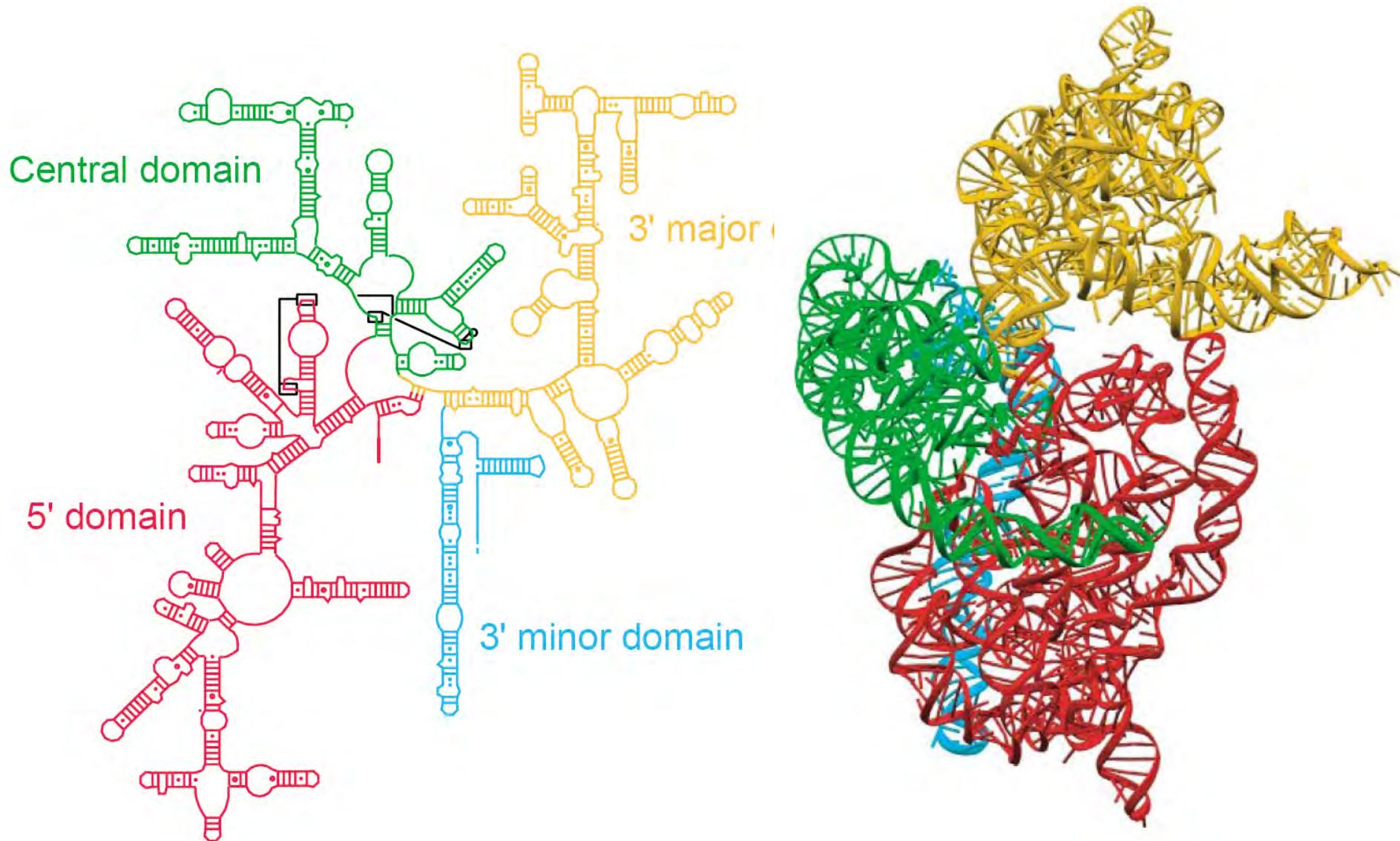
**Figure 13-2a**  
*Molecular Cell Biology, Sixth Edition*  
© 2008 W. H. Freeman and Company





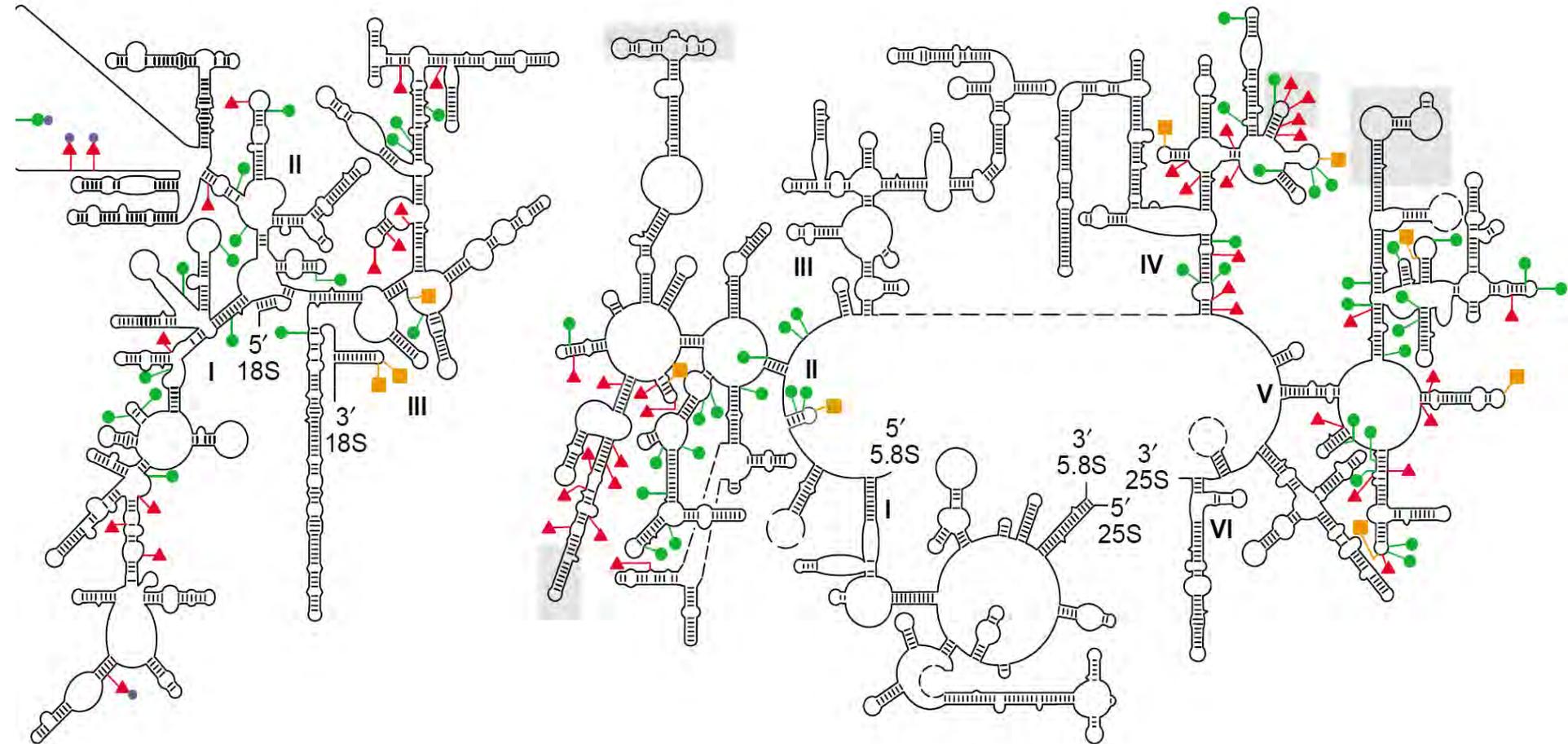
**Figure 4-23**  
*Molecular Cell Biology, Sixth Edition*  
© 2008 W. H. Freeman and Company

# Il cuore a RNA dei ribosomi



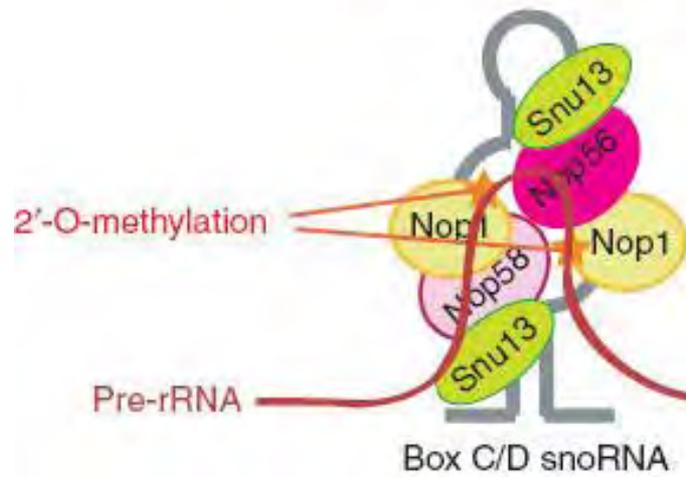
**Modelli strutturali dell'RNA ribosomiale 16S**

# Centinaia (!) di piccoli RNA nucleolari (snoRNA ) guidano modificazioni chimiche sito-specifiche degli RNA dei ribosomi

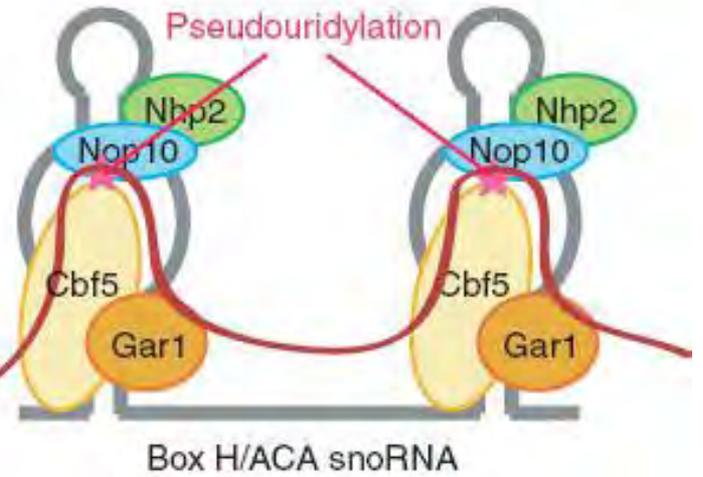


Mappa delle modificazioni chimiche sito-specifiche degli RNA ribosomiali del lievito, ognuna mediata da un diverso snoRNA

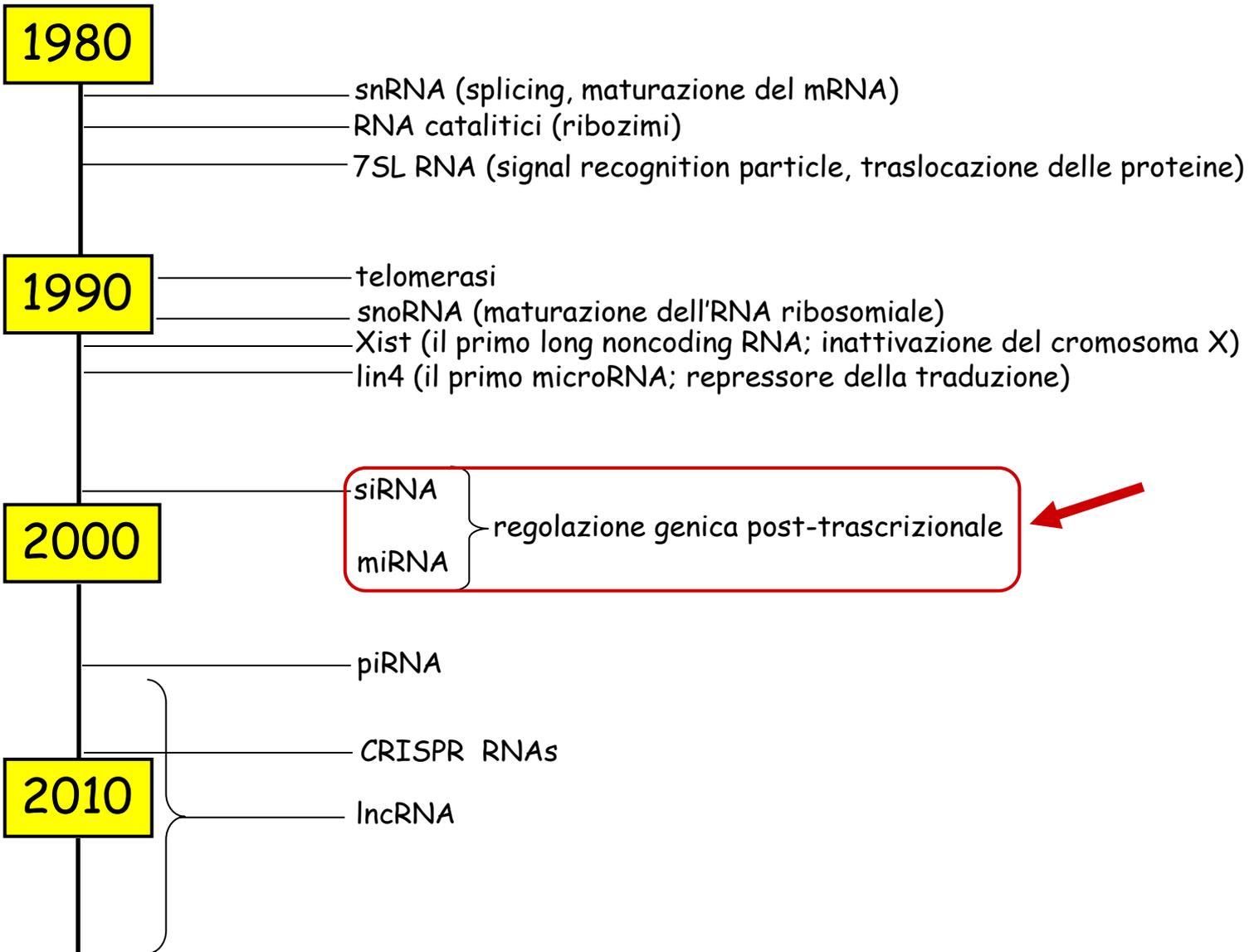
Box C/D snoRNP



Box H/ACA snoRNP



# "The noncoding RNA revolution"



## Altri piccoli RNA guida: siRNA, miRNA, piRNA...

...possono guidare complessi multiproteici su RNA bersaglio nel citoplasma, con conseguente

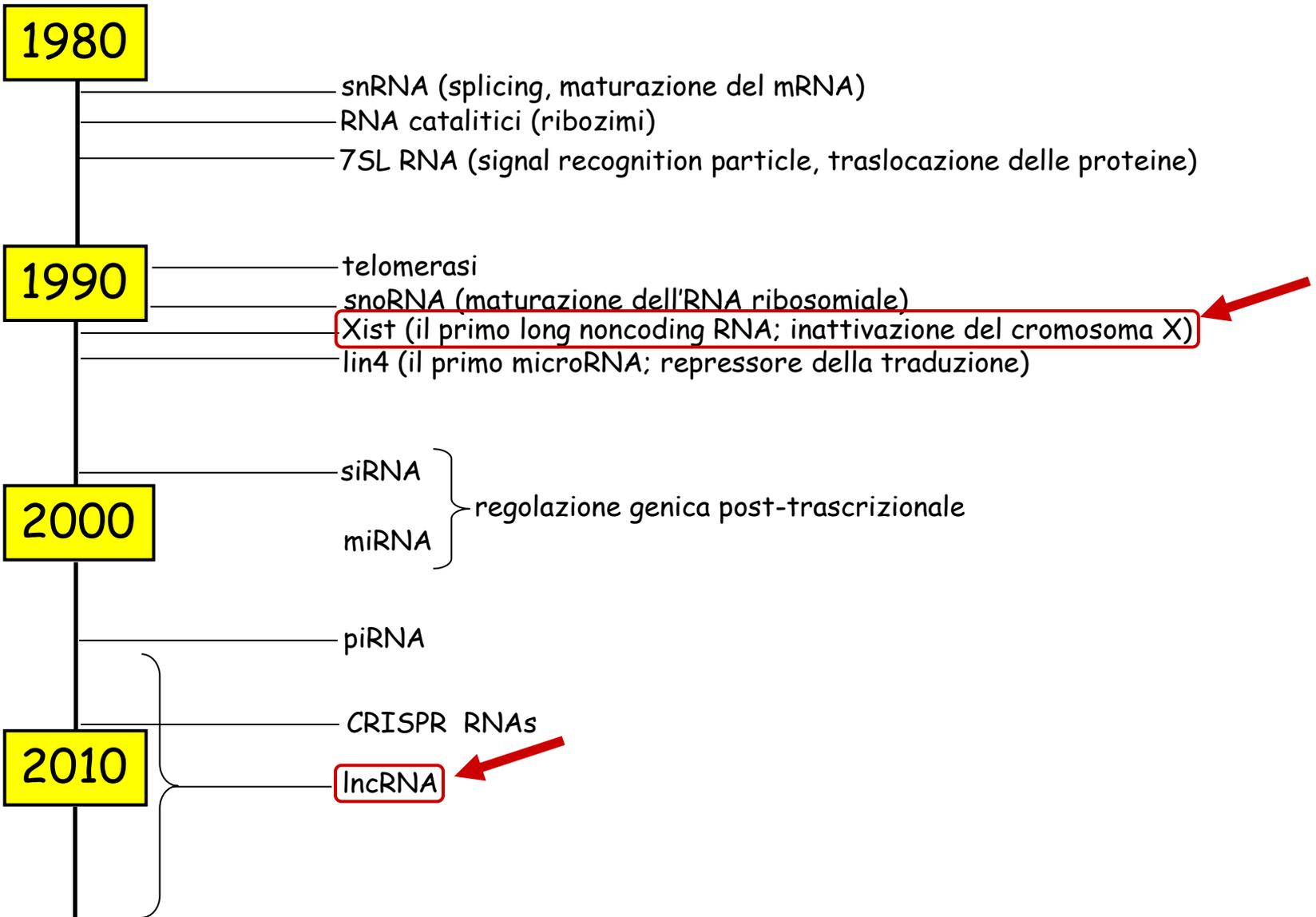
inibizione della traduzione o degradazione dell'RNA bersaglio



Ci sono circa 1000 diversi miRNA nelle cellule umane;  
ognuno può controllare decine/centinaia di mRNA;  
ogni mRNA può essere controllato da decine di miRNA diversi

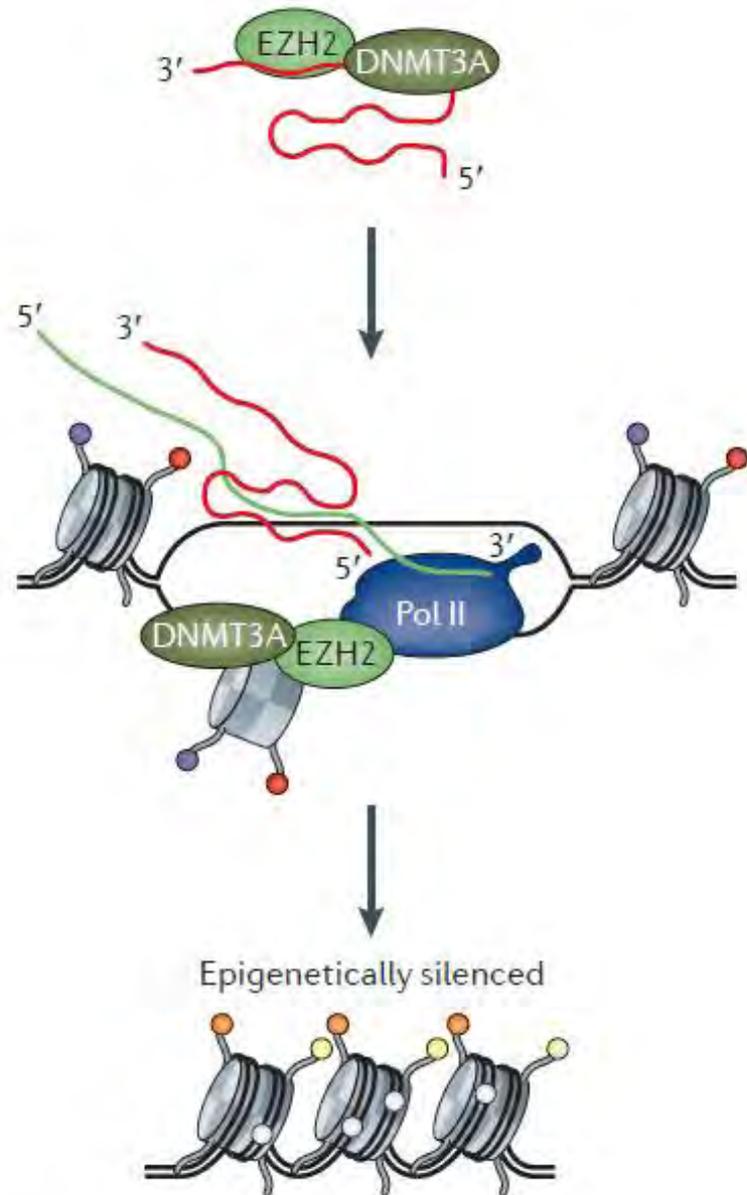


# "The noncoding RNA revolution"



...anche i *long noncoding RNAs (lncRNAs)* possono guidare la generazione di strutture cromatiniche repressive

Ne esistono probabilmente varie migliaia



**Xist**, il primo *lncRNA* identificato (~17.000 b) riveste uno dei due cromosomi X nelle femmine di mammifero, portando alla sua inattivazione

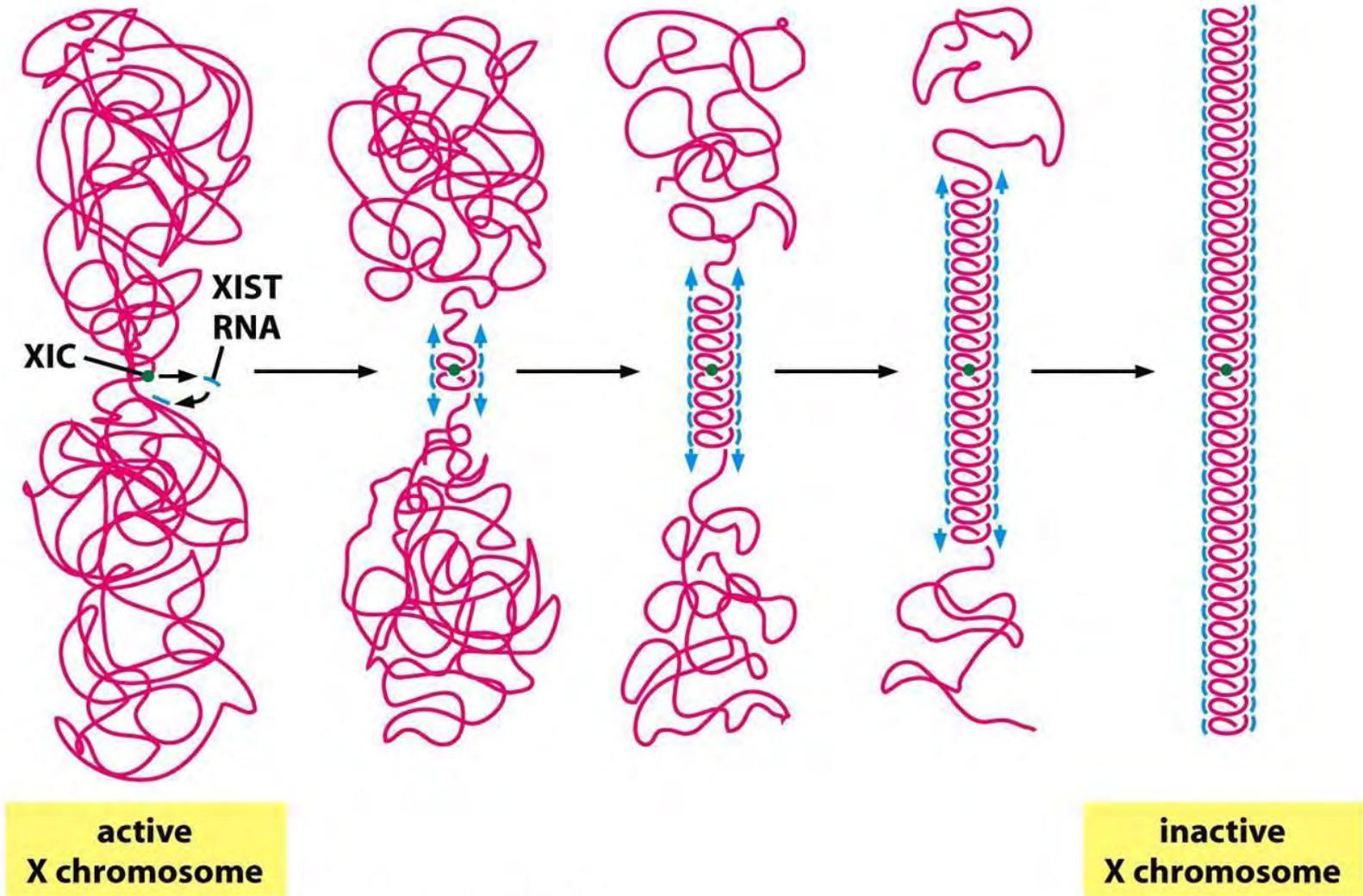
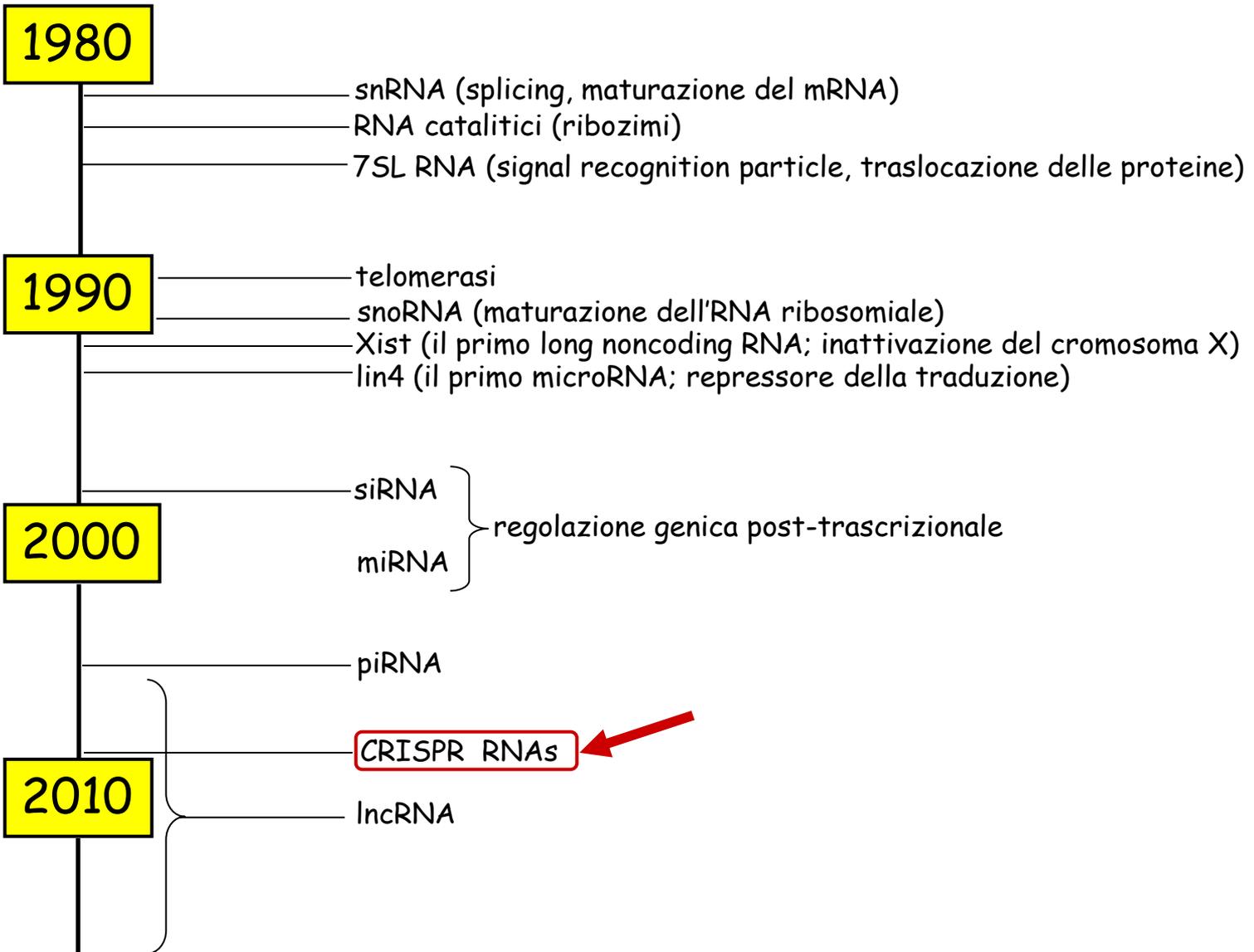


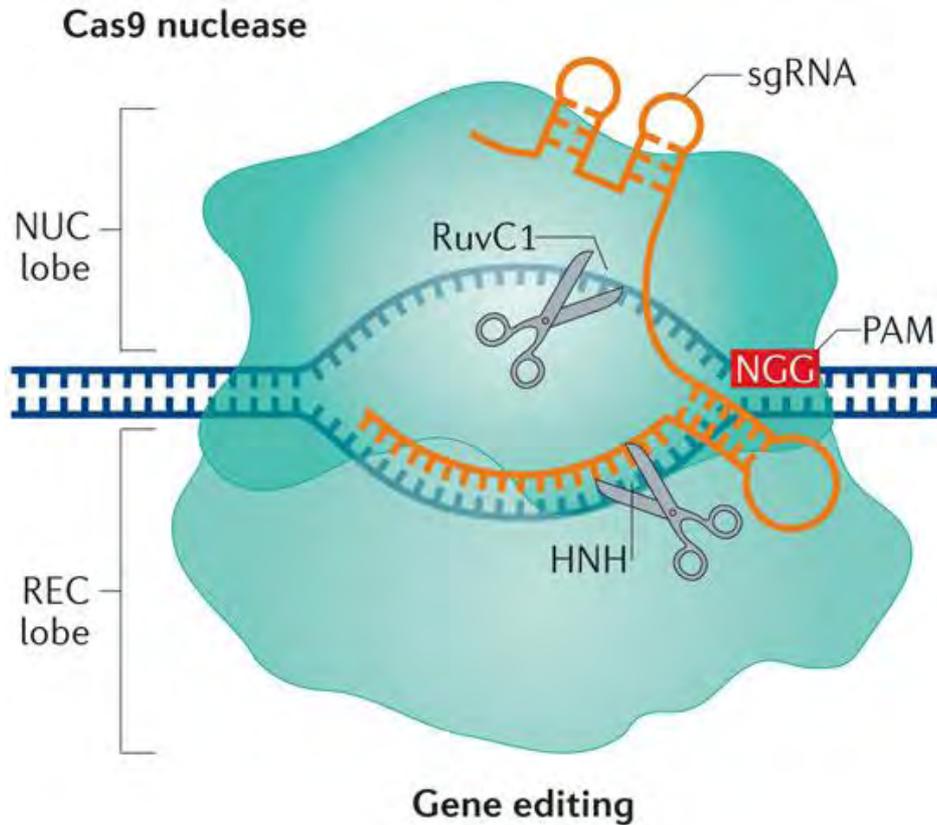
Figure 7-90 Molecular Biology of the Cell 5/e (© Garland Science 2008)

# "The noncoding RNA revolution"

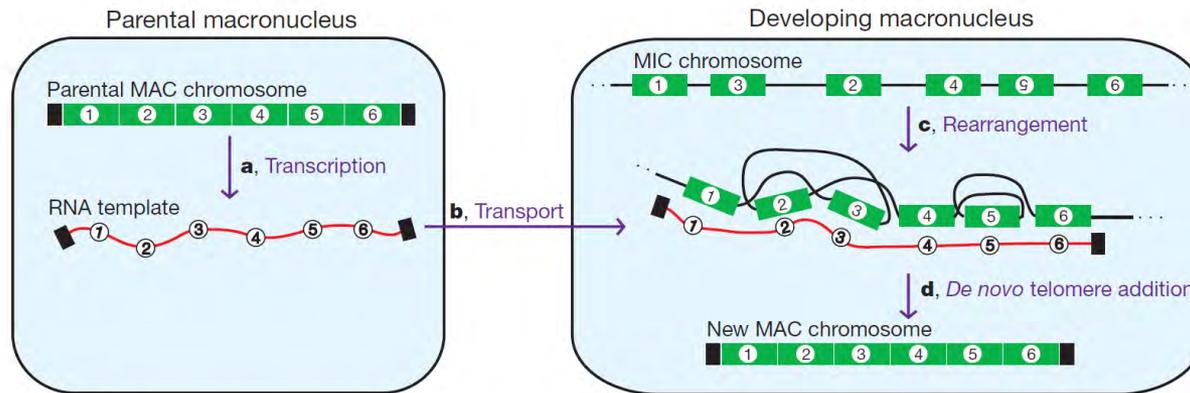
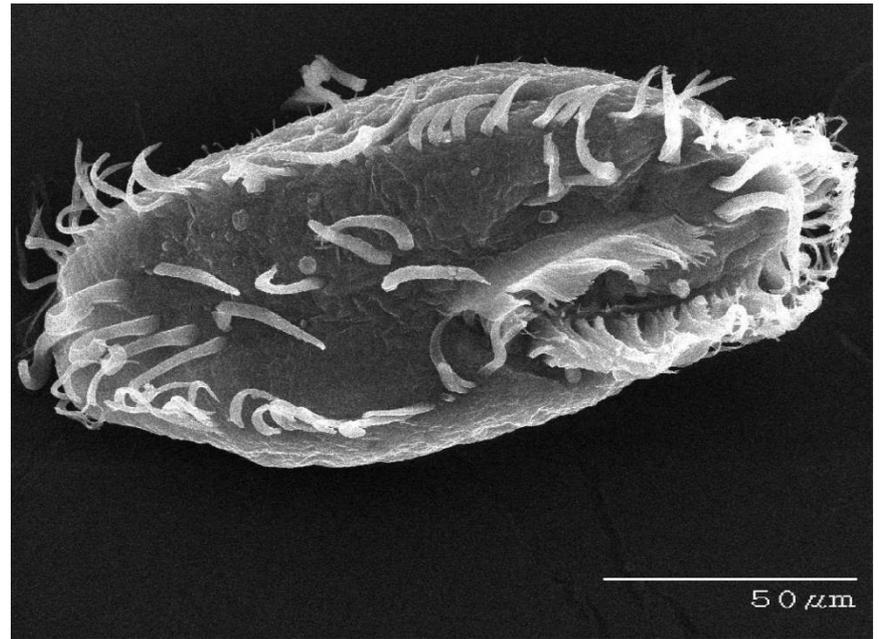


# RNA che guidano la modificazione del genoma...

...la nucleasi batterica Cas9 può essere guidata con precisione da piccoli RNA a sequenze bersaglio nel DNA genomico, che essa taglia



# RNA che guidano il riarrangiamento estensivo di un genoma...



**Figure 5 | Model for RNA guiding of genome rearrangements during macronuclear development in *Oxytricha*.** **a**, Bidirectional RNA transcription of all DNA nanochromosomes (including injected DNA) in the old, maternal macronucleus (MAC) before its degradation. **b**, Transport of these RNA transcripts to the newly developing macronucleus, where they may act as scaffolds to guide rearrangements (deletion, permutation and inversion) of corresponding micronuclear (MIC) DNA sequences (**c**). This

step would be notable and unprecedented, but perhaps possible if there were either local or extensive strand-separation of both the RNA template and the developing DNA (see ref. 20). In this illustration, segments 2 and 3 are switched and segment 5 is inverted (number upside down). **d**, *De novo* telomere addition (black rectangles) and amplification completes formation of new macronuclear nanochromosomes.

siRNA  
miRNA  
lncRNA



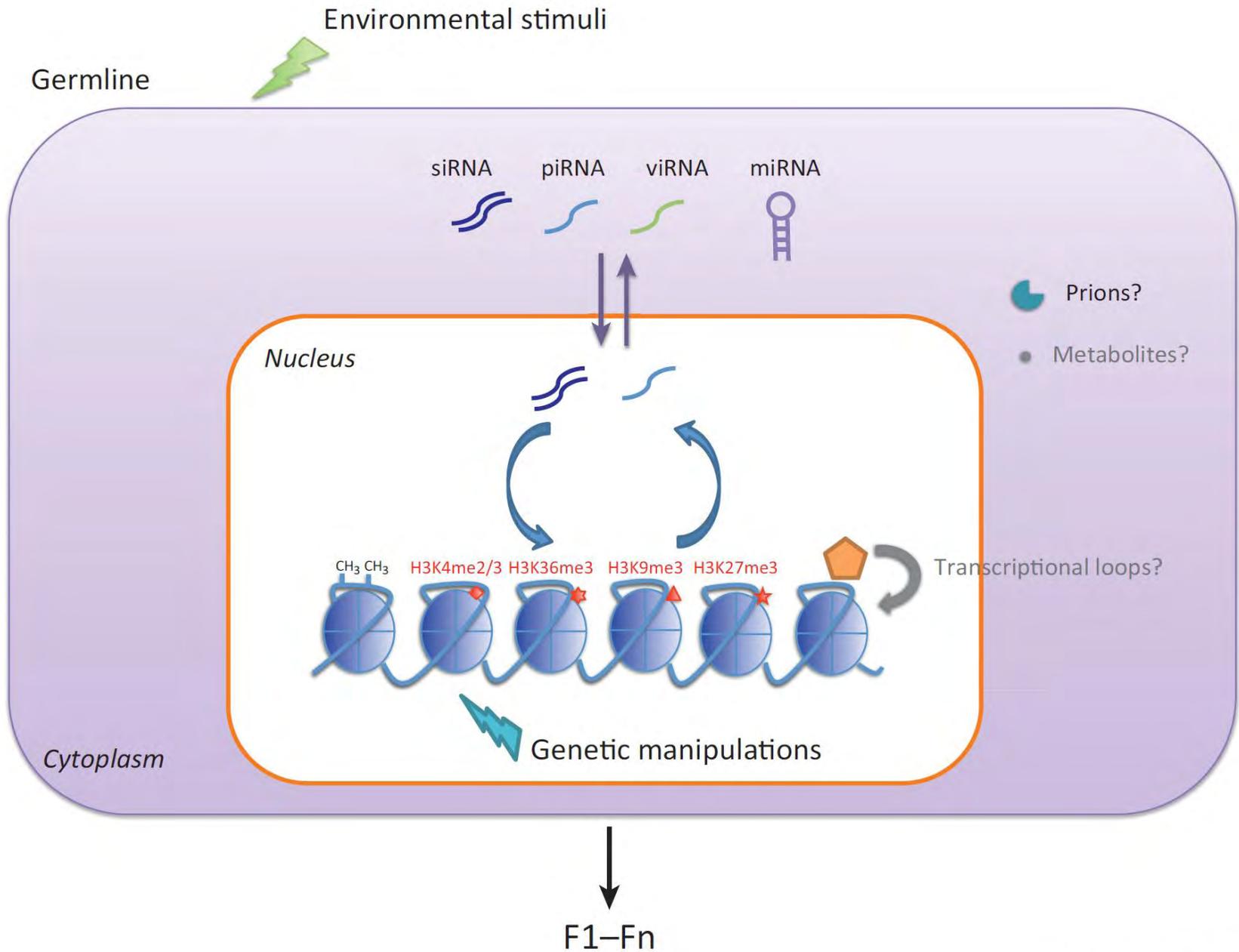
silenziamento genico programmato

CRISPR RNAs

- modificazione mirata del genoma
- spegnimento/accensione mirata della trascrizione genica

# Eredità epigenetica transgenerazionale...





# Comunicazione intercellulare mediata da microvescicole

