Nucleotide excision repair, repairs chemically modified bases that distort DNA shape such as adducts. NER proteins slide along the DNA looking for bulges and other distortion in the DNA. NER is important in removing thymine dimers, a common type of DNA adduct caused by UV light.

NER defects can lead to Xeroderma Pigmentosum. Dimers interfere with DNA replication and transcription. 30 proteins execute NER and defect were identified in individuals with XP. Individuals with XP have high susceptibility for melanoma and squamous cell carcinoma. Mutations in XP-A to XP-G cause NER defects.

Exploiting tumour defects can be a big step in curing cancer;

- Synthetic lethality arises when a combination of deficiencies in the expression of two or more genes leads to cell death,whereas deficiency in only one of these genes does not.
- BRCA is a tumour suppressor, it helps repair DNA double strand breaks and in doing so protects against breast cancer.
- Many women with breast cancer have loss of BRCA gene function
- Breast cancers with BRCA deficiency depend on PAPR activation to correct SSB and hence become sensitive to PARP inhibition.

Normally breast cells have intact BRCA and PARP inhibition will not be toxic. This is because DSB generated by PARP inhibition will be repaired by intact BRCA function. Because breast cells have BRCA deficiency, blocking PARP activity will cause DSB accumulation due to the lack of BRCA.

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RNA Polymerase II and Initiation

There are 4 main processes that regulate protein concentration,these are the rates of;

- Transcription (73%)
- mRNA translation (8%)
- Protein Degradation (8%)
- mRNA degradation (11%)

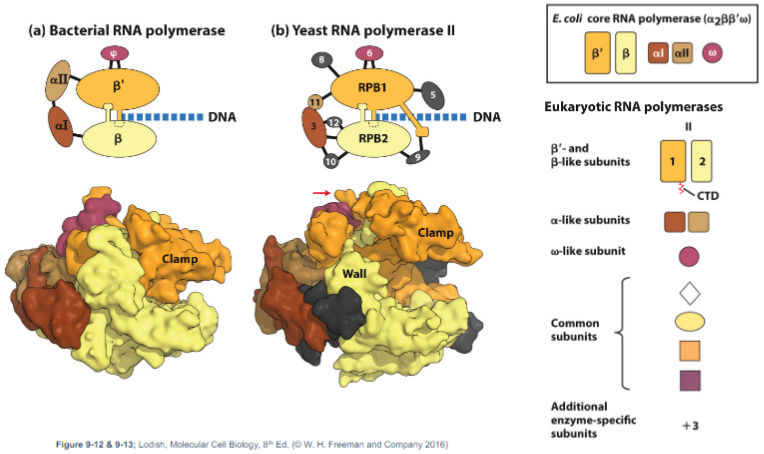

Figure 9-12 & 9-13; Lodish, Molecular Cell Biology, 8th Ed. (© W. H. Freeman and Company 2016)

RNA polymerase II transcribes RNA that encode for proteins.

RNA polymerase II is a large protein composed of many different subunits. Eukaryotic RNA polymerase II has a carboxy-terminal domain located on the largest subunit (RPB1) and is composed of 7 amino acids which are repeated 26x in yeast and 52x in vertebrates. The carboxy-terminal domain is important and it acts as a phosphorylation site which is vital for the regulation of the enzyme.

3. Stimulation of elongation through the recruitment of P-TEFB

Eukaryotes and Translation;

CAP binding complex is comprised of different proteins . The first key protein is eIF4E, the cap binding protein. It binds to EIF4G which is the scaffolding subunit that brings the complex together by binding to the cap binding protein, eIF4A and PAPG.

Rate limiting steps are the key targets for regulation and deregulation.

Transcription Initiation in Eukaryotes Requires Many Proteins;

In contrast to bacteria, which contain a single type of RNA polymerase, eukaryotic nuclei have three: RNA polymerase 1, 2, and 3. The three polymerases are structurally similar to one another and share some common subunits, but they transcribe different categories of genes;

Type of Polymerase	**Genes Transcribed**
RNA polymerase I	5.8S, 18S AND 28S rRNA genes
RNA polymerase II	All protein-coding genes, plus snoRNA genes, miRNA genes, siRNA genes, ncRNA genes and most sRNA genes.
RNA polymerase III	tRNA genes, 5S rRNA genes, some snRNA genes and genes for other small RNAs

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Eukaryotic RNA polymerase II has many structural similarities to bacterial RNA polymerase. But there are several important differences in the way in which the bacterial and eukaryotic enzymes function, two of which concern us immediately;

1. While bacterial RNA polymerase requires only a single transcription-initiation factor to begin transcription, eukaryotic RNA polymerases require many such factors, collectively called the general transcription factors
2. Eukaryotic transcription initiation must take place on DNA that is packaged into nucleosomes and higher-order forms of chromatin structure, features that are absent from bacterial chromosomes.

RNA Polymerase II Requires a Set of General Transcription Factors;

The general transcription factors help to position eukaryotic RNA polymerase correctly at the promoter, aid in pulling apart the two strands of DNA to allow transcription to begin, and release RNA polymerase from the promoter to start its elongation mode. The proteins are general because they are needed at nearly all promoters used by RNA polymerase II. They consist of a set of interacting proteins denoted as TFFIA, TFIIB, TFIIC, TFIID, and so on. In a broad sense the eukaryotes general transcription factors carry out functions equivalent to