and hematopoiesis, and deletion of Elp3 causes morphological defects in neurons, and results in larval lethality at the pupal stage.[296–298] This may link to yet another twist to the elongator story *via* codon-dependent regulation of translation: lysine codon usage bias, coupled to tRNA modifications, influences translation of Cdr2, a central regulator of mitosis and cytokinesis.[299,300]

18.5.7 Lessons from SAM-Independent FeS Proteins?

SAM-independent FeS clusters were discovered, and recognized as such, long before the radical SAM enzymes. Like radical SAM enzymes, FeS proteins are usually oxygen- and redox-sensitive, and are involved in basic processes in all life on earth.[301–308] The FeS cluster of the regulator of fumarate and nitrate reduction (FNR) illustrates the swift reaction time of FeS proteins. Under anaerobic conditions a [4Fe–4S] cluster enables FNR to dimerize and activate anaerobic genes.[309,310] Oxygen results in oxidation of [4Fe–4S] (to a [2Fe–2S] cluster), which inactivates the dimer and results in a swift, and if necessary temporary, switch to aerobic gene expression.[311] Assembly of FeS proteins requires a scaffold complex,[18–20,307,312–320] and mutations in scaffold genes cause severe, often fatal disease, *e.g.* Friedreich's ataxia.[321,322]

Several DNA base excision repair (BER) enzymes are FeS proteins.[18–20,307,314,315] Interestingly, four FeS DNA helicases are associated with severe human disease and aging: XPD, FancJ, RTEL, and DDX11.[316] XPD (Xeroderma pigmentosum (XP) group D) functions in DNA nucleotide exision repair as well as transcription, and is linked to XP, Cockayne syndrome (CS) and trichothiodystrophy (TTD).[323–325] FancJ interacts with BRCA1 and is associated with breast cancer and genomic instability in Fanconi anemia.[326,327] RTEL/Rtel1 has a role in telomere maintenance.[316] DDX11 (also called ChlRI/Chl1/Ctf1) causes Warsaw Breakage Syndrome (WABS), is embryonically lethal in mice, is required for rRNA transcription dependent on histone epigenetic modifications, is involved in chromosome transmission fidelity and sister-chromatid cohesion, is present at the replication fork as a putative replication licensing factor, and is essential for survival of melanoma cells.[328–334] Disruption of the FeS cluster results in clinically relevant mutations, which were confirmed in yeast.[335] Such FeS-dependent diseases raise the question of whether human radical SAM patients exist with similar serious defects and short life span as a result (see Section 22.7). Will PARP inhibitors perhaps be useful for radical SAM studies?[336]

In recent years XPD was shown to be essential for genome integrity and nuclear division in *e.g.* mouse and Drosophila, but this is not the end of the story.[337–344] Like P53 and some DNA repair enzymes,[345–347] XPD can sense redox changes and oxidative stress in DNA, which may enhance detection of lesions or alterations in base stacking over long distances.[348] In the case of P53, oxidative stress leads to DNA-mediated oxidation and disulfide bond formation in P53, which differentially affects binding of P53 to different promoters.[347,349] In the case of DNA lesions, XPD and/or FeS-containing BER enzymes may act alone or together,[307,314,315] and this DNA-mediated signaling