I. Introduction

Proteins, a fundamental molecule of life, are essential for the cell's survival. Proteins are synthesized in the cell by a process called translation, where a protein is made using an mRNA template that is transcribed from DNA in the nucleus. The 80S ribosomal complexes that are composed of the 60S and 40S ribosomal subunits are important for protein synthesis as they translate the mRNA into an amino acid sequence that eventually undergoes modification to form a functional protein. The process of recruiting ribosomes to the mRNA is mediated by the Eukaryotic translation Initiation Factors (eIFs). eIF6 (Eukaryotic translation Initiation Factor 6) is one such initiation factor that is closely involved in both the synthesis of the 60S ribosomal subunit and in regulating the association of the ribosomal subunits.

II. The Role of eIF6 in Ribosome Assembly

eIF6 is essential for the synthesis of the 60S ribosomal subunit and for mediating interactions between the 60S and 40S ribosomal subunits. eIF6 associates with the 60S both in the nucleus and cytoplasm and its association is important for proper maturation of the 60S and to prevent premature association of the 40S. However, eIF6 has to be released from the mature 60S to allow 40S to bind and form the active 80S complex that carries out protein synthesis. If eIF6 is not released, it will prevent 40S binding, which will inhibit protein synthesis. On the other hand, if eIF6 is released too early or if there is not enough eIF6, 60S prematurely binds to 40S that is not loaded with mRNA and this leads to inactive 80S formation, which also inhibits protein synthesis. Release of eIF6 is therefore a key step in initiating protein synthesis and has to be regulated.

III. eIF6 structure

eIF6 binds to the 60S subunit by interacting with the ribosomal protein L23 (RPL23) near the sarcin-ricin loop of 28S RNA. This interaction prevents the binding of the 40S subunit. Once eIF6 is released from the 60S during ribosomal maturation, then 40S can bind to the 60S subunit. Structurally, eIF6 has a five-fold pseudosymmetry and two large, flat surfaces. The larger of the two flat surfaces contains a scaffold where the active site residues are located. Hydrophobic and hydrophilic residues on the surface of eIF6 are involved in the interaction with RPL23. These specific amino acid residues are individually colored to show their importance in mediating interactions between eIF6 and RPL23 and in preventing subunit association.

IV. Cancer and Protein Synthesis

Cancer cells exhibit higher rates of protein synthesis that is mediated by deregulating eIF6, which results in the deregulation of mRNA translation. Targeting the activity of eIF6, especially eIF6, can dramatically affect tumor growth. eIF6 is over expressed in various cancers. However, we are yet to understand as to how eIF6 is over-expressed in cancer cells and how alteration of its anti-association activity contributes to tumor growth. Understanding how eIF6 and other eIFs are deregulated in cancer will help to develop drugs that specifically target the eIFs, to slow down or stop cancer progression.

V. Connecting to eIF6 to Cancer

An oncogene is a gene that has the potential to cause cancer. When oncogenes are activated it results in uncontrolled growth and proliferation with an inhibition of cell death that causes cancer. An anti-oncogene or tumor suppressor gene, is a gene that helps stop a cell from becoming cancerous. eIF6 behaves like a putative oncogene and exhibits gene amplification in several cancers. Deregulation of eIF6 bypasses the tumor suppression cellular protocols.

The important role of eIF6 in tumorigenesis was identified using mouse studies. Partial loss of eIF6 (heterozygous- eIF6+/-; mice) did not affect normal growth or development in mice. But the cells lacking eIF6 were greatly resistant to tumorigenesis induced by the combination of Ras oncogene activation and p53 tumor suppressor loss (Fig 5a). Similar results were seen when cells were made cancerous by the combined expression of the Ras and Myc oncogenes. While wild type cells were easily made cancerous by the combined expression of the Ras and Myc oncogene, cells lacking eIF6 were quite resistant to tumor formation. These results show that without sufficient eIF6, cells are very resistant to becoming cancerous (Fig 5b).

VI. Conclusions

eIF6 is critical for both 60S ribosome biogenesis and for initiating protein synthesis. Previous experiments show that eIF6 is upregulated in human cancer cells and loss of eIF6 impedes tumorigenesis by inhibiting efficient protein synthesis. It may be possible to inhibit protein synthesis by modifying the timing of eIF6 release or by depleting eIF6, which can in turn disrupt tumor growth as shown by the heterozygous condition in mice. For better understanding the regulation of eIF6, scientists can develop new drug targets that can potentially slow the cancer epidemic by slowing cancer cell growth.

Figure 1: The process of synthesizing a protein from mRNA template.

Figure 2: eIF6 role in ribosome synthesis and subunit association.

Figure 3: a. Image of the 60S ribosomal subunit showing specific interactions between RPL23 and eIF6. b. Enlarged image of eIF6 bound to RPL23 showing the specific sites of interaction.

Figure 4: Deregulation of eIF6 leads to high rates of protein synthesis that in turn cause uncontrolled growth and division with accumulation of mutations that leads to cancer.

Figure 5: a. Mouse cells with partial eIF6 loss show lower rates of tumorigenesis with p53-tumor suppressor loss and Ras oncogene activation. b. Mouse cells with partial eIF6 loss were resistant to tumor formation induced by the Ras and Myc oncogenes.

References


The PI and co-authors gratefully acknowledge the support of the University of Missoula, the National Institutes of Health, and the American Cancer Society (Grant 212). This work was supported by the National Institutes of Health (R33CA149866) and the National Cancer Institute (R01CA163556). The authors thank the reviewers for their helpful comments on the manuscript.