Diverse Presentation of Neurotoxicity After CAR-T Therapy in Multiple Myeloma Patients

Michelly Abreu[1], ANP/GNP, Nilesh Kalariya[1], ANP, PhD, Sherry Adkins[1], APRN, Chirag Patel[2], MD, Sudhakar Tummala[2], MD, Hans Lee[1], MD, Muzaffar Qazilbash[3], MD, Mahmoud Gaballa[1], MD, Jessica Chen[1] APRN, Krina Patel[1], MD

[1]Department of Lymphoma/Myeloma, [2]Department of Neuro-Oncology, [3]Department of Stem Cell Transplantation, The University of Texas MD Anderson Cancer Center, Houston, TX

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Introduction

- Chimeric antigen receptor (CAR) T-cell therapy shows remarkable response rates in refractory hematological malignancies[1]
- Cytokine release syndrome (CRS) and neurotoxicity remain major adverse events
- Sporadic cases of unusual neurotoxicity lack understanding of pathogenic mechanism
- This case series discuss three cases with uncommon neurotoxicity presentations after receiving ciltacabtagene autoleucel (cilta-cel, Carvykti), a BCMA specific CAR T-cell therapy for multiple myeloma (MM)

Cases Presentations

Case # 1- Progressive Multifocal Leukoencephalopathy (PML):

- 59-year-old female presented with acute renal failure, hyponatremia, and grade 1 CRS (fever) ON Day +13 s/p cilta-cel
- Brain MRI was concerning for posterior reversible encephalopathy syndrome (PRES) but absence of any neurological abnormalities
- The patient was treated with Tocilizumab and dexamethasone with resolution of symptoms
- The disease response at Day +30 showed complete remission (CR)
- On Day +62, the patient presented with progressive neurologic deterioration - brain MRI showed brain enhancement lesion, electroencephalogram (EEG) was negative, neurofilament light chain (NFL) level progressively increased (see Table 1)
- The patient was treated with dexamethasone, antiviral and antibacterial
- Persistence of difficulty with language and higher visual function was concerning for late onset of neurotoxicity related to cilta-cel
- The treatment changed to high dose dexamethasone, thiamine, levetiracetam, and lacosamide
- Repeat brain MRI revealed extensive brain changes, concerning for progressive progressive multifocal leukoencephalopathy (PML) which was confirmed with positive JC virus in the cerebral spine fluid
- Further treatment with corticosteroids, experimental agent for PML, and intravenous immunoglobulin (IVIG) failed with progressive deterioration in the patient's condition.
- Later the patient had seizure and became stuporous with right gaze preference
- Repeat brain MRI revealed further progressive disease (Figure 1)
- Patient transition to hospice and deceased two weeks later

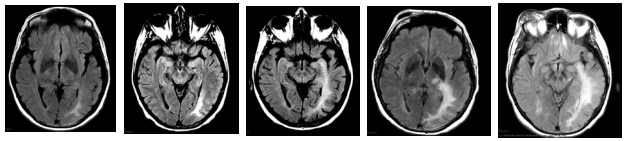
Case # 2- Polyneuropathy:

- 33-year-old male had grade 1 CRS on Day +8 s/p cilta-cel infusion followed by resolution of CRS with Tocilizumab, no neurotoxicity noted
- After 7 months s/p cilta-cel, the patient developed numbness to face, hands, and feet
- Electromyography (EMG) and nerve conduction study showed electrophysiologic evidence for severe, chronic, median neuropathy at the right and left wrists
- In lieu of unremarkable extensive work-up, diagnosis of polyneuropathy as a late side-effect of CAR T-cell therapy was established
- Supportive care treatment provided
- Two months later tingling in feet resolved but minimal residual tingling in the hands and face persisted
- The patient had mild residual polyneuropathy on most recent visit and remains in CR

Case # 3- Bell's Palsy:

- 74-year-old male had grade 1 CRS and grade 1 ICANS on Day +7 s/p cilta-cel infusion followed by resolution of CRS and ICANS on Day +8 with Tocilizumab, Dexamethasone, levetiracetam
- On Day +21 s/p cilta-cel, the patient presented with right lip drooping and difficulty chewing
- The patient was negative for unilateral weakness to any other body sites, slurred speech, visual disturbances, fever, or altered mental status
- Brain MRI was unremarkable for enhancing brain lesions or leptomeningeal disease
- Infectious disease work-up was negative for other etiology
- Working diagnosis of Bell's palsy was established
- Treated empirically with glucocorticoid for 10 days including dose tapering
- Later due to persistence Bell's palsy, two doses of intravenous immunoglobulin (IVIG) were given although Immunoglobulin G level was normal at 1548 mg/dL.
- Complete resolution of Bell's palsy after completion of glucocorticoid and IVIG treatment.

Figure 1. *Progressive changes in brain images*



Day 13 Day 19 Day 63 Day 74 Day 82

Table 1. *Blood test results on days* ***0****, 30, 60, and 90*

Blood Test (reference range)	D0	D30	D60	D90
NFL (<=20.8 pg/mL)	No result	188	437	952
CD3+CD4+ Absolute Quantitative (263-1426 cells/mcL)	120	73	85	49
Immunoglobulin G level	462	510	706	No result
Platelet (140-440K/uL)	92	21	26	20
Hemoglobin (12.0-16.0 gm/dL)	8.1	11.9	8	9.8
WBC (4.0-11.0 K/uL)	0.9	2.2	2.3	2.4
ANC (1.00-4.80 K/uL)	0.79	1.58	1.01	1.32
CMV PCR (<=0.0 IU/mL)	111.0	62.6	462	<34.5

Discussion

- Uncommon presentations of neurotoxicity post CAR T-cell therapy have been described[2]
- Physiopathology remains unclear and most cases are without abnormality in brain imaging[3]
- Increased blood-brain barrier permeability and loss of integrity are proposed as possible pathologic mechanisms
- First-line treatment is dexamethasone, but other steroids can be considered
- Antiseizure prophylaxis is also recommended
- In BCMA-directed therapies, neurotoxicity develops due to on-target, off-tumor effect on B-cells and presence of BCMA in neural tissue
- PML could be caused by reactivation of JC virus in immunocompromised individuals
- NFL levels could help in monitoring and predict rate of loss of neurons in the CNS[4] and development of ICANS[5]
- Other therapeutic approaches include mirtazapine[6], pembrolizumab[7], JCV-specific T cells[8], thiamine[9], and adoptive transfer of T-cells
- Polyneuropathy could be caused by several possible etiologies
- Treatment is multimodal with focus on associated symptoms
- Bell's palsy's etiology remains unclear but thought to be triggered by inflammation of the facial nerve, leading to its compression, ischemia and demyelination[10]
- Diagnosis usually established through an exclusion
- Corticosteroids are the first choice, supported by evidence of meta-analysis studies[11]
- Prognosis is favorable, symptoms frequently resolve within weeks or months with treatment
- Patients without treatment may have residual symptoms including permanent eye injury

Conclusion

- BCMA-directed CAR T-cell therapy is a breakthrough treatment of MM and continues to advance
- Neurotoxicity with usual and unusual symptoms post therapy bears clinical and scientific relevance
- Early recognition is key to prevent development of severe neurotoxicity
- Further research is warranted to investigate causes, risk stratification, and treatment of neurotoxicity caused by CAR T-cell therapies and ensure better clinical outcomes

References

1. Zhang X, et al., CAR-T Cell Therapy in Hematological Malignancies : Current Opportunities and Challenges. Frontiers in Immunology. 2022 Jun 10;13.
2. Krishnamoorthy S, et al., CAR-T therapy in solid organ transplant recipients with treatment refractory posttransplant lymphoproliferative disorder. Am J Transplant. 2021 Feb;21(2):809-814. doi: 10.1111/ajt.16367.
3. Belin C, et al., Description of neurotoxicity in a series of patients treated with CAR T-cell therapy. Sci Rep. 2020 Nov 4;10(1):18997. doi: 10.1038/s41598-020-76055-9.
4. Barro C, et al., Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. Brain. 2018 May 30;141(8):2382–91.
5. Butt OH, et al., Pre-Infusion Neurofilament Light Chain (NfL) Levels Predict the Development of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) - a Multicenter Retrospective Study. Blood. 2021;138(Supplement 1):2841–2841. doi: 10.1182/blood-2021-149674.
6. Jamilloux Y, et al., Treatment of Progressive Multifocal Leukoencephalopathy with Mirtazapine. Clinical Drug Investigation. 2016 Jul 11;36(10):783–9.
7. Bernard-Valnet R, et al., Advances in Treatment of Progressive Multifocal Leukoencephalopathy. Annals of Neurology. 2021 Sep 7;90(6):865–73.
9. Koutsavlis I. Progressive multifocal leukoencephalopathy in multiple myeloma. A literature review and lessons to learn. Annals of Hematology. 2020 Oct 3;100(1):1–10.
10. Tiemstra JD, and Khatkhate N. Bell's palsy: diagnosis and management. Am Fam Physician. 2007 Oct 1;76(7):997-1002.
11. Heckmann JG, et al., Therapie der idiopathischen Fazialisparese (Bell's palsy) Akt Neurol. 2017;44:712–727

Translation Initiation in Cancer: A Novel Target for Therapy[1]

Funda Meric[2] and Kelly K. Hunt
Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Abstract

Translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled with cell cycle progression and cell growth. Several alterations in translational control occur in cancer. Variant mRNA sequences can alter the translational efficiency of individual mRNA molecules, which in turn play a role in cancer biology. Changes in the expression or availability of components of the translational machinery and in the activation of translation through signal transduction pathways can lead to more global changes, such as an increase in the overall rate of protein synthesis and translational activation of the mRNA molecules involved in cell growth and proliferation. We review the basic principles of translational control, the alterations encountered in cancer, and selected therapies targeting translation initiation to help elucida

Introduction

The fundamental principle of molecular therapeutics in can- cer is to exploit the differences in gene expression between cancer cells and normal cells. With the advent of cDNA array technology, most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable either to DNA amplification or to differences in transcription. Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability.

The power of translational regulation has been best recognized among developmental biologists, because transcription does not occur in early embryogenesis in eukaryotes. For ex- ample, in Xenopus, the period of transcriptional quiescence continues until the embryo reaches midblastula transition, the 4000-cell stage. Therefore, all necessary mRNA molecules are transcribed during oogenesis and stockpiled in a translationally inactive, masked form. The mRNA are translationally activated at appropriate times during oocyte maturation, fertilization, and early embryogenesis and thus, are under strict translational control.

Translation has an established role in cell growth. Basi- cally, an increase in protein synthesis occurs as a conse- quence of mitogenesis. Until recently, however, little was known about the alterations in mRNA translation in cancer, and much is yet to be discovered about their role in the development and progression of cancer. Here we review the basic principles of translational control, the alterations en- countered in cancer, and selected therapies targeting translation initiation to elucidate potential new therapeutic avenues.

Basic Principles of Translational Control

Mechanism of Translation Initiation
Translation initiation is the main step in translational regulation. Translation initiation is a complex process in which the initiator tRNA and the 40S and 60S ribosomal subunits are recruited to the 5′ end of a mRNA molecule and assembled by eukaryotic translation initiation factors into an 80S ribosome at the start codon of the mRNA (Fig. 1). The 5′ end of eukaryotic mRNA is capped, i.e., contains the cap structure m7GpppN (7-methylguanosine-triphospho-5′-ribonucleoside). Most translation in eukaryotes occurs in a cap-dependent fashion, i.e., the cap is specifically recognized by the eIF4E,3 which binds the 5′ cap. The eIF4F translation initiation complex is then formed by the assembly of eIF4E, the RNA helicase eIF4A, and eIF4G, a scaffolding protein that mediates the binding of the 40S ribosomal subunit to the mRNA molecule through interaction with the eIF3 protein present on the 40S ribosome. eIF4A and eIF4B participate in melting the secondary structure of the 5′ UTR of the mRNA. The 43S initiation complex (40S/eIF2/Met-tRNA/GTP complex) scans the mRNA in a 5′→3′ direction until it encounters an AUG start codon. This start codon is then base-paired to the anticodon of initiator tRNA, forming the 48S initiation complex. The initiation factors are then displaced from the 48S complex, and the 60S ribosome joins to form the 80S ribosome.

Unlike most eukaryotic translation, translation initiation of certain mRNAs, such as the picornavirus RNA, is cap independent and occurs by internal ribosome entry. This mechanism does not require eIF4E. Either the 43S complex can bind the initiation codon directly through interaction with the IRES in the 5′ UTR such as in the encephalomyocarditis virus, or it can initially attach to the IRES and then reach the initiation codon by scanning or transfer, as is the case with the poliovirus (1).

Regulation of Translation Initiation

Translation initiation can be regulated by alterations in the expression or phosphorylation status of the various factors involved. Key components in translational regulation that may provide potential therapeutic targets follow.

eIF4E
eIF4E plays a central role in translation regulation. It is the least abundant of the initiation factors and is considered the rate-limiting component for initiation of cap-dependent translation. eIF4E may also be involved in mRNA splicing, mRNA 3′ processing, and mRNA nucleocytoplasmic transport (2). eIF4E expression can be increased at the transcriptional level in response to serum or growth factors (3). eIF4E overexpression may cause preferential translation of mRNAs containing excessive secondary structure in their 5′ UTR that are normally discriminated against by the translational machinery and thus are inefficiently translated (4–7). As examples of this, overexpression of eIF4E promotes increased translation of vascular endothelial growth factor, fibroblast growth factor-2, and cyclin D1 (2, 8, 9).

Another mechanism of control is the regulation of eIF4E phosphorylation. eIF4E phosphorylation is mediated by the mitogen-activated protein kinase-interacting kinase 1, which is activated by the mitogen-activated pathway activating extracellular signal-related kinases and the stress-activated pathway acting through p38 mitogen-activated protein kinase (10–13). Several mitogens, such as serum, platelet-derived growth factor, epidermal growth factor, insulin, angiotensin II, src kinase overexpression, and ras overexpression, lead to eIF4E phosphorylation (14). The phosphorylation status of eIF4E is usually correlated with the translational rate and growth status of the cell; however; eIF4E phosphorylation has also been observed in response to some cellular stresses when translational rates actually decrease (15). Thus, further study is needed to understand the effects of eIF4E phosphorylation on eIF4E activity.

Another mechanism of regulation is the alteration of eIF4E availability by the binding of eIF4E to the eIF4E-binding proteins (4E-BP, also known as PHAS-I). 4E-BPs compete with eIF4G for a binding site in eIF4E. The binding of eIF4E to the best characterized eIF4E-binding protein, 4E-BP1, is regulated by 4E-BP1 phosphorylation. Hypophosphorylated 4E-BP1 binds to eIF4E, whereas 4E-BP1 hyperphosphorylation decreases this binding. Insulin, angiotensin, epidermal growth factor, platelet-derived growth factor, hepatocyte growth factor, nerve growth factor, insulin-like growth factors I and II, interleukin 3, granulocyte-macrophage colony-stimulating factor + steel factor, gastrin, and the adenovirus have all been reported to induce phosphorylation of 4E-BP1 and to decrease the ability of 4E-BP1 to bind eIF4E (15, 16). Conversely, deprivation of nutrients or growth factors results in 4E-BP1 dephosphorylation, an increase in eIF4E binding, and a decrease in cap-dependent translation.

The mTOR Signaling Pathway.

The macrolide antibiotic rapamycin (Siralimus; Wyeth-Ayerst Research, Collegeville, PA) has been the subject of intensive study because it inhibits signal transduction pathways involved in T-cell activation. The rapamycin-sensitive component of these pathways is mTOR (also called FRAP or RAFT1). mTOR is the mammalian homologue of the yeast TOR proteins that regulate G1 progression and translation in response to nutrient availability (24). mTOR is a serine-threonine kinase that modulates translation initiation by altering the phosphorylation status of 4E-BP1 and S6K (Fig. 2; Ref. 25).

4E-BP1 is phosphorylated on multiple residues. mTOR phosphorylates the Thr-37 and Thr-46 residues of 4E-BP1 in vitro (26); however, phosphorylation at these sites is not associated with a loss of eIF4E binding. Phosphorylation of Thr-37 and Thr-46 is required for subsequent phosphorylation at several COOH-terminal, serum-sensitive sites; a combination of these phosphorylation events appears to be needed to inhibit the binding of 4E-BP1 to eIF4E (25). The product of the ATM gene, p38/MSK1 pathway, and protein kinase Cσ also play a role in 4E-BP1 phosphorylation (27–29).

S6K and 4E-BP1 are also regulated, in part, by PI3K and its downstream protein kinase Akt. PTEN is a phosphatase that negatively regulates PI3K signaling. PTEN null cells have constitutively active of Akt, with increased S6K activity and S6 phosphorylation (30). S6K activity is inhibited both by PI3K inhibitors wortmannin and LY294002 and by mTOR inhibitor rapamycin (24). Akt phosphorylates Ser-2448 in mTOR in vitro, and this site is phosphorylated upon Akt activation in vivo (31–33). Thus, mTOR is regulated by the PI3K/Akt pathway; however, this does not appear to be the only mode of regulation of mTOR activity. Whether the PI3K pathway also regulates S6K and 4E-BP1 phosphorylation independent of mTOR is controversial.

Interestingly, mTOR autophosphorylation is blocked by wortmannin but not by rapamycin (34). This seeming inconsistency suggests that mTOR-responsive regulation of 4E-BP1 and S6K activity occurs through a mechanism other than intrinsic mTOR kinase activity. An alternate pathway for 4E-BP1 and S6K phosphorylation by mTOR activity is by the inhibition of a phosphatase. Treatment with calyculin A, an inhibitor of phosphatases 1 and 2A, reduces rapamycin-induced dephosphorylation of 4E-BP1 and S6K by rapamycin (35). PP2A interacts with full-length S6K but not with a S6K mutant that is resistant to dephosphorylation resulting from rapamycin. mTOR phosphorylates PP2A in vitro; however, how this process alters PP2A activity is not known. These results are consistent with the model that phosphorylation of a phosphatase by mTOR prevents dephosphorylation of 4E-BP1 and S6K, and conversely, that nutrient deprivation and rapamycin block inhibition of the phosphatase by mTOR.

Polyadenylation

The poly(A) tail in eukaryotic mRNA is important in enhancing translation initiation and mRNA stability. Polyadenylation plays a key role in regulating gene expression during oogenesis and early embryogenesis. Some mRNA that are translationally inactive in the oocyte are polyadenylated concomitantly with translational activation in oocyte maturation, whereas other mRNAs that are translationally active during oogenesis are deadenylated and translationally silenced (36–38). Thus, control of poly(A) tail synthesis is an important regulatory step in gene expression. The 5′ cap and poly(A) tail are thought to function synergistically to regulate mRNA translational efficiency (39, 40).

RNA Packaging

Most RNA-binding proteins are assembled on a transcript at the time of transcription, thus determining the translational fate of the transcript (41). A highly conserved family of Y-box proteins is found in cytoplasmic messenger ribonucleoprotein particles, where the proteins are thought to play a role in restricting the recruitment of mRNA to the translational machinery (41–43). The major mRNA-associated protein, YB-1, destabilizes the interaction of eIF4E and the 5′ mRNA cap in vitro, and overexpression of YB-1 results in translational repression in vivo (44). Thus, alterations in RNA packaging can also play an important role in translational regulation.

Translation Alterations Encountered in Cancer

Three main alterations at the translational level occur in cancer: variations in mRNA sequences that increase or decrease translational efficiency, changes in the expression or availability of components of the translational machinery, and activation of translation through aberrantly activated signal transduction pathways. The first alteration affects the translation of an individual mRNA that may play a role in carcinogenesis. The second and third alterations can lead to more global changes, such as an increase in the overall rate of protein synthesis, and the translational activation of several mRNA species.

Variations in mRNA Sequence

Variations in mRNA sequence affect the translational efficiency of the transcript. A brief description of these variations and examples of each mechanism follow.

Mutations

Mutations in the mRNA sequence, especially in the 5′ UTR, can alter its translational efficiency, as seen in the following examples.

C-MYC
Saito et al. proposed that translation of full-length c-myc is repressed, whereas in several Burkitt lymphomas that have deletions of the mRNA 5′ UTR, translation of c-myc is more efficient (45). More recently, it was reported that the 5′ UTR of c-myc contains an IRES, and thus c-myc translation can be initiated by a cap-independent as well as a cap-dependent mechanism (46, 47). In patients with multiple myeloma, a C→T mutation in the c-myc IRES was identified (48) and found to cause an enhanced initiation of translation via internal ribosomal entry (49).

BRCA1
A somatic point mutation (117 G→C) in position −3 with respect to the start codon of the BRCA1 gene was identified in a highly aggressive sporadic breast cancer (50). Chimeric constructs consisting of the wild-type or mutated BRCA1 5′ UTR and a downstream luciferase reporter demonstrated a decrease in the translational efficiency with the 5′ UTR mutation.

CYCLIN-DEPENDENT KINASE INHIBITOR 2A
Some inherited melanoma kindreds have a G→T transversion at base −34 of cyclin-dependent kinase inhibitor-2A, which encodes a cyclin-dependent kinase 4/cyclin-dependent kinase 6 kinase inhibitor important in G1 checkpoint regulation (51). This mutation gives rise to a novel AUG translation initiation codon, creating an upstream open reading frame that competes for scanning ribosomes and decreases translation from the wild-type AUG.

Alternate Splicing and Alternate Transcription Start Sites
Alterations in splicing and alternate transcription sites can lead to variations in 5′ UTR sequence, length, and secondary structure, ultimately impacting translational efficiency.

Toward the Future

Translation is a crucial process in every cell. However, several alterations in translational control occur in cancer. Cancer cells appear to need an aberrantly activated translational state for survival, thus allowing the targeting of translation initiation with surprisingly low toxicity. Components of the translational machinery, such as eIF4E, and signal transduction pathways involved in translation initiation, such mTOR, represent promising targets for cancer therapy. Inhibitors of the mTOR have already shown some preliminary activity in clinical trials. It is possible that with the development of better predictive markers and better patient selection, response rates to single-agent therapy can be improved. Similar to other cytostatic agents, however, mTOR inhibitors are most likely to achieve clinical utility in combination therapy. In the interim, our increasing understanding of translation initiation and signal transduction pathways promise to lead to the identification of new therapeutic targets in the near future.

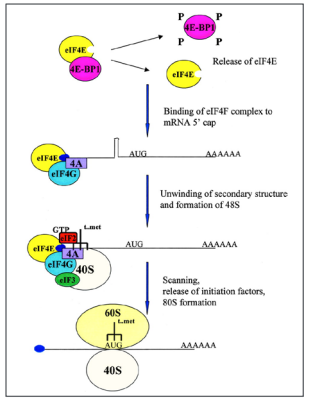


Fig. 1. Translation initiation in eukaryotes. The 4E-BPs are hyperphosphorylated to release eIF4E so that it can interact with the 5′ cap, and the eIF4F initiation complex is assembled. The interaction of poly(A) binding protein with the initiation complex and circularization of the mRNA is not depicted in the diagram. The secondary structure of the 5′ UTR is melted, the 40S ribosomal subunit is bound to eIF3, and the ternary complex consisting of eIF2, GTP, and the Met-tRNA are recruited to the mRNA. The ribosome scans the mRNA in a 5′→3′ direction until an AUG start codon is found in the appropriate sequence context. The initiation factors are released, and the large ribosomal subunit is recruited.

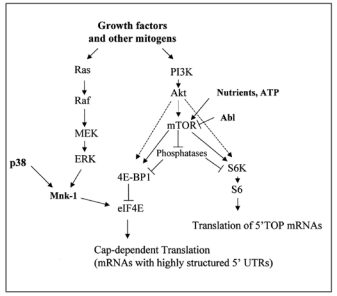


Fig. 2. Regulation of translation initiation by signal transduction pathways. Signaling via p38, extracellular signal-related kinase, PI3K, and mTOR can all activate translation initiation.

Acknowledgements
We thank Gayle Nesom from The University of Texas M. D. Anderson Cancer Center Department of Scientific Publications for editorial assistance and Dr. Elmer Bernstam for assistance with manuscript preparation.

Footnotes
1F. M. is supported by The University of Texas M. D. Anderson Cancer Center Physician-Scientist Program and by NIH Grant 1KO8-CA 91895-01. K. K. H. is supported by Department of Defense Award DAMD-17-97-1-7162.
2 To whom requests for reprints should be addressed, at Department of Surgical Oncology, Box 444, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: (713) 745-4453; Fax: (713) 745-4926; E-mail: fmeric@mdanderson.org
3 The abbreviations used are: eIF4E, eukaryotic initiation factor 4E; UTR, untranslated region; IRES, internal ribosome entry site; 4E-BP1, eukaryotic initiation factor 4E-binding protein 1; S6K, ribosomal p70 S6 kinase; mTOR, mammalian target of rapamycin; ATM, ataxia telangiectasia mutated; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog deleted from chromosome 10; PP2A, protein phosphatase 2A; TGF-β3, transforming growth factor-β3; PAP, poly(A) polymerase; EPA, eicosopentaenoic acid; mda-7, melanoma differentiation-associated gene 7.

Accepted July 22, 2002.
Received May 16, 2002.
Revision received July 12, 2002.
Molecular Cancer Therapeutics

References
1 **Pestova, T. V., Kolupaeva, V. G., Lomakin, I. B., Pilipenko, E. V., Shatsky, I. N., Agol, V. I., and Hellen, C. U.** Molecular mechanisms of translation initiation in eukaryotes.Proc. Natl. Acad. Sci. USA , 98: 7029 –7036,2001 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar
2 **Rosenwald, I. B., Kaspar, R., Rousseau, D., Gehrke, L., Leboulch, P., Chen, J. J., Schmidt, E. V., Sonenberg, N., and London, I. M.** Eukaryotic translation initiation factor 4E regulates expression of cyclin D1 at transcriptional and post-transcriptional levels.J. Biol. Chem. , 270: 21176 –21180,1995 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar
3 **Rosenwald, I. B., Hutzler, M. J., Wang, S., Savas, L., and Fraire, A. E.** Expression of eukaryotic translation initiation factors 4E and 2α is increased frequently in bronchioloalveolar but not in squamous cell carcinomas of the lung.Cancer (Phila.) , 92: 2164 –2171,2001 .MD Anderson Full TextCrossRefPubMedGoogle Scholar
4 **Darveau, A., Pelletier, J., and Sonenberg, N.** Differential efficiencies of in vitro translation of mouse c-myc transcripts differing in the 5′ untranslated region.Proc. Natl. Acad. Sci. USA , 82: 2315 –2319,1985 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar, Kozak, M. Influences of mRNA secondary structure on initiation by eukaryotic ribosomes.Proc. Natl. Acad. Sci. USA , 83: 2850 –2854,1986 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar, Koromilas, A. E., Lazaris-Karatzas, A., and Sonenberg, N. mRNAs containing extensive secondary structure in their 5′ non-coding region translate efficiently in cells overexpressing initiation factor eIF-4E.EMBO J. , 11: 4153 –4158,1992 .MD Anderson Full TextPubMedGoogle Scholar
5 **Rinker-Schaeffer, C. W., Graff, J. R., De Benedetti, A., Zimmer, S. G., and Rhoads, R. E.** Decreasing the level of translation initiation factor 4E with antisense RNA causes reversal of ras-mediated transformation and tumorigenesis of cloned rat embryo fibroblasts.Int. J. Cancer , 55: 841 –847,1993 .MD Anderson Full TextCrossRefPubMedGoogle Scholar
6 **Kevil, C. G., De Benedetti, A., Payne, D. K., Coe, L. L., Laroux, F. S., and Alexander, J. S.** Translational regulation of vascular permeability factor by eukaryotic initiation factor 4E: implications for tumor angiogenesis.Int. J. Cancer , 65: 785 –790,1996 .MD Anderson Full TextCrossRefPubMedGoogle Scholar
7 **Nathan, C. A., Franklin, S., Abreo, F. W., Nassar, R., De Benedetti, A., and Glass, J.** Analysis of surgical margins with the molecular marker eIF4E: a prognostic factor in patients with head and neck cancer.J. Clin. Oncol. , 17: 2909 –2914,1999 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar
8 **Fukunaga, R., and Hunter, T.** MNK1, a new MAP kinase-activated protein kinase, isolated by a novel expression screening method for identifying protein kinase substrates.EMBO J. , 16: 1921 –1933,1997 .MD Anderson Full TextAbstractGoogle Scholar, Waskiewicz, A. J., Flynn, A., Proud, C. G., and Cooper, J. A. Mitogen-activated protein kinases activate the serine/threonine kinases Mnk1 and Mnk2.EMBO J. , 16: 1909 –1920,1997 .MD Anderson Full TextAbstractGoogle Scholar, Wang, X., Flynn, A., Waskiewicz, A. J., Webb, B. L., Vries, R. G., Baines, I. A., Cooper, J. A., and Proud, C. G. The phosphorylation of eukaryotic initiation factor eIF4E in response to phorbol esters, cell stresses, and cytokines is mediated by distinct MAP kinase pathways.J. Biol. Chem. , 273: 9373 –9377,1998 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar

Translation Initiation in Cancer: A Novel Target for Therapy[1]

Funda Meric[2] and Kelly K. Hunt
Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Abstract

Translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled with cell cycle progression and cell growth. Several alterations in translational control occur in cancer. Variant mRNA sequences can alter the translational efficiency of individual mRNA molecules, which in turn play a role in cancer biology. Changes in the expression or availability of components of the translational machinery and in the activation of translation through signal transduction pathways can lead to more global changes, such as an increase in the overall rate of protein synthesis and translational activation of the mRNA molecules involved in cell growth and proliferation. We review the basic principles of translational control, the alterations encountered in cancer, and selected therapies targeting translation initiation to help elucida

Introduction

The fundamental principle of molecular therapeutics in can- cer is to exploit the differences in gene expression between cancer cells and normal cells. With the advent of cDNA array technology, most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable either to DNA amplification or to differences in transcription. Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability.

The power of translational regulation has been best recognized among developmental biologists, because transcription does not occur in early embryogenesis in eukaryotes. For ex- ample, in Xenopus, the period of transcriptional quiescence continues until the embryo reaches midblastula transition, the 4000-cell stage. Therefore, all necessary mRNA molecules are transcribed during oogenesis and stockpiled in a translationally inactive, masked form. The mRNA are translationally activated at appropriate times during oocyte maturation, fertilization, and early embryogenesis and thus, are under strict translational control.

Translation has an established role in cell growth. Basi- cally, an increase in protein synthesis occurs as a conse- quence of mitogenesis. Until recently, however, little was known about the alterations in mRNA translation in cancer, and much is yet to be discovered about their role in the development and progression of cancer. Here we review the basic principles of translational control, the alterations en- countered in cancer, and selected therapies targeting translation initiation to elucidate potential new therapeutic avenues.

Basic Principles of Translational Control

Mechanism of Translation Initiation
Translation initiation is the main step in translational regulation. Translation initiation is a complex process in which the initiator tRNA and the 40S and 60S ribosomal subunits are recruited to the 5′ end of a mRNA molecule and assembled by eukaryotic translation initiation factors into an 80S ribosome at the start codon of the mRNA (Fig. 1). The 5′ end of eukaryotic mRNA is capped, i.e., contains the cap structure m7GpppN (7-methylguanosine-triphospho-5′-ribonucleoside). Most translation in eukaryotes occurs in a cap-dependent fashion, i.e., the cap is specifically recognized by the eIF4E,3 which binds the 5′ cap

The eIF4F translation initiation complex is then formed by the assembly of eIF4E, the RNA helicase eIF4A, and eIF4G, a scaffolding protein that mediates the binding of the 40S ribosomal subunit to the mRNA molecule through interaction with the eIF3 protein present on the 40S ribosome. eIF4A and eIF4B participate in melting the secondary structure of the 5′ UTR of the mRNA. The 43S initiation complex (40S/eIF2/Met-tRNA/GTP complex) scans the mRNA in a 5′→3′ direction until it encounters an AUG start codon. This start codon is then base-paired to the anticodon of initiator tRNA, forming the 48S initiation complex. The initiation factors are then displaced from the 48S complex, and the 60S ribosome joins to form the 80S ribosome.

Unlike most eukaryotic translation, translation initiation of certain mRNAs, such as the picornavirus RNA, is cap independent and occurs by internal ribosome entry. This mechanism does not require eIF4E. Either the 43S complex can bind the initiation codon directly through interaction with the IRES in the 5′ UTR such as in the encephalomyocarditis virus, or it can initially attach to the IRES and then reach the initiation codon by scanning or transfer, as is the case with the poliovirus (1).

Regulation of Translation Initiation

Translation initiation can be regulated by alterations in the expression or phosphorylation status of the various factors involved. Key components in translational regulation that may provide potential therapeutic targets follow.

eIF4E

eIF4E plays a central role in translation regulation. It is the least abundant of the initiation factors and is considered the rate-limiting component for initiation of cap-dependent translation. eIF4E may also be involved in mRNA splicing, mRNA 3′ processing, and mRNA nucleocytoplasmic transport (2). eIF4E expression can be increased at the transcriptional level in response to serum or growth factors (3). eIF4E overexpression may cause preferential translation of mRNAs containing excessive secondary structure in their 5′ UTR that are normally discriminated against by the translational machinery and thus are inefficiently translated (4–7). As examples of this, overexpression of eIF4E promotes increased translation of vascular endothelial growth factor, fibroblast growth factor-2, and cyclin D1 (2, 8, 9).

Another mechanism of control is the regulation of eIF4E phosphorylation. eIF4E phosphorylation is mediated by the mitogen-activated protein kinase-interacting kinase 1, which is activated by the mitogen-activated pathway activating extracellular signal-related kinases and the stress-activated pathway acting through p38 mitogen-activated protein kinase (10–13). Several mitogens, such as serum, platelet-derived growth factor, epidermal growth factor, insulin, angiotensin II, src kinase overexpression, and ras overexpression, lead to eIF4E phosphorylation (14). The phosphorylation status of eIF4E is usually correlated with the translational rate and growth status of the cell; however; eIF4E phosphorylation has also been observed in response to some cellular stresses when translational rates actually decrease (15). Thus, further study is needed to understand the effects of eIF4E phosphorylation on eIF4E activity.

Another mechanism of regulation is the alteration of eIF4E availability by the binding of eIF4E to the eIF4E-binding proteins (4E-BP, also known as PHAS-I). 4E-BPs compete with eIF4G for a binding site in eIF4E. The binding of eIF4E to the best characterized eIF4E-binding protein, 4E-BP1, is regulated by 4E-BP1 phosphorylation. Hypophosphorylated 4E-BP1 binds to eIF4E, whereas 4E-BP1 hyperphosphorylation decreases this binding. Insulin, angiotensin, epidermal growth factor, platelet-derived growth factor, hepatocyte growth factor, nerve growth factor,insulin-like growth factors I and II, interleukin 3, granulocyte-macrophage colony-stimulating factor + steel factor, gastrin, and the adenovirus have all been reported to induce phosphorylation of 4E-BP1 and to decrease the ability of 4E-BP1 to bind eIF4E (15, 16). Conversely, deprivation of nutrients or growth factors results in 4E-BP1 dephosphorylation, an increase in eIF4E binding, and a decrease in cap-dependent translation.

The mTOR Signaling Pathway.

The macrolide antibiotic rapamycin (Siralimus; Wyeth-Ayerst Research, Collegeville, PA) has been the subject of intensive study because it inhibits signal transduction pathways involved in T-cell activation. The rapamycin-sensitive component of these pathways is mTOR (also called FRAP or RAFT1). mTOR is the mammalian homologue of the yeast TOR proteins that regulate G1 progression and translation in response to nutrient availability (24). mTOR is a serine-threonine kinase that modulates translation initiation by altering the phosphorylation status of 4E-BP1 and S6K (Fig. 2; Ref. 25).

4E-BP1 is phosphorylated on multiple residues. mTOR phosphorylates the Thr-37 and Thr-46 residues of 4E-BP1 in vitro (26); however, phosphorylation at these sites is not associated with a loss of eIF4E binding. Phosphorylation of Thr-37 and Thr-46 is required for subsequent phosphorylation at several COOH-terminal, serum-sensitive sites; a combination of these phosphorylation events appears to be needed to inhibit the binding of 4E-BP1 to eIF4E (25). The product of the ATM gene, p38/MSK1 pathway, and protein kinase Cα also play a role in 4E-BP1 phosphorylation (27–29).

S6K and 4E-BP1 are also regulated, in part, by PI3K and its downstream protein kinase Akt. PTEN is a phosphatase that negatively regulates PI3K signaling. PTEN null cells have constitutively active of Akt, with increased S6K activity and S6 phosphorylation (30). S6K activity is inhibited both by PI3K inhibitors wortmannin and LY294002 and by mTOR inhibitor rapamycin (24). Akt phosphorylates Ser-2448 in mTOR in vitro, and this site is phosphorylated upon Akt activation in vivo (31–33). Thus, mTOR is regulated by the PI3K/Akt pathway; however, this does not appear to be the only mode of regulation of mTOR activity. Whether the PI3K pathway also regulates S6K and 4E-BP1 phosphorylation independent of mTOR is controversial.

Interestingly, mTOR autophosphorylation is blocked by wortmannin but not by rapamycin (34). This seeming inconsistency suggests that mTOR-responsive regulation of 4E-BP1 and S6K activity occurs through a mechanism other than intrinsic mTOR kinase activity. An alternate pathway for 4E-BP1 and S6K phosphorylation by mTOR activity is by the inhibition of a phosphatase. Treatment with calyculin A, an inhibitor of phosphatases 1 and 2A, reduces rapamycin-induced dephosphorylation of 4E-BP1 and S6K by rapamycin (35). PP2A interacts with full-length S6K but not with a S6K mutant that is resistant to dephosphorylation resulting from rapamycin. mTOR phosphorylates PP2A in vitro; however, how this process alters PP2A activity is not known. These results are consistent with the model that phosphorylation of a phosphatase by mTOR prevents dephosphorylation of 4E-BP1 and S6K, and conversely, that nutrient deprivation and rapamycin block inhibition of the phosphatase by mTOR.

Polyadenylation

The poly(A) tail in eukaryotic mRNA is important in enhancing translation initiation and mRNA stability. Polyadenylation plays a key role in regulating gene expression during oogenesis and early embryogenesis. Some mRNA that are translationally inactive in the oocyte are polyadenylated concomitantly with translational activation in oocyte maturation, whereas other mRNAs that are translationally active during oogenesis are deadenylated and translationally silenced (36–38). Thus, control of poly(A) tail synthesis is an important regulatory step in gene expression. The 5′ cap and poly(A) tail are thought to function synergistically to regulate mRNA translational efficiency (39, 40).

RNA Packaging

Most RNA-binding proteins are assembled on a transcript at the time of transcription, thus determining the translational fate of the transcript (41). A highly conserved family of Y-box proteins is found in cytoplasmic messenger ribonucleoprotein particles, where the proteins are thought to play a role in restricting the recruitment of mRNA to the translational machinery (41–43). The major mRNA-associated protein, YB-1, destabilizes the interaction of eIF4E and the 5′ mRNA cap in vitro, and overexpression of YB-1 results in translational repression in vivo (44). Thus, alterations in RNA packaging can also play an important role in translational regulation.

Translation Alterations Encountered in Cancer

Three main alterations at the translational level occur in cancer: variations in mRNA sequences that increase or decrease translational efficiency, changes in the expression or availability of components of the translational machinery, and activation of translation through aberrantly activated signal transduction pathways. The first alteration affects the translation of an individual mRNA that may play a role in carcinogenesis. The second and third alterations can lead to more global changes, such as an increase in the overall rate of protein synthesis, and the translational activation of several mRNA species.

Variations in mRNA Sequence

Variations in mRNA sequence affect the translational efficiency of the transcript. A brief description of these variations and examples of each mechanism follow.

Mutations

Mutations in the mRNA sequence, especially in the 5′ UTR, can alter its translational efficiency, as seen in the following examples.

C-MYC

Saito et al. proposed that translation of full-length c-myc is repressed, whereas in several Burkitt lymphomas that have deletions of the mRNA 5′ UTR, translation of c-myc is more efficient (45). More recently, it was reported that the 5′ UTR of c-myc contains an IRES, and thus c-myc translation can be initiated by a cap-independent as well as a cap-dependent mechanism (46, 47). In patients with multiple myeloma, a C→T mutation in the c-myc IRES was identified (48) and found to cause an enhanced initiation of translation via internal ribosomal entry (49).

BRCA1

A somatic point mutation (117 G→C) in position −3 with respect to the start codon of the BRCA1 gene was identified in a highly aggressive sporadic breast cancer (50). Chimeric constructs consisting of the wild-type or mutated BRCA1 5′ UTR and a downstream luciferase reporter demonstrated a decrease in the translational efficiency with the 5′ UTR mutation.

CYCLIN-DEPENDENT KINASE INHIBITOR 2A

Some inherited melanoma kindreds have a G→T transversion at base −34 of cyclin-dependent kinase inhibitor-2A, which encodes a cyclin-dependent kinase 4/cyclin-dependent kinase 6 kinase inhibitor important in G1 checkpoint regulation (51). This mutation gives rise to a novel AUG translation initiation codon, creating an upstream open reading frame that competes for scanning ribosomes and decreases translation from the wild-type AUG.

Alternate Splicing and Alternate Transcription Start Sites
Alterations in splicing and alternate transcription sites can lead to variations in 5′ UTR sequence, length, and secondary structure, ultimately impacting translational efficiency.

Toward the Future

Translation is a crucial process in every cell. However, several alterations in translational control occur in cancer. Cancer cells appear to need an aberrantly activated translational state for survival, thus allowing the targeting of translation initiation with surprisingly low toxicity. Components of the translational machinery, such as eIF4E, and signal transduction pathways involved in translation initiation, such mTOR, represent promising targets for cancer therapy. Inhibitors of the mTOR have already shown some preliminary activity in clinical trials. It is possible that with the development of better predictive markers and better patient selection, response rates to single-agent therapy can be improved. Similar to other cytostatic agents, however, mTOR inhibitors are most likely to achieve clinical utility in combination therapy. In the interim, our increasing understanding of translation initiation and signal transduction pathways promise to lead to the identification of new therapeutic targets in the near future.

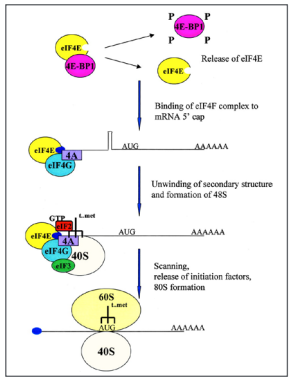


Fig. 1. Translation initiation in eukaryotes. The 4E-BPs are hyperphosphorylated to release eIF4E so that it can interact with the 5′ cap, and the eIF4F initiation complex is assembled. The interaction of poly(A) binding protein with the initiation complex and circularization of the mRNA is not depicted in the diagram. The secondary structure of the 5′ UTR is melted, the 40S ribosomal subunit is bound to eIF3, and the ternary complex consisting of eIF2, GTP, and the Met-tRNA are recruited to the mRNA. The ribosome scans the mRNA in a 5′→3′ direction until an AUG start codon is found in the appropriate sequence context. The initiation factors are released, and the large ribosomal subunit is recruited.

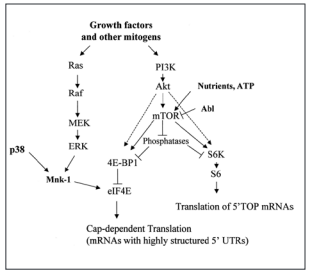


Fig. 2. Regulation of translation initiation by signal transduction pathways. Signaling via p38, extracellular signal-related kinase, PI3K, and mTOR can all activate translation initiation.

Acknowledgements

We thank Gayle Nesom from The University of Texas M. D. Anderson Cancer Center Department of Scientific Publications for editorial assistance and Dr. Elmer Bernstam for assistance with manuscript preparation.

Footnotes

1F. M. is supported by The University of Texas M. D. Anderson Cancer Center Physician-Scientist Program and by NIH Grant 1KO8-CA 91895-01. K. K. H. is supported by Department of Defense Award DAMD-17-97-1-7162.
2 To whom requests for reprints should be addressed, at Department of Surgical Oncology, Box 444, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: (713) 745-4453; Fax: (713) 745-4926; E-mail: fmeric@mdanderson.org
3 The abbreviations used are: eIF4E, eukaryotic initiation factor 4E; UTR, untranslated region; IRES, internal ribosome entry site; 4E-BP1, eukaryotic initiation factor 4E-binding protein 1; S6K, ribosomal p70 S6 kinase; mTOR, mammalian target of rapamycin; ATM, ataxia telangiectasia mutated; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog deleted from chromosome 10; PP2A, protein phosphatase 2A; TGF-β3, transforming growth factor-β3; PAP, poly(A) polymerase; EPA, eicosopentaenoic acid; mda-7, melanoma differentiation-associated gene 7.

Accepted July 22, 2002.
Received May 16, 2002.
Revision received July 12, 2002.
Molecular Cancer Therapeutics

References

1 **Pestova, T. V., Kolupaeva, V. G., Lomakin, I. B., Pilipenko, E. V., Shatsky, I. N., Agol, V. I., and Hellen, C. U.** Molecular mechanisms of translation initiation in eukaryotes.Proc. Natl. Acad. Sci. USA , 98: 7029 –7036,2001 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar
2 **Rosenwald, I. B., Kaspar, R., Rousseau, D., Gehrke, L., Leboulch, P., Chen, J. J., Schmidt, E. V., Sonenberg, N., and London, I. M.** Eukaryotic translation initiation factor 4E regulates expression of cyclin D1 at transcriptional and post-transcriptional levels.J. Biol. Chem. , 270: 21176 –21180,1995 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar
3 **Rosenwald, I. B., Hutzler, M. J., Wang, S., Savas, L., and Fraire, A. E.** Expression of eukaryotic translation initiation factors 4E and 2α is increased frequently in bronchioloalveolar but not in squamous cell carcinomas of the lung.Cancer (Phila.) , 92: 2164 –2171,2001 .MD Anderson Full TextCrossRefPubMedGoogle Scholar
4 **Darveau, A., Pelletier, J., and Sonenberg, N.** Differential efficiencies of in vitro translation of mouse c-myc transcripts differing in the 5′ untranslated region.Proc. Natl. Acad. Sci. USA , 82: 2315 –2319,1985 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar, Kozak, M. Influences of mRNA secondary structure on initiation by eukaryotic ribosomes.Proc. Natl. Acad. Sci. USA , 83: 2850 –2854,1986 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar, Koromilas, A. E., Lazaris-Karatzas, A., and Sonenberg, N. mRNAs containing extensive secondary structure in their 5′ non-coding region translate efficiently in cells overexpressing initiation factor eIF-4E.EMBO J. , 11: 4153 –4158,1992 .MD Anderson Full TextPubMedGoogle Scholar
5 **Rinker-Schaeffer, C. W., Graff, J. R., De Benedetti, A., Zimmer, S. G., and Rhoads, R. E.** Decreasing the level of translation initiation factor 4E with antisense RNA causes reversal of ras-mediated transformation and tumorigenesis of cloned rat embryo fibroblasts.Int. J. Cancer , 55: 841 –847,1993 .MD Anderson Full TextCrossRefPubMedGoogle Scholar
6 **Kevil, C. G., De Benedetti, A., Payne, D. K., Coe, L. L., Laroux, F. S., and Alexander, J. S.** Translational regulation of vascular permeability factor by eukaryotic initiation factor 4E: implications for tumor angiogenesis.Int. J. Cancer , 65: 785 –790,1996 .MD Anderson Full TextCrossRefPubMedGoogle Scholar
7 **Nathan, C. A., Franklin, S., Abreo, F. W., Nassar, R., De Benedetti, A., and Glass, J.** Analysis of surgical margins with the molecular marker eIF4E: a prognostic factor in patients with head and neck cancer.J. Clin. Oncol. , 17: 2909 –2914,1999 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar
8 **Fukunaga, R., and Hunter, T.** MNK1, a new MAP kinase-activated protein kinase, isolated by a novel expression screening method for identifying protein kinase substrates.EMBO J. , 16: 1921 –1933,1997 .MD Anderson Full TextAbstractGoogle Scholar, Waskiewicz, A. J., Flynn, A., Proud, C. G., and Cooper, J. A. Mitogen-activated protein kinases activate the serine/threonine kinases Mnk1 and Mnk2.EMBO J. , 16: 1909 –1920,1997 .MD Anderson Full TextAbstractGoogle Scholar, Wang, X., Flynn, A., Waskiewicz, A. J., Webb, B. L., Vries, R. G., Baines, I. A., Cooper, J. A., and Proud, C. G. The phosphorylation of eukaryotic initiation factor eIF4E in response to phorbol esters, cell stresses, and cytokines is mediated by distinct MAP kinase pathways.J. Biol. Chem. , 273: 9373 –9377,1998 .MD Anderson Full TextAbstract/FREE Full TextGoogle Scholar

Let's Talk about Pelvic Exenterations: Counseling Women on Living with the Life-Challenging Physical and Emotional Changes

Irene R. Korcz, PhD, LCSW
Department of Social Work, University of Texas MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Abstract

The towering Arch of St. Louis is a metaphor for the learning curve in counseling women about the operative procedure of pelvic exenteration. Many health care professionals do not understand the extent of the surgery involved in this procedure. Pelvic exenteration is a radical surgical procedure that is used with some women who have centrally recurrent cervical cancer. The procedure is indicated when other therapies, such as previous surgery or radiation, have failed to stop the inexorable spread of the disease. It is the most radical and life changing of all the surgeries performed with women who have gynecologic cancers and, for many, it is the last hope on ameliorating a devastating disease.

The three types of pelvic exenteration procedures include anterior, posterior, and total exenterations (Larrison & Cloutier, 2004). These procedures involve resection of most of the internal pelvic organs, including the reproductive, urinary and lower gastrointestinal organs and creating new openings for the passage of bodily wastes. These openings, or stomas, are the urostomy, colostomy and ileostomy (Salom & Penalver, 2003). The second part of the procedure is reconstructive with the creation of a neovagina and reinforcement of the internal pelvic cavity (Salom & Penalver, 2003).

The goal of pelvic exenteration is curative, life-sparing and also life-challenging. However, the loss of these internal organs brings drastic lifestyle changes, thus impacting the emotions, physical appearance and body image (Cloutier & Larrison, 2004; Steginga & Dunn, 1997).

This poster will provide a gateway to understanding the three types of exenterations and the far-reaching impact upon the lives of those undergoing the procedure as well as their families, friends and significant others.

Oncology social workers and other healthcare team professionals will be able to gain a new perspective on taking leadership roles in counseling women who are undergoing pelvic exenterations. Case studies of women, who have undergone the procedures, will be presented to illustrate their emotional, functional, intimacy and relationship concerns. Counseling strategies for helping women identify their social support networks for personal coping will be explored.

Development Of Pelvic Exenteration: The Past as Prologue to the Future

During the first half of the 20th century, Dr. Alexander Brunschwig led the way in developing an aggressive surgical approach for pelvic malignancies. Dr. Brunschwig speculated that cancer of the cervix and endometrium could be eradicated in the body by removing en-bloc all of the internal pelvic viscera. (Brunschwig, 1948). At the time, many doctors in the medical profession objected to the pelvic exenteration surgery on moral and ethical grounds.

In 1948, Dr. Brunschwig was considered an outstanding leader in thenewly developing era of surgical gynecology. After performing a series of 592 pelvic exenterations, Dr. Brunschwig published the findings of his research (Brunschwig & Daniel, 1960). It was found that surgical complications were numerous, the operative mortality rate of 23% was considerable, and the 5-year survival of 17% was small (Averette et al., 1984). The outcome of Dr. Brunschwig's early research indicated that for patients who could not undergo complete removal of their tumors, the option of pelvic exenteration did not offer a significant survival benefit (Paley & Shah, 2009).

Research On Pelvic Exenteration For Recurrent Cancer

Over the past five decades there have been additional advances in patient selection criteria for pelvic exenteration surgery as well as refinement in surgical techniques. These factors have led to a change for the better in outcomes. The most recent institutional statistics now report operative mortality under 5% and a 5-year survival of approximately 50% (Paley & Shah, 2009).

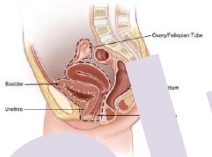
Current Research on Pelvic Exenteration for Gynecologic Malignancies

In 2010, surgeons in the Dept. of Gynecologic Oncology at the University of Texas MD Anderson Cancer Center in Houston, Texas, performed 14 total pelvic exenterations (Soliman, 2010). In a current research study on pelvic exenteration for gynecologic malignancy at the MD Anderson Cancer Center, 12 of the 14 patients have consented to participate. The objectives of the study are to determine the types of complications experienced by women who undergo pelvic exenteration and to determine if the number of complications differs by vaginal and bladder reconstruction types (Soliman, 2010). An additional objective of this research is to longitudinally assess quality life, sexual functioning, and symptoms in women who haveof undergone pelvic exenteration for gynecologic malignancies. This study will focus on quality of life issues specific to vaginal and bladder reconstruction (Soliman, 2010).

Types of Pelvic Exenteration Operative Procedures

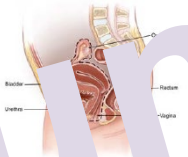
(Cloutier & Larrison, 2004)

Anterior Pelvic Exenteration



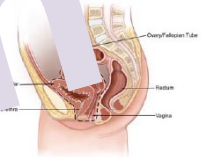
Anterior Exenteration (AE):
- Performed when the bladder is involved with cancer,
- but the bowel is not.
- Preserves the rectosigmoid bowel.
- Removes the uterus, ovaries, cervix, fallopian tubes,
- vagina and bladder.
- Hysterectomy, oophorectomy, cystectomy with urinary diversion and possibly vaginal reconstruction are performed.
- Vaginal reconstruction is widely used now.
- Reconstruction helps to fill in the pelvic void left after
- removal of all the internal organs.

Anterior Pelvic Exenteration



Posterior Exenteration (PE):
- Performed when the cancer involves the bowel, but not the bladder.
- Preserves the bladder.
- Removes the uterus, ovaries, cervix, fallopian tubes, vagina, bowel and rectum.
- Involves the creation of a colostomy and possibly vaginal reconstruction.

Total Pelvic Exenteration



Total Pelvic Exenteration (TPE):
- This is the most extensive of all the exenteration procedures.
- Includes hysterectomy, oopherectomy, cystectomy with
- urinary diversion, vaginectomy and lower bowel/rectum
- resection.
- There will be two ostomies if bowel is not connected to the
- rectum at the time of surgery.

The Total Pelvic Exenteration is performed in three Phases:
- **First Phase:** Assessment of disease status and lymph node status:
- If lymph nodes are found to have cancer involvement,
- the procedure is aborted.
- If no lymph node involvement is found, then procedure continues.
- **Second Phase:** All pelvic organs and other structures are removed.
- **Third Phase:** Reconstruction is performed with the creation of a urinary diversion, colostomy and a neovagina (if selected by patient).

Case Studies

Case Study #1
- 60 year old single, white, never-married, female living out of state.
- Patient was diagnosed with recurrent vaginal melanoma.
- She was asked to provide her advance directives for her chart.
- Patient underwent total pelvic exenteration with colostomy, ileal conduit, appendectomy and VRAM vaginal reconstruction.
- Recovered well from her surgery with no complications.
- Discharged home with two nieces as caregivers on post-op day 10.
- Initially took short-term disability from her job; later received SSDI benefits.
- Social work assisted patient with housing resources prior to and after surgery.
- Patient was able to do some household chores and grocery shopping using a motorized wheelchair.
- She experienced weakness and fatigue upon exertion from activities.
- At the time of her 3 month clinic visit, the patient developed suspicious pulmonary nodules and was referred to an oncologist in her local community for re-staging and systemic therapy.

Case Study #2
- 39 year old married, white, female homemaker who lived locally in Houston, Texas.
- Patient was diagnosed with stage IIIA moderately differentiated recurrent adenocarcinoma of the endocervix.
- Patient had completed her advance directives prior to her surgery.
- Patient underwent a total pelvic exenteration with colostomy, ileal conduit and reconstruction of vaginal defect and reconstruction of anterior abdominal wall.
- Patient was counseled extensively by Psychiatry for anxiety prior to surgery and while in the hospital.
- Social worker provided counseling on sexuality and intimacy.
- During hospital recovery, patient experienced slow return of bowel function and small bowel obstruction.
- On post-op day 21, patient was discharged home in stable condition with home health services and spouse as caregiver.
- At time of post-op clinic visits, patient was doing well as outpatient and able to take care of family.

Case Study #3
- 55 year old married, white female who lived in west Texas.
- Patient was diagnosed with metastatic adenocarcinoma of the vagina.
- Patient received extensive pre-surgery counseling by Psychiatry as she was apprehensive about the surgery and anticipated life changes.
- Outpatient social worker met with patient and family for psychosocial assessment, and patient completed her advance directives.
- She underwent a total pelvic exenteration with colostomy, ileal conduit and modified VRAM vaginal reconstruction.
- While in hospital, social worker met with spouse for financial concerns about airline and hotel costs.
- Social worker counseled with the patient on her occupational concerns.
- Patient was stable during hospital course and was discharged on post-op day 15.
- Patient planned to stay with family in Houston, and a home health referral was made.

Case Study #4
- 69 year old married, white, female who lived locally in Houston, Texas.
- Patient was diagnosed with recurrent vaginal squamous cell carcinomas, status post radiation.
- Outpatient social worker met with patient and spouse for psychosocial assessment, and patient was asked to provide her advance directives.
- In her meeting with the medical team, the patient declined the functional vaginal reconstruction, as she and spouse were not sexually active
- Patient underwent a posterior pelvic exenteration with removal of rectosigmoid colon with the anus, the posterior vagina and the vulva and perineum en-bloc resection with gracillus flap vaginal reconstruction.
- While in the hospital, social worker met with patient to provide expressive supportive counseling and assess home care needs.
- Patient developed small wound separation in the lower surgical abdominal wound bed fascia on the seventh day post-op and was treated with wound vac therapy.
- On post-op day 16, patient was discharged to home in stable condition with home health services, and spouse as her primary caregiver.

Potential Postoperative Medical Complications:

(Cloutier & Larrison, 2004)
- **During recovery:** Surgical complications of wound infection, blood loss, respiratory problems, and bowel obstructions.
- **Within 18 months of surgery:** Wound breakdown, fistulas, DVT, intestinal ileus or obstruction, anastamosis breakdown or leak, ureteral stricture, pyelonephrosis, or urinary tract infection, renal failure and flap necrosis.
- **Other possible long-term complications:** Peristomal hernia, prolapse of stoma, and problems with the urinary diversion, i.e., stone formation, mucous collection in conduit and bowel obstruction.

Potential Postoperative Psychosocial Complications:

(Carter, et al., 2004)
- Anxiety, sadness, grief, depression
- Anger, loneliness, guilt, fears about the future
- Fears of loss of social support
- Sexuality/changes in body image
- Relationship concerns for spouse, children, friends
- Changes in bodily functions/care of stomas or conduits
- Lack of employment, occupational or money issues
- Decrease in physical and social activities
- Adjustment to a changed quality of life
- Loss of control over bowel and bladder functions
- Fear of recurrence
- Concerns of not being able to care for oneself
- Impaired sexual adjustment and self-consciousness due to colostomy, ileostomy, vaginal dryness

Counseling the Patient: Three Phases

I. Pre-Operative Counseling:
- Counseling related to the patient selection process for recurrent pelvic cancer.
- Type of procedure to be performed: Total pelvic exenteration; anterior or posterior pelvic exenteration
- Explanation of ileal conduit, colostomy, neovaginal reconstruction using flaps
- Informed Consent: Counseling regarding the risks and benefits involved in the exenteration procedures and the bodily changes that will occur as a result of the surgery.
- Psychosocial Assessment
- Assessment of Sexual Functioning
- Advance Directives

II.Counseling during recovery in hospital:
- Expressive supportive counseling
- Coping with emotional feelings and physical changes
- Home care, resources, transportation and social support network
- Discharge planning and Case management services

Acknowledgement:
Lynn Cloutier, RN, MSN, AOCN, ACN, Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, for all her assistance with background information on pelvic exenteration.