

Department of Biochemistry

Fall 2013 Seminar Series



Presented by

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Monday and Tuesday, November 11 & 12, at 3:30

Deans Auditorium (PFEN 241)

Tales from the cellular underworld: mRNA decay and disease

mRNA decay is critical for cells to maintain homeostasis in a changing developmental and/or environmental milieu (Schoenberg and Maquat, 2012). It follows that many human diseases are due to deficiencies in the cellular mRNA decay machinery and/or mutations that disrupt the proper decay of particular mRNAs. In mammalian cells, two different messenger ribonucleoproteins (mRNPs) serve as templates for protein synthesis. Newly synthesized CBP80/CBP20-bound mRNPs initially undergo a pioneer round of translation (Maquat et al., 2010). One purpose of this round of translation is to ensure the quality of gene expression, as exemplified by nonsense-mediated mRNA decay (NMD) (Trcek et al., 2013). NMD largely functions to eliminate mRNAs that prematurely terminate translation, although it also contributes to proper gene control, and it targets CBP80/CBP20-bound mRNPs. CBP80/CBP20-bound mRNPs are remodeled to eIF4E-bound mRNPs as a consequence of the pioneer round of translation as well as independently of translation (Sato and Maquat, 2009). While eIF4E-bound mRNPs direct the bulk of cellular protein synthesis, they are largely immune to NMD.

Rules for predicting which premature termination codons (PTCs) trigger NMD will be discussed. The importance of NMD as a means to protect cells from the deleterious effects of truncated proteins will be exemplified using the long list of autosomal dominantly inherited human diseases that are due to the presence of PTCs that fail to trigger NMD. The mechanism of NMD will also be overviewed, including how CBP80, which is acquired by newly synthesized transcripts within nuclei, promotes NMD at multiple steps by directing specific mRNP rearrangements in the cytoplasm (Hwang et al., 2010). Additionally, the importance of translational repression (Isken et al., 2008) and RNA helicase function (Kurosaki and Maquat, 2013) to NMD will be described.

"Alu"strious effects on human RNA metabolism via 3'UTR sequences: New mechanisms of post-transcriptional gene regulation

Staufen1-mediated mRNA decay (SMD), which occurs when translation terminates sufficiently upstream of a STAU-binding site (SBS), is important for myogenesis, adipogenesis and many other developmental and homeostatic pathways¹. An SBS can be created by intramolecular base-pairing within an mRNA 3'-untranslated region (3'UTR) or by intermolecular base-pairing between a 3'UTR and a long non-coding RNA (lncRNA), which we call a 1/2-sbsRNA. Intermolecular base-pairing in humans involves Alu elements, which are a type of small interspersed repetitive element (SINE)², whereas intermolecular base-pairing in rodents involves B or identifier (ID) SINES³. Roles of STAU1 dimerization⁴ and the STAU1 paralog STAU2⁵ in SMD will be discussed. A new mechanism by which mRNAs crosstalk in a way that involves direct mRNA-mRNA interactions between 3'UTR Alu elements in each mRNA will also be described. SMD of each duplexed mRNA occurs provided each is translated; if only one mRNA is translated, then it alone is targeted for SMD, explaining why those 1/2-sbsRNAs characterized to date are not targeted for SMD. We demonstrate the importance of mRNA-mRNA-triggered SMD to the processes of cell migration and invasion in studies of the mRNA encoding CUB domain-containing protein 1 (CDCP1), which functions at the cell surface as an anti-apoptotic agent that promotes tumor-cell viability during metastatic colonization⁶. Our findings uncover a previously unappreciated role for mammalian-cell mRNAs. This unexpected function, together with our discovery of how STAU1 binding to inverted repeated 3'UTR Alu elements (IRAlus) competes with nuclear p54^{nrb} binding, that latter of which mediates the nuclear retention of 3'UTR IRAlus mRNAs in paraspeckles, and also with cytoplasmic protein kinase R (PKR) binding, which mediates the translational repression of 3'UTR IRAlus⁷, adds new and unanticipated layers of complexity to the intricate network of post-transcriptional interactions that regulate gene expression.

About the Beach Lectures:

David W. Beach was born in 1925 in London, England. Following service in the Royal Navy, he married Doris Holmes and began his career as a Chartered Accountant. Feeling the urge to expand his horizons, he moved to Canada and began a series of jobs in the aluminum industry that included General Manager of Kawneer, Canada and Vice-President of Kawneer, Inc. As Vice-President of ALUMAX Aluminum Corporation he was instrumental in making it one of the largest and most profitable aluminum companies in the world, prior to his retirement. Inspired by his son's enthusiasm for science, he has chosen to share his good fortune by supporting this biochemistry graduate program. This long-term support is intended to promote intellectual curiosity, a commitment to excellence, and an appreciation of science in all those involved.