**Investigating dynamic layers of cellular information transfer**

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In this lecture, I will discuss two examples, where information transfer during transcription and translation is dynamically regulated.

The first example deals with riboswitches. Riboswitches are gene regulatory elements located in the 5’-untranslated regions of messenger RNA (mRNA). Ligand binding to an aptamer domain of riboswitches induces either the up- or down-regulation of the expression of ligand-associated genes. Riboswitch regulate gene expression either at the level of transcription or translation. For transcriptional riboswitches, ligand binding supposedly induces a conformational switch between mutually exclusive antiterminator or terminator conformations that represent the on- and off-states of the switches. We show that in stark contrast to this classical model for riboswitch function three different transcriptional riboswitches adopt the terminator conformation (off-state) at thermodynamic equilibrium regardless of the presence or absence of the ligand. By investigating the guanine- and hypoxanthine*-*sensing *xpt-pbuX* riboswitch from *Bacillus subtilis*, we find that in contrast to the full-length mRNA, transcription intermediates undergo ligand-dependent conformational changes. Importantly, in the absence of ligand, the RNA was able to adopt the antiterminator conformation in a transcription intermediate that was kinetically trapped and did not refold fast enough to form the longer and more stable terminator conformation in the limited time window available during transcription. This kinetic trapping allows the RNA-polymerase to escape from the termination site before the terminator is folded and to maintain gene expression in the absence of ligand. In the presence of ligand, early ligand binding stabilised the aptamer domain, suppressed the formation of the antiterminator conformation, and, thus, accelerated formation of the terminator conformation by at least two orders of magnitude, leading to gene repression. Transcriptional regulation therefore executes the genetic decision during a single-round of transcription and is critically dependent on the kinetics of ligand binding and RNA refolding that constantly change as the length of the mRNA chain grows during transcription.

The second example deals with protein folding and reports that differential usage of synonymous codons governs co-translational folding and final protein structure. The genetic code is degenerate, with up to six synonymous codons encoding a given amino acid in the protein. The occurrence of synonymous codons in open reading frames (ORFs) of genes is not random, suggesting the existence of evolutionary constraints on codon choice. In this lecture I will present data demonstrating that synonymous codon usage governs the kinetics of translation, co-and post-translational protein folding and final protein structure. The ribosome-bound nascent chains of the mammalian eye lens protein, gamma-B crystallin, expressed from two gene variants with different synonymous codon composition but encoding the same polypeptide, attain different conformations as indicated by altered in vivo stability and in vitro protease resistance. Our 2D NMR spectroscopic data suggest that the observed structural differences are associated with different cysteine oxidation states of the synonymous variants. Synonymous codon usage was found to alter local and global rates of translation and affect the efficiency of co-translational folding of protein domains as well as the ultimate stable conformation attained by the protein.