

Biological Roles of Non-coding RNA

Non-coding RNAs other than tRNA and rRNA were initially considered to be “genomic junk” since they did not encode proteins. However, their roles in regulating gene expression were discovered over the past few decades and continue to be extensively researched. Based on their length, non-coding RNAs may be classified as small regulatory RNAs (< 100

nucleotides) or long non-coding RNAs (> 200 nucleotides). Both small regulatory RNAs and long non-coding RNAs regulate gene expression by altering various stages of transcription and translation. Non-coding RNAs affect mRNA splicing—removal of protein non-coding segments and joining the protein coding sequences. In this manner, they control the formation of different protein variants from a single gene. Small regulatory RNAs such as microRNAs (miRNAs) and small interfering RNAs (siRNAs) bind to complementary sequences on mRNA and inhibit protein synthesis either by blocking the access of the translation machinery to mRNA or by degrading the mRNA itself. Long non-coding RNAs interact with and regulate enzymes that chemically modify DNA and histones (proteins that help package DNA in the nucleus) to either activate or repress transcription. RNA-mediated regulation of gene expression is widespread in bacteria. Regulatory sequences in mRNA called riboswitches act as environmental sensors by detecting changes in temperature and nutrient levels. Riboswitch-based regulation depends on the formation of two mutually exclusive and stable conformations of the RNA secondary structure. The secondary structure switches between two conformations to turn gene expression on or off in response to environmental changes. For example, when the bacteria *Listeria monocytogenes* infects a host, the higher body temperature of the host breaks down the secondary structure in the 5' untranslated region of the bacterial mRNA. This exposes a ribosome-binding site on the mRNA and initiates protein translation, enabling the bacteria to live and grow within the host organism. Some riboswitches detect end products of metabolic pathways and serve as feedback controls for transcription or translation. For instance, the thiamine pyrophosphate riboswitch regulates thiamine biosynthesis in bacteria. When an adequate concentration of thiamine has been synthesized, it binds to the riboswitch and changes its conformation. This change in conformation blocks the translation initiation site and stops protein synthesis. Compounds that closely resemble thiamine in structure are being studied as potential antibacterial agents. These drugs are intended to bind the riboswitch in the absence of thiamine and cause a conformational change that blocks the translation of proteins required for thiamine biosynthesis. Since the bacteria will be unable to produce this nutrient, they will stop growing and eventually die. As riboswitches are more commonly found in prokaryotes than eukaryotes, riboswitch-targeting antibacterials would have minimal adverse effects on mammalian hosts.