Riboregulation as a new player in the control of cellular metabolism: clues from the cryo-EM structure of serine hydroxymethyltransferase-RNA complex

Sharon Spizzichino – University of Rome La Sapienza

Recent evidence indicates that RNA can directly regulate protein activity, either by affecting its function or mediating the assembly of multiprotein complexes, thereby modulating various cellular processes, including metabolism [1]. This novel mechanism is known as riboregulation. Interestingly, many metabolic enzymes have recently been found to exhibit non-canonical RNA-binding properties in living cells. However, only a few examples of RNA-mediated regulation (riboregulation) are available [2,3], and none have been structurally characterized. Here I will present the cryo-EM structure of the complex between cytosolic serine hydroxymethyltransferase (SHMT1) and its cognate RNA modulator [4]. This complex selectively inhibit serine cleavage activity but not its reverse reaction, serine synthesis. The RNA binds with a 1:4 stoichiometry, and its position in the structure suggests that the tetrameric assembly, characteristic of eukaryotic SHMTs, is crucial for RNA binding. RNA binding induces a conformational change in two of the four protein subunits, resulting in a conformation characterized by a significant degree of disorder in the active site. These findings suggest that RNA acts as a conformational switch, allosterically regulating the enzyme and preventing the necessary conformational rearrangement necessary for the serine cleavage reaction. Our results offer a mechanistic explanation on how RNA affects enzyme function in a substrate-specific manner. This observation not only enhances our understanding of RNA's role in allosterically controlling metabolic enzymes but also offers potential strategies for targeting these enzymes in RNA-mediated therapies.