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2 - ROLE OF MIR-7 IN CHOLESTEROL BIOSYNTHESIS

M. Torrecilla-Parra[1], M. Fernández-de Frutos[1], A. Pérez-García[1], G. de la Peña[2,3], V. Pardo-Márquez[1], Y. Martín-Martín[1], D. Gómez-Coronado[2,3], R. Busto[2,3] and C.M. Ramírez[1]

[1]Grupo de Regulación Postranscripcional de las Enfermedades Metabólicas. Instituto Madrileño de Estudios Avanzados en Alimentación-IMDEA Alimentación. Madrid. [2]CIBER de Fisiopatología de la Obesidad y Nutrición. Instituto de Salud Carlos III. Madrid. [3]Servicio de Bioquímica-Investigación. Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS). Hospital Universitario Ramón y Cajal. Madrid.

Resumen

Cholesterol is an essential macromolecule for mammalian cells. In the brain, cholesterol homeostasis is tightly regulated by *de novo* synthesis, uptake and efflux and dysregulations of this pathway are linked with neurodegenerative pathologies such as Alzheimer disease (AD). In addition to classical regulation of these processes by transcriptional factors such as Liver X receptor (LXR) or Sterol Regulatory Element Binding Proteins (SREBPs), microRNAs could be key elements in cholesterol homeostasis and in AD1. Previous studies of our group have demonstrated the role of miR-7 in regulating insulin signaling, an important metabolic pathway linked with AD. In this context, we aimed to explore if miR-7 could influence cholesterol biosynthesis, due to its close relationship with AD. To do so, we performed bioinformatic analysis that indicated that important biosynthetic enzymes of the pathway are potentially targeted by miR-7, including DHCR7, SC5D, DHCR24. Western blot and qPCR analysis in human (SH-SY5Y) and mouse (N2a) neuroblastoma cell lines overexpressing miR-7 showed a significant inhibition of these genes. Further analysis of the 3'-UTR activity indicated that miR-7 directly binds with these targets. To assess the functional outcome of these findings we performed cholesterol synthesis assays in miR-7 overexpressing cells. Our results showed that miR-7 inhibits cholesterol synthesis and promotes the accumulation of desmosterol in N2a, which correlates with the posttranscriptional regulation of DHCR24 enzyme. Further analysis indicated that both, miR-7 levels are modulated by cholesterol content, probably by transcriptional regulation of SREBP2. Altogether, these results suggest a novel and intriguing feedback loop of regulation of cholesterol homeostasis by posttranscriptional mechanisms.