THE ROLE OF POLYAMINES IN HYPUSINE FORMATION, CELL PROLIFERATION AND CANCER

Myung Hee Park

National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, USA

Polyamines are ubiquitous and essential in all living cells and are intricately regulated at the level of biosynthesis, metabolism and transport. Whereas a bulk of cellular polyamines are bound to nucleic acids, and are presumed to be important in the regulation of transcription and translation, a small portion of polyamine spermidine is covalently incorporated into one essential cellular protein, eukaryotic translation initiation factor 5A (eIF5A), to form a unique polyamine-derived amino acid hypusine [N^{ε}-(4-amino-2-hydroxybutyl)lysine]. Hypusine is formed in eIF5A posttranslationally by two sequential enzymatic steps. In the first step, deoxyhypusine synthase catalyzes the transfer of 4-aminobutyl moiety of spermidine to one specific lysine residue to form an intermediate, deoxyhypusine residue. In the second step, deoxyhypusine hydroxylase catalyzes hydroxylation of deoxyhypusine side chain to complete hypusine synthesis and eIF5A maturation. Both eIF5A protein and its hypusine modification are vital for mammalian cell proliferation. The synthesis of hypusine in eIF5A is drastically increased upon stimulation of growth of cultured mammalian cells. Increased expression of eIF5A and the hypusine modification enzymes are observed in neoplastic or cancerous tissues, suggesting eIF5A as a potential diagnostic marker of, or a target for intervention in aberrant cell proliferation. Chemical inhibitors of deoxyhypusine synthase and deoxyhypusine hydroxylase exert strong anti-proliferative activity against a panel of human cancer cell lines. eIF5A and the hypusine biosynthetic enzymes present novel potential targets for cancer chemoprevention and chemotherapy.