STUDY OF QUEUOSINE SALVAGE AND FUNCTION IN EUKARYOTES; A FORGOTTEN MICRONUTRIENT

Abstract Text:

Queuine is a largely forgotten bacterial-derived micronutrient that is obtained exclusively from the gut; a preeminent small-molecule of the gut-brain axis. Our contention is that queuine is important in metabolism and development—mammals are born sterile and queuine free—and induces long-lasting effects into adulthood, particularly in the brain. At least 5 unique enzyme activities are involved in queuine utilisation in mammals, 4 of which remained undefined. Our long-term goals are to clarify how queuine contributes to human health, raise scientific and public awareness about its importance and exploit the newly defined pathways for therapeutic purposes. The specific objectives of this study are to identify and characterise the unknown queuine mechanistic enzymes and to define how queuine deficiency affects neuronal metabolism and differentiation. Our central hypothesis is that the near universal conservation of queuine emanates from an essential (albeit subtle) role in metabolism—through affecting ribosomal translation—that influences differentiation and that in animals protects against age-related neurological decline. Our rationale is based on numerous observations from the early literature, and recent bioinformatic, biochemical, and gene-knockout studies from the Crécy and Kelly laboratories. Our specific aims will demonstrate that; (Aim 1) queuine transport is dependent on unique uptake receptors; (Aim 2) DUF2419 family proteins are required for queuine salvage; (Aim 3) queuine hypermodification with mannose and galactose is required for intracellular retention; and (Aim 4) neuronal function is compromised in the absence of queuine. At conclusion the project will have furnished the scientific community with tangible resources to interrogate queuine's physiological role and supply new tools for therapeutic development. The significance of the work derives from the universality of queuine as a micronutrient for eukaryotic life with consequences for healthy aging. The research is innovative because it, i. tackles an unaddressed fundamental unknown of life, ii. is relevant to age-related neurological decline (a major present-day concern) and iii. merges team expertise in bioinformatics, genetics, chemistry, biochemistry, crystallography and metabolomics.

Public Health Relevance Statement:

Queuine is a micronutrient from the gut that is important for human physiology and aging, and in particular in the brain. This research will identify how queuine is processed in the human body and how it influences brain cell proliferation, metabolism and function.