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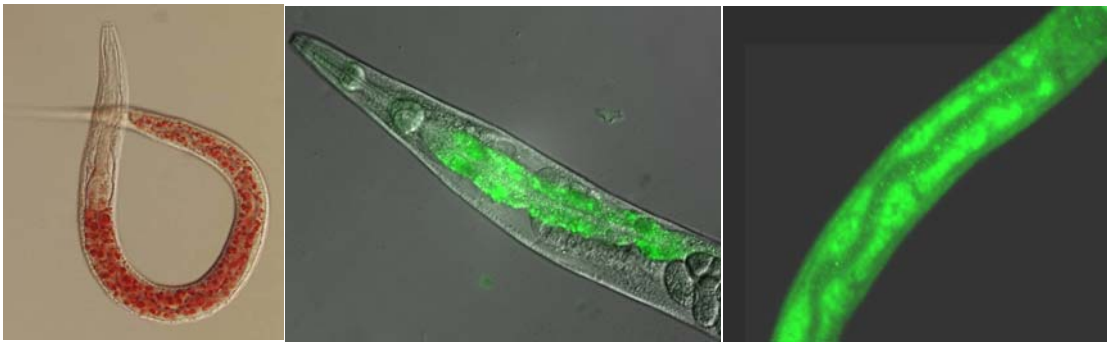
Lipid metabolic disorder is a critical risk factor for metabolic syndrome, triggering debilitating diseases like obesity and diabetes. Diabetes is the epicenter of important medical issues, representing a major international public health threat and is the leading cause of blindness, renal disease, and non-traumatic loss of limb. Accumulation of fat in adipose tissue, muscles and liver and/or the defects in their ability to metabolize fatty acids, results in insulin resistance. This triggers an early pathogenesis of type 2 diabetes (T2D). Although the connection between obesity and T2D is clear, primary genetic and metabolic factors for causing insulin resistance and the precise sequence of events leading to the development of T2D remain undetermined. The discovery that factors controlling energy metabolism are conserved between mammals and *Caenorhabditis elegans* has provided a new and powerful strategy to delineate the molecular pathways that lead to T2D. We have recently published novel findings establishing that *C. elegans* kruppel-like factor (*klf-3*) controls fatty acid (FA) biosynthesis, mitochondrial proliferation, and beta-oxidation. We have also shown that *klf-3* controls essential genes involved in insulin signaling; KLF-3 selectively acts on insulin components to regulate insulin pathway activity and integrate their crosstalk into the network of fat metabolism. We propose to build on these findings to dissect the fundamental details about how fat accumulation, an obese state in the worm, mimics the major risk factor in T2D in humans and deregulate the insulin signaling system. Our long term research goal is to to use our discoveries to power translational research that delivers innovative therapeutic and preventative options for diabetes. Our working model is *C. elegans*. In addition, we will use cell culture and mouse models to answer specific questions whenever it is advantageous. Biochemical analyses to test chemical interference with protein function will be performed to understand, in addition to the genetic details, the precise role of KLF protein and its physical interactions in a living organism.

Project 1: Role of *klf-3* in FA synthesis and beta-oxidation: Fat storage is coordinately regulated through signaling networks that integrate biochemical pathways of fat deposition, mobilization and utilization. My laboratory conducts research investigating the intracellular mechanisms that regulate fat storage. We are particularly interested in the role that Krüppel-like family of transcription factors, KLFs play in the regulation of lipid metabolic enzymes to fat deposition, mobilization and utilization. Recent studies from my laboratory have shown that a member of this family, *klf-3* is one of the important regulators of two key processes in lipid metabolism; fatty acid beta-oxidation and lipoprotein assembly and transport. Our efforts include investigation of how *klf* interacts with lipid metabolism regulatory machinery, characterization of specific pathway targets, and genetic manipulation of these targets to know more about the mechanism of excess fat accumulation in human. Mammals store excessive amounts of energy substrates in the form of intracellular triglyceride (TG) deposits in lipid droplets, which are most prominent in mammalian adipose tissues; the major storage site for fat. During starvation, TG is hydrolyzed into fatty acids (FAs) to provide energy. Breakdown of fatty acyl-CoAs to acetyl-CoA occurs via beta-oxidation enzymes, where several parallel pathways with intersecting substrate specificities are used. We take advantage of the availability of *Caenorhabditis elegans* models, its genomic databases, and the availability of mutants associated with fat metabolism in order to understand the complexity of fat metabolism. *Klf-3* mutations cause accumulation of enlarged, neutral lipid rich intestinal droplets; however, it does not change the normal feeding behavior of the mutant animal. The KLF-3 activity appeared to be necessary for maintaining the normal expression of enzymes that are essential in FA synthesis and mitochondrial or peroxisomal beta-oxidation pathway and may therefore modulate these processes that mediate lipid metabolism.

Project 2: The role of *klf-3* in lipoprotein assembly and secretion: Dietary lipids are absorbed from the small intestines and transported to various organs and tissues to maintain lipid/cholesterol homeostasis. Because of non-polar nature of lipids, mammals have evolved a mechanism that allows the conversion of insoluble lipids into lipoproteins so that it can be transported and delivered to its destination. For transportation, the assembly of triglyceride-rich lipoproteins requires the formation of a complex between apolipoprotein B (apoB), a structural protein, and microsomal triglyceride transfer protein (MTP), an endoplasmic resident chaperone. MTP and apoB interact during lipoprotein assembly to facilitate lipoprotein production and therefore genetic loss of either apoB or MTP results in the inability of both the liver and intestine to secrete very low density lipoprotein (VLDL). Regulation of the assembly and secretion of apoB-containing lipoproteins has become an active area of investigation as it is known that overproduction of apoB-containing lipoproteins may be responsible for coronary artery disease and hyperlipidemia. We are interested in the mechanisms underlying lipoprotein assembly and transport, to better understand the regulatory role of *klf-3* in these processes, and identify novel targets for new therapies, which may be tested in vertebrate models. We found that similar to *klf-3,* mutants of *dsc-4* (*mq920*), the homolog of MTP or *vit* genes (*vit-2* and *5)* that are homologous to human apoB retain more fat than wild-type and perhaps unable to efficiently transport stored fat for energy. Our data suggest that *klf-3*, *dsc-4* and *vit* genes coordinate lipid transport but how these molecules act together to synchronize this process is under investigation. We are also investigating whether the molecules and mechanisms involved in fat metabolism is conserved across species including mammals. As such, our plan is to clarify the functional correlation between the *C elegans* and mammals.



Klf-3 (ok1975) **klf-3:gfp** **KLF-3 protein expression**

Project 3: Regulation of fat metabolism and cell death

Many epidemiological studies have indicated a strong association between obesity and cancer but the molecular bases of this connection is poorly understood. We have shown that suppression of *Ce-klf-1* activity results in fat accumulation and increased cell death. The important role of KLF-1 in fat storage and cell death pathways with properties of a tumor suppressor provides a conceptual framework to link fat accumulation with tumor growth. Our aim has been to understand the mechanistic basis of the disease. By investigating how both processes are regulated, and are influenced by KLF-1, we will elucidate aspects of fat storage and its relation to apoptosis. We are using a variety of techniques, including genetics, molecular biology, cell biology, and behavioral assays, to examine the development, distribution, and function of KLF-1 in fat storage and or cell death pathways. *C. elegans klf-1* is homologous to mammalian KLF4, KLF5, and KLF6, the highly characterized KLFs in regard to apoptosis. These KLFs are also involved in mammalian adipogenesis. Our long term research goal is to develop preventative and therapeutic strategies for obesity that may aid in prevention and treatment of cancer.

Selected Publications

J. Zhang, S. K. Hashmi, F. Cheema, N. Al-Nasser, R. Bakheet, R. S. Parhar, F. Al-Mohanna, R. Gaugler, M. M. Hussain, and **S. Hashmi** (2013). Regulation of lipoprotein assembly, secretion and fatty acid □-oxidation by Krüppel-like transcription factor, *klf-3*. Journal of Molecular Biology. http://dx.doi.org/10.1016/j.jmb.2013.04.020

S. Hashmi, Yi Wang, R. Parhar, K. Collison, W. Conca, F. Al-Mohanna, and R. Gaugler. (2013). A *C. elegans* model to study human metabolic regulation. Nutrition and Metabolism. 10: 31-42.

J. Zhang, R. Bakheet, R. S. Parhar, Cheng-Han Huang, M. M. Hussain, X. Pan, S. S. Siddiqui and **S. Hashmi** (2011). Regulation of fat storage and reproduction by Krüppel-like transcription factor KLF-3 and fat associated genes in *Caenorhabditis elegans.* Journal of Molecular Biology 411: 537-553. (**Front cover**)

S. Hashmi, J. Zhang, S. S. Siddiqui, R. S. Parhar**,** R. Bakheet, and Futwan Al-Mohanna (2011). Partner in fat metabolism: Role of KLFs in fat burning and reproductive behavior. 3 Biotech. 1: 59-72. **(**DOI 10.1007/s13205-011-0016-6)

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Q. Ji, **S. Hashmi**, Z. Liu, J. Zhang, Y. Chen, and C-H. Huang (2006). CeRH1 (*rhr-1*), the major rhesus gene of *Caenorhabditis elegans* is essential for embryonic development. Proceedings of the National Academy of Science, USA 103: 5881-5886.

Current Research Support

KACST Biotechnology Initiative & AAAS (2012-2015)