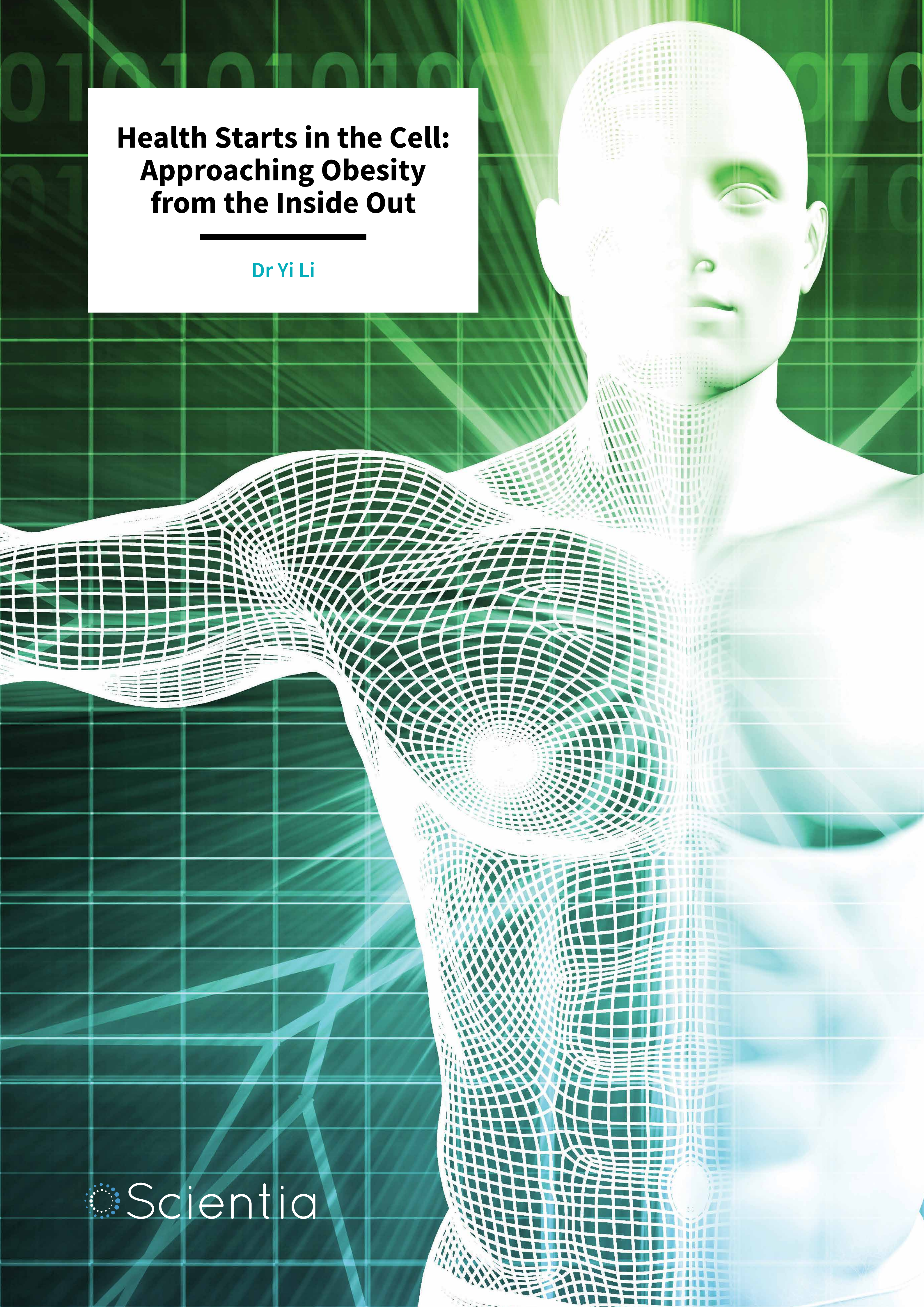
# Health Starts in the Cell: Approaching Obesity from the Inside Out

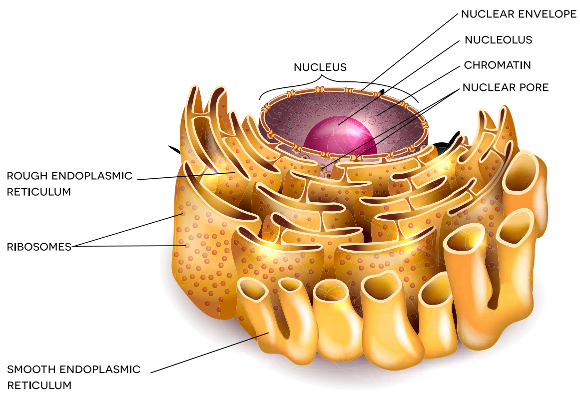
Dr Yi Li



Scientia

# HEALTH STARTS IN THE CELL: APPROACHING OBESITY FROM THE INSIDE OUT

Over the last few decades, obesity has become substantial public health concern. Obesity is associated with a myriad of other ailments and is on the rise in most developed countries. As with many chronic diseases, the development of an obese body type is often more complex than expected and involves a combination of environmental factors, genetic predisposition, and lifestyle choices. **Dr Yi Li**, of Texas A&M University – Kingsville, studies interactions between our environment and the inner workings of our cells to generate novel insights about chronic diseases such as obesity.




*Nucleus and endoplasmic reticulum*

**On Top of Your Genes**

Two decades ago, scientists were eagerly looking to genetics to unlock all of the mysteries about chronic diseases, hoping for a silver bullet to cure all human ails. Researchers were on the hunt for *the* gene for obesity and *the* gene for diabetes and *the* gene for male pattern baldness. As with many things in life and in science, it turned out that the closer they looked, the more complicated it got. While science has identified gene variations that appear to play a role in some chronic diseases, no obvious villains emerged. In fact, it became even more obvious that regardless of genetics, factors such as nutrition and lifestyle played important roles in health outcomes.

It makes sense that scientists were looking to genes for answers – genes influence our health by providing instructions for a cell to make proteins. These proteins go on to shape the behaviour of the cell, which shapes the behaviour of the tissue that cell resides in, ultimately shaping every aspect of our overall health and behaviour. The type of proteins that a given cell makes influences the type of cell it becomes during development. However, every cell in your body, from the neurons in your brain, to the light receptors in your eye, to the cells that form your skin, has the exact same set of genes but is only expressing the genes it needs to perform its duty. Alterations in the rates that a certain cell type expresses different genes are often associated with disease conditions, such as obesity, diabetes, and cancer.

So, what determines which genes a cell expresses and how often it expresses them? A suite of processes collectively known as epigenetics. Epigenetics literally means 'on top of genetics' – these processes control which genes are expressed and when, but are not controlled by genes themselves. The technology to study many epigenetic processes has only become widely available in the past decade, so we still have a great deal to learn about the role they play in health. What has become clear is that unlike genes, many epigenetic features can be readily influenced by factors such as diet and lifestyle. Epigenetics represents the link that ties our life experiences to how our genes are expressed.

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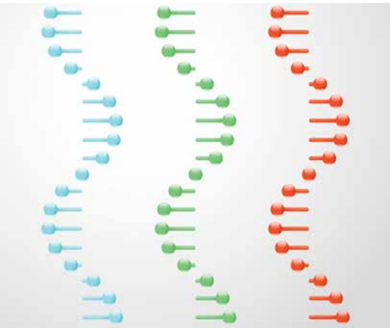

Dr Yi Li, an Assistant Professor of Nutrition at Texas A&M University-Kingsville, is working to understand how these external factors shift the activity inside our cells in hopes of identifying targets for treatments that could someday help people struggling with chronic metabolic diseases. He explains, ‘I have been trying to address how endoplasmic reticulum stress and epigenetic modifications induced by nutrition factors, including elevated blood lipid and glucose levels, are involved in regulation of genes related with development of obesity and type 2 diabetes.’

## Managing Stress

Dr Li’s fascination with the inner workings of the cell and its role in chronic disease began during his graduate work on the endoplasmic reticulum (ER). The ER is a cellular organelle that resides in every cell in your body. Along the curved walls of the ER, your cells build the proteins and fats that influence nearly every activity that occurs in your body. The majority of your hormones, neurotransmitters, and the building blocks for your cells are manufactured in the ER. Proper function of the ER is critical for cellular health, so when the organelle becomes distressed it can cause the cell to shut down and even die.

Transcription factors are a type of proteins with the ability to start the process of translating genes into new proteins. Dr Li’s ER research focused on a group of transcription factors that are often involved in metabolism and stress responses. He found during stressful events, such as cellular starvation, one of these factors, known as C/EBPß, is synthesised using the genetic information from one single gene as two isoforms: LIP, a transcription repressor and LAP, a transcription activator. Early during a stress event levels of the two factors remained similar, but as stress wore on, the transcription repressing factor became more prevalent under some situations. Ultimately this combination of LAP and LIP began to repress the expression of factors that are protective against the effects of stress, while allowing genes that induce cell death to be translated. In adipose tissue, the levels of LAP and LIP isoforms of C/EBPß are regulated by ER stress and they are subsequently involved in regulation of other genes functioning in adipogenesis in development of obesity.

Dr Li’s results demonstrate how responses to metabolic stress are complex and can damage cells over time, as well as identify potential targets, such as LIP, for stress preventative treatments.

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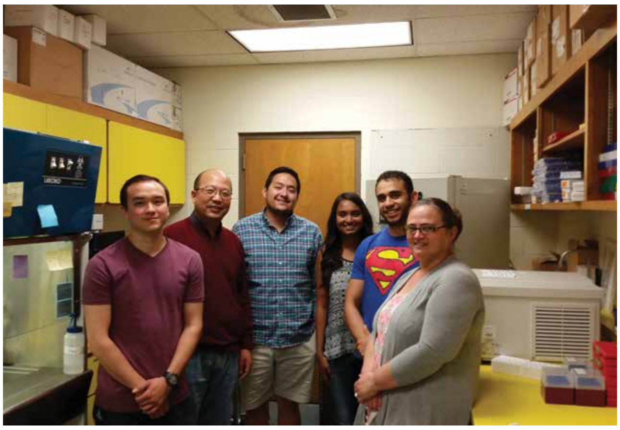

**Epigenetics and Obesity**

As Dr Li’s career has progressed, he has become interested in other cellular mechanisms that modulate short term cellular responses to changing conditions, particularly those that are involved in obesity. He has shifted his focus to epigenetics in hopes of understanding how these processes that alter gene expression are influencing the cell. Dr Li’s work focuses on two key epigenetic processes: DNA methylation and microRNAs (miRNA).

DNA methylation occurs when a methyl compound attaches to a cytosine – one of the four nucleotides that compose DNA. Methylated DNA is often expressed less frequently than its unmethylated counterparts. Numerous studies have demonstrated that methylation is influenced by changes in nutrition and exercise, along with other environmental factors.

Messenger RNA (mRNA) is intermediary between DNA and the cellular components that build proteins. During protein synthesis, mRNA copies of a gene are made and then transported to the ER for translation into a protein. miRNA are tiny snippets of RNA that alter gene expression by interfering with this process, usually by binding with the RNA copy of the gene and rendering it useless. As with DNA methylation, miRNA usually serves to decrease the expression of a gene.

While epigenetic processes such as DNA methylation and miRNA production can be influenced by events that occur during your life, they can also potentially be passed on to future generations. Not all epigenetic marks can be passed to children, but those that can have a strong chance of influencing childhood, and subsequent adult, health. Dr Li is interested in determining which epigenetic factors could potentially pass to an infant and place the child at higher risk for obesity. His current work is identifying methylation and miRNA markers that are associated with obesity in adults, determining their function in the cell, and finding if it is possible for these markers to be passed on to the next generation.

**Shaping the Future of Preventative Medicine**

In a five-year project plan, Dr Li and his team are planning to track the health of obese parents and their new born children to identify how these factors come together to shape childhood risk of obesity. In preliminary studies, Dr Li has made some critical discoveries that could shape how we approach childhood health. He describes, ‘In recent years, we have revealed that saturated fatty acids and polyunsaturated fatty acids differentially regulate genes involved in adipogenesis via epigenetic modifications.’

Put simply, Dr Li has demonstrated that exposure to saturated and polyunsaturated fats shift epigenetic mechanisms in the cell that play a role in the formation of new fat cells. He has found evidence that changes in both DNA methylation and miRNA activity take place in response to these nutritional events, influencing both metabolism and fat cell growth. Interestingly, many of the same factors involved in ER stress are influenced by these diet-induced epigenetic changes. If it is found that these changes can be passed on to future generations, it could hold the key to preventative interventions for children at high risk of developing obesity.

**Building a Healthier Future**

As our understanding of the relationship between our life experiences and the intricate workings of our cells deepens, it has become clear that genetics alone will not solve the world’s health problems. Innovative research in epigenetics and cell biology will reveal clues about how our environments shape our health and how that influences the health of our children. Dr Li’s research program will provide a foundation for future treatments to prevent obesity and other metabolic conditions in the next generation.

# Meet the researcher

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Dr Yi Li obtained his PhD in Nutritional Biochemistry from Case Western Reserve University (Cleveland, Ohio, USA) in 2009. The focus of his doctoral work was regulation of gene expression by endoplasmic reticulum stress. Following postdoctoral positions at Yale School of Medicine (New Haven, Connecticut, USA) and Duke University (Durham, North Carolina, USA), Dr Li joined the faculty of Human Nutrition program at Texas A&M University-Kingsville, where he currently serves as an Assistant Professor of Human Nutrition. Dr Li's current work focuses on nutrition induced epigenetic modifications that regulate gene expression in obesity and type 2 diabetes. Dr Li is an active research supervisor and serves on the editorial boards of several journals in his field of expertise as part of his ongoing contribution to science.

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## KEY COLLABORATORS

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## FURTHER READING

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