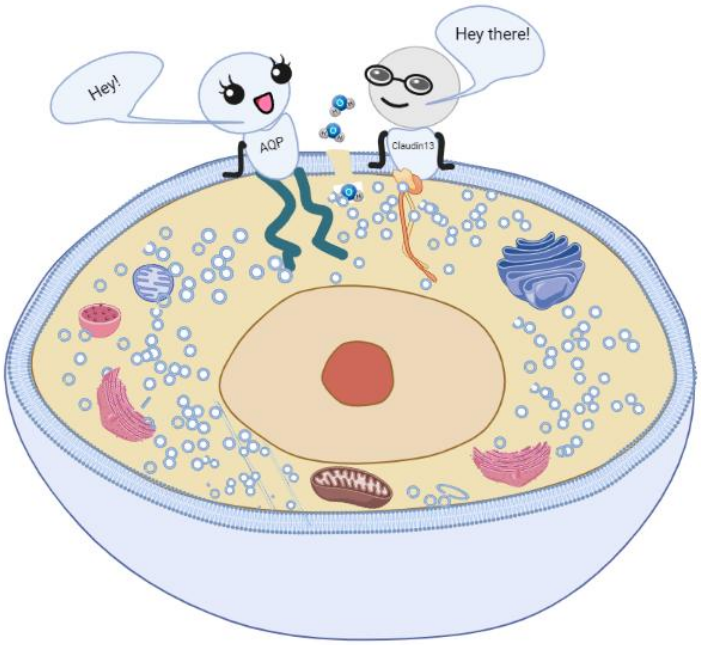
Diving in the Pool of Water Channels

`Can you guess who is a tiny hero in the theatre of life? I went into a flashback of a conversation I had with my friend (claudin-3, also a protein in a cell membrane). One fine evening, we were sitting at the edge of the cell membrane, talking about the human body and its complex structure, when he asked me this question. The cell, I answered cheerfully while swinging my legs in the jelly-like cytoplasm. Well, I knew a cell is a basic unit of life, and many years ago life originated from a single cell. The cell is our chief for whom all biomolecules such as DNA, RNA, enzymes, and proteins work together. In mammals 70% of a cell's weight is water. Water is virtually involved in all chemical reactions. It is very essential for all cellular activities, but have you ever wondered who is helping it to get inside the cells? Well, we are not surprised if you did not think of us. For years, we are serving as a plumbing system of cells by letting water move through us. Despite our ubiquitous presence and diverse roles, humans could not identify us, and it was thought a phenomenon of diffusion is helping in the exchange of water. Though it had been suspected for a long time that water movement is facilitated by channels or pores because it was obscure how kidney and red blood cells exchange a massive quantity of water just by diffusion.



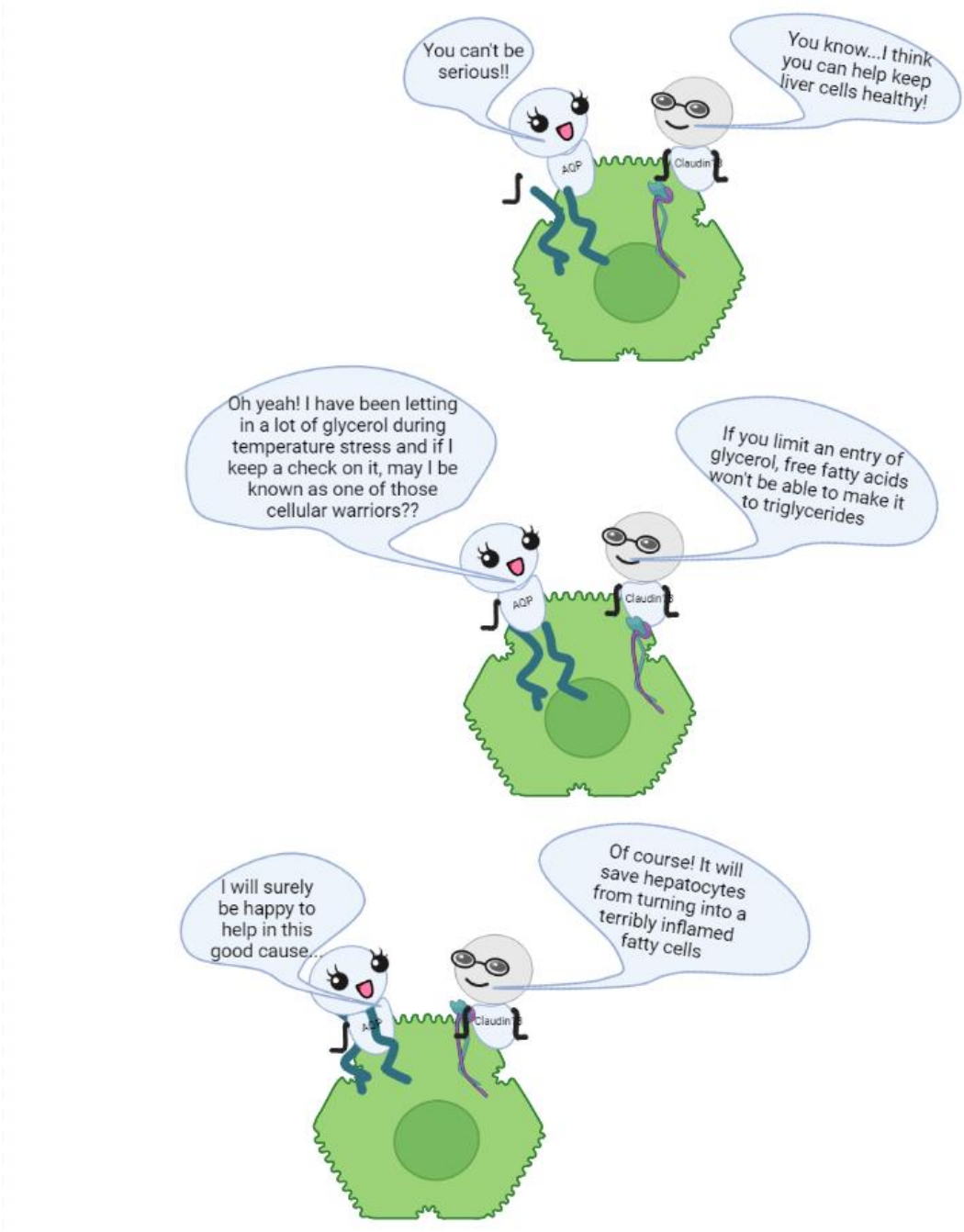
Fortunately, in 1992, researchers stumbled upon an unknown protein while studying Rhesus factor proteins in red blood cell membranes. Consistently, they got contaminating bands around 28kDa. When they dug a little deeper and also found its presence in kidney cells, they finally isolated and purified it. Because of its presence in these two cells which are highly

permeable to water, they wondered if this could be the long-sought water channel. To test the hypothesis, they placed two types of oocytes in distilled water, one test oocyte in which they injected mRNA encoding for unknown protein and the other one, a control oocyte which was without its mRNA. To their excitement, water flowed in and resulted in swelling and bursting of the test oocyte, whereas the control oocyte remained intact. The secret of the unknown protein was finally discovered, and we were isolated, purified, and given an identity as a molecule. Hurray! That was a crowning moment for us. They named us "AQUAPORINS (AQPs)" which could justify our efforts of letting water pass through us which maintains cell shape, and osmotic pressure, and participate in many reactions taking place in cells. However, they soon realized we do not just let water pass through us, but we are also involved in the transport of glycerol, urea, and some other solutes. As the research progressed, new members were added to our family which were having the same signature amino acid sequence and now we are a family of 13 (AQP0-AQP12). In mammals, our 13 isoforms are expressed in a wide range of tissues and vital organs such as the liver, kidney, brain, spleen, intestine, etc. Based on what we let pass through us, we were grouped as classical aquaporin, permeable to water; aquaglyceroporin, permeable to small uncharged solutes like glycerol along with water, and; unorthodox aquaporin, its permeability is still unclear.

As usual, we were busy doing our job but got disturbed when a girl spun liver and adipose tissues at a very high speed and isolated us from the rest of the protein pool. It was fun, we had butterflies in our stomachs during the ride but at the same time, we were sad without our fellow proteins. We asked her, why did she isolate us. She told that she did not intend to trouble us but wanted to study our expression patterns in the liver and adipose tissues. We were excited to know more about her research as it involved us. She further told that she is studying our expression patterns during temperature stress in the bovine liver and wanted to know the metabolic changes in the body to deal with this stress.

We asked her, why bovine liver? She answered that the liver is a vital organ, it maintains homeostasis of important nutrients, synthesizes bile for solubilizing fats, and is also a body's detoxifier! She also told us that because we give a way for glycerol to pass through cell membranes, our involvement in the liver and adipose tissues is crucial. I knew glycerol is the carbon backbone of triglycerides (TGs) but did not know it is an important substrate for the control of fat accumulation. She told us, that mostly we are doing our job excellently which gives everyone energy for their routine work during conditions like fasting. In such situations, the fat present in adipose tissue is the major source of glycerol and free fatty acid (FFA) after

lipolysis which the liver can process to provide energy. But the trouble was when there was a higher influx of glycerol into the liver, especially from visceral adipocytes and we were not able to control the traffic. She told us that it is because we are letting all the glycerol into the liver, it can lead to the synthesis of TGs which get deposited and lead to a disease called “fatty liver”. It means animals have extra fat in the liver and it can lead to liver damage.



A similar situation arises during heat stress when fatty acid and carbohydrate metabolism is disturbed. Heat stress is not at all cool! This may result in the depletion of nutrients and energy sources. This also alters the physiology of an organism and affects multiple tissues while adapting itself to changing climatic conditions. These changes can be manifested at many levels including behavioural, molecular, genomic, transcriptomic, proteomic, and metabolomic levels.

We realized that the liver is at the center of the overall metabolism of an organism. She further told, that typically, when animals have decreased feed consumption under heat stress, the liver has to perform a major role in maintaining levels of circulating nutrients such as glucose, glycerol, and TGs. As a result, excess TGs in adipose tissue are hydrolyzed into free FFA and glycerol. These glycerol molecules are transported to the liver and if combined with FFA, form TG which may lead to many liver diseases in the bovines. Hepatic steatosis (fatty liver), common in post-parturient animals, is one such liver disease. This disease can have fatal consequences, including negative effects on the overall health, reproduction, and milk composition in bovines.

We felt very bad because we were putting the liver in trouble and we didn't even realize it. We told her that our intention was not to hurt anybody and asked if there is any way to mitigate this problem. She told that she is trying to address this issue and we have a great role to play in this good cause. In order to use such inhibitors, first studying our gene and protein expression along with oxidative stress biomarkers in the bovine liver and adipose tissues is essential. Since we are widely expressed in liver and adipose tissue, knowledge of our family members' expression and their regulation in heat stress will provide useful information for understanding the metabolic status of animals and the pathophysiology of liver diseases.

She is screening potential inhibitors which can bind our target amino acids and prevent diseases such as fatty liver in bovines by reducing the influx of glycerol. For this, she is studying the effect of various biologically active compounds found in plants called phytochemicals on bovine liver cells (hepatocytes). By culturing hepatocytes in a laboratory and treating them with these potential inhibitors at different concentrations can give us clues about potential modulators. These modulators could help reduce the influx of glycerol in hepatocytes and in turn TG accumulation. This can help keep the liver cells healthy and prevent them from turning into those terribly inflamed fatty cells.