Insulin resistance is a systemic defect that can simultaneously affect several tissues in the body and is a major factor in type 2 diabetes. There are many proposed causes of insulin resistance, but the precise underlying mechanisms that influence its long-term progression are still unclear. Mathematical models provide a way to study the role of potential mechanisms of dysfunction. In this talk, I will present mathematical models that describe how certain intracellular processes can contribute to reduced insulin signaling in skeletal muscle tissue. These models suggest that a perfect storm of environmental and genetic influences can guide the cell into an insulin-resistant state as a means of protection. I will also discuss simulation results of the models and implications for further health complications.