A prevalent problem around the world is the occurrence of metabolic diseases, such as diabetes and insulin resistance, which can result when expanding fat tissue becomes dysfunctional. Our lab and others have found that a key to having healthy fat tissue is for it to be supplied by a high number of small blood vessels, called capillaries. Generally, women are more protected from obesity related metabolic disease than men and we found previously that female mice had more capillaries in their fat. The goal of this study was to study the endothelial cells that make up the capillaries to find differences in how they behave male and female mice. To do this, we compared the transcriptomes of the endothelial cells taken from fat tissue of high fat fed male and female mice. Thousands of genes were differentially produced in male and female cells. When comparing the signaling pathways represented by these differentially produced genes, we found that the male capillary cells had enriched inflammation-related genes, while the female cells were enriched in genes related to cell maintenance and proliferation. These differences were maintained in cultured cells, showing that they exist regardless of environment. Female endothelial cells proliferated faster while male endothelial cells showed greater sensitivity to inflammatory signals. Beyond obesity, these sex-differences in gene expression were observed in aged endothelial cells, with male cells once again having higher levels of inflammation-related genes. Overall, our data indicate that endothelial cells of females better resist endothelial dysfunction caused by obesity or aging, as compared to males. These insights into the distinct molecular events that differ between male and female endothelial cells during the development of obesity can help to explain why females may remain healthier in these conditions.