Abstract

A sperm that fertilizes an egg has successfully survived multiple checkpoints within the female reproductive tract, termed pre-fertilization events. The leukocytic response is a pre-fertilization event in which sperm trigger an immunological response that promotes homing of circulating leukocytes to the uterine lumen to destroy the majority of sperm. Like in all mammalian cells, various glycoconjugates decorate the sperm surface. Sialic acids are very abundant at the sperm surface as these monosccharide cap the majority of glycan chains and have documented roles in regulating migration through cervical mucus, formation of the sperm oviductal reservoir, and sperm capacitation. However, the role of sperm sialic acids in the leukocytic reaction remains unknown. Sialic acids and their cognate endogenous ligands Siglecs (sialic acid-binding immunoglobulin-like lectins) play a pivotal role in regulating immune responses in many cellular and disease states. We sought to investigate the role of sperm sialic acids for inhibition of neutrophil activation, as neutrophils are one of the major immune cells of the leukocytic reaction. In addition, we sought to determine if Siglecs are expressed by human and mouse endometrium, as the endometrium has an established role initiating the leukocytic reaction. Surprisingly, capacitated, less sialylated sperm did not increase neutrophil activation *in vitro*. However, we identified the novel expression of Siglecs on the endometrium, their regulation by estrogen, and their interaction with sialylated sperm. Our data indicate that sperm sialic acids may interact with endometrial Siglecs to promote sperm survival during the leukocytic reaction.

Summary Figure: Sperm sialic acid and endometrial Siglecs may interact to modulate the female immune response to sperm.
Both human and the mouse endometrium express inhibitory Siglecs (Siglec-10 and Siglec-3, respectively). When bound by sialic acid on sperm, the expressed inhibitory Siglecs may inhibit the immune response of the endometrium by inhibiting the release of cytokines, complement or other pro-inflammatory proteins via SHP-1 signaling. Sperm may further directly interact with neutrophils and macrophages and inhibit their immune response.