How red blood cells (RBCs)' mechanical / physical properties are related to health and disease states? How does spleen’s mechanical filtering function play a key role in different RBC diseases? Recent progresses in nanomechanics tools in experiments and computer simulations enable unprecedented opportunities to address these questions in depth. RBCs are critical for human health as they transport oxygen as well as carbon dioxide in and out of every part of human body. A discocyte RBC has a diameter of about 8 micrometers, while it has to go through the smallest capillaries as small as 3-4 micrometers in diameter, or thin spleen interendothelial slits with a height of 1-2 micrometers or less. Due to the large distortion involved in passing through these tiny openings, a RBC has to maintain appreciable deformability throughout its lifespan. Red blood cell diseases, such as Plasmodium falciparum malaria, heredity spherocytosis and sickle cell disease, are known to alter the deformability and/or adhesion of the diseased RBCs, causing various complications in microcirculation. The presentation will focus on RBC’s mechanical property changes and morphological alterations versus spleen’s mechanical filtration function at different health and disease states. Our recent studies show that the spleen not only filters out RBCs with impaired deformability and abnormal shapes but also alters progressively the RBC geometries due to the disease-specific molecular defects in RBC membrane.