Skin interfaces directly with the outside world and as a result is equipped with variety of strategies to cope with environmental challenges. These include constant control of microorganisms residing on skin, such as bacteria or viruses, that are able to infect this organ and lead to skin pathology. Among molecules of potential relevance in skin barrier defense is small protein, secretory leukocyte protease inhibitor (SLPI). SLPI is present in healthy, and even more abundantly in a diseased skin, such as in people suffering from eczema. These people are often infected with bacteria or viruses. Here we propose to delineate previously uncharacterized roles for SLPI in cutaneous colonization and infection with microbes that are associated with skin pathology. Given an increasing number of infections caused by antibiotic-resistant microorganisms, it is important to fully understand how these microorganisms are tolerated or eliminated in skin microenvironment.