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When the kidney is stressed or damaged, it expresses a series of proteins that can be found in the urine. We discovered that the NGAL (Lipocalin2) gene is expressed by the TALH and the Collecting Ducts between three-six hours after damage, and its full length protein appears in the urine (uNGAL) in milligram/L quantities. The data derive from neonates, children, and adults (Annals of Int Medicine, 2008), as well as from mice and rats, and have been widely reproduced in studies that examine uNGAL as a biomarker of the inciting stimulus. Sepsis, particularly sepsis that induces overt kidney failure is the most inductive stimulus. Using our bioluminescent-fluorescent NGAL reporter mouse, we found that uNGAL is strictly dependent on the dose and timing of the stimulus to the kidney (Nature Medicine, 2011), and that among these stimuli, sepsis, especially leading to overt kidney failure, is its strongest inducer. These human and animal data raise the question of the origin, the molecular responsiveness, and the function of NGAL in the urogential system exposed to infection. Hypotheses In this R01 Renewal we have examined the hypothesis that uNGAL is an essential (and unrecognized) component of innate defense against urinary infections, and that its mechanism of action differs from most other components of the immune system. We propose that NGAL achieves bacteriostasis in the urinary tract by a novel mechanism of iron chelation, which prevents the transfer of iron from host to bacteria (R.Strong, Fred Hutchinson). NGAL recognizes iron that is specifically targeted to bacteria by “siderophores” and non-specifically targeted by metabolic product called catechol (NatureChemical Biology, 2010), the chemistry of which can withstand the rigorous environments of different segments of the urinary system. These hypotheses re-establish the well known, but perhaps dormant view that sequestration of iron is a critical mechanism of bacteriostasis. Moreover they invoke a new cell type in the defense of the urinary tract, the alpha-intercalated cell which is a sources of NGAL in both infection and in aseptic kidney stimuli. The data raise the question of the importance of these cells and urinary acidification in immune defense. In sum,using an infectious model we will investigate the origins of NGAL by use of NGAL-reporter mice and floxed-NGAL mice; the function of NGAL as an iron chelator by use of special mutant species of NGAL (in collaboration with R. Strong) and our conditional KO; and we will examine the role of the intercalated cell by cell specific KOs. We propose that these experiments explain why uNGAL is massively expressed in the damaged kidney and they test the notion that NGAL is a conserved defense against uro-gential infections regardless of the inducing stimulus.
