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Abstract
Urogenital tract infection is highly prevalent disease that annually afflicts more than 250 million people worldwide, with 90% of these infections caused by gram negative E. coli. We believe that the uroepithelia of the distal tubule detects and secretes a bacteriostatic molecule called neutrophil gelatinase-associated lipocalin (NGAL). We have shown that urinary NGAL (uNGAL) is expressed at mg/L levels after either septic or aseptic diseases of the kidney (Paragas, Nature Medicine 2011) and has two potential functions, epithelial growth and/or bacteriostasis. NGAL is critical to innate immunity because it binds siderophores which bacteria require to import iron. We were surprised to find that uNGAL was secreted specifically by the Intercalated Cell of the distal tubule (Paragas, Nature Medicine, 2011). Here we will examine hypothesis that an unrecognized function of the distal tubular cells of the kidney is to deliver the bacteriostatic protein, NGAL to the bladder from the alpha Intercalated Cell. We believe that NGAL is sufficient to inhibit iron acquisition from the urinary milieu as a previously unrecognized means to control bacterial growth. We will test this function in the urinary tract using a model of localized infection, transurethral bacterial injection, a well characterized mouse model of urinary tract infections (UTI). We will determine whether the intercalated cells are sufficient and necessary to inhibit a pathogenic strain of E. coli (CFT073) from colonizing the bladder by secreting NGAL. First we will examine the molecular actions of NGAL by studying whether its inhibition of bacterial growth depends on the expression of Enterochelin (Ent), the cognate siderophore of NGAL as well as the recognition sites for Ent in the NGAL calyx. Next we will test whether dietary and genetic modifications of distal tubular cells leads to more or less severe UTIs. We examine whether intercalated cells are necessary for NGAL secretion in a UTI using genetically modified mouse models. Finally we will use reporter mice to immuno-dissect the kidney to generate pure populations of distal tubular cells by FACS for ChiP analysis of NGAL transcription factors. These data are of great significance to the millions of people who suffer from acute and chronic urinary tract infections worldwide and they may permit the development of novel bacteriostatic therapeutics based on NGAL to complement antibacterial agents.