Gene Therapy (2013) **20,** 119 – 120

www.nature.com/gt

NEWS AND COMMENTARY

Cathelicidin gene therapy for colitis

Cathelicidin gene therapy: a new therapeutic option in ulcerative colitis and beyond?

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Gene Therapy (2013) **20,** 119–120; doi:10.1038/gt.2012.23; published online 29 March 2012

Cathelicidins are natural antimicrobial peptides synthesized and stored in neutrophils, macrophages and also in epithelial cells of gut, skin, cornea and lungs.[1-4] Cathelicidins are present in all mammalian species and exert a potent, broad-spectrum antimicrobial activity against bacteria, viruses, fungi and some parasites by disrupting the membranes of these microorganisms.[1-3] In mice, the cathelicidin cathelin-related antimicrobial peptide (CRAMP) is encoded by the gene *Cnlp*. In humans, the cathelicidin LL-37 is encoded by the gene *camp*.[1-3,5]

Cathelicidins have a critical role in mammalian innate immune defense against invasive bacterial and viral infections; in addition, they regulate adaptive immune responses by recruiting or activating immune cells.[1-3,5-8] A recent study showed a new role for mouse cathelicidin mCRAMP in the adaptive immune response by demonstrating that cathelicidin can alter T-cell-dependent activation of the humoral response *in vivo* and thus modulate the activities of both B and T lymphocytes.[8] In addition, cathelicidins have been shown to modulate many physiological processes that involve non-immune cells, such as activation of wound healing, re-epithelialization, angiogenesis, cartilage remodeling and so on.[1-4]

Cathelicidins are constitutively expressed at baseline in neutrophils and macrophages and epithelial cells of gastrointestinal tract, lungs and skin, where they form a defense barrier against pathogen overgrowth and invasion.[1,2,5-7] Cathelicidin expression is regulated at transcriptional, post-transcriptional and post-translational levels in a tissue-specific manner.[7] Vitamin D3 induces cathelicidin expression in keratinocytes and monocytes but not in colonic epithelial cells, whereas butyrate induces cathelicidin in colonic epithelia but not in keratinocytes or monocytes.[7]

Cathelicidins are stored as inactive precursor pro-peptides consisting of a well conserved N-terminal cathelin-like domain and a highly variable C-terminal antibacterial domain.[1,2] Enzymatic cleavage of the cathelin domain from the pro-peptide liberates the biologically active antimicrobial peptide.[1,2] These peptides not only have broad-spectrum antimicrobial activities, but also modulate inflammation by altering cytokine response and chemoattraction of inflammatory cells in diseased tissues.[1-4] In response to injury and/or infection cathelicidins are inducibly upregulated, which represents an adaptive defense mechanism.[4,5] Recent study indicates that, in colonic murine mucosa, bacterial DNA upregulates cathelicidin expression via Toll-like receptor 9 and the MAPK/Erk1/Erk2 pathway.[9] Due to their pleiotropic properties and actions, cathelicidins may contribute to immune pathology of chronic diseases that affect skin, gut and joints, in which cathelicidin expression is dysregulated.[5] The current literature suggests cathelicidin LL37 dysregulation in pathologic mechanisms of several chronic auto-immune or auto-inflammatory diseases.[5]

In relation to colitis, recent evidence indicates that colonic bacteria have a pathogenic role in intestinal inflammation.[10] Studies showed that germ-free animals do not develop intestinal inflammation.[10] It is well-established that the interaction between the intestinal flora and the mucosal defense system has a role in initiating inflammatory bowel disease and impairment of healing.[10] Cathelicidin produced by colonic epithelial cells may have an important role in innate defense against epithelial colonization with epithelial cell pathogens.[6]

In 2007, Professor Cho's group demonstrated for the first time that topical, intracolonic administration of synthetic mouse cathelicidin (mCRAMP) significantly prevents development of experimental, dextran sulfate sodium (DSS)-induced ulcerative colitis in mice.[11] Cathelicidin treatment significantly reduced the number of fecal bacteria, reversed the decrease in mucus thickness by upregulating the expression of the mucin MUC1-4 genes and reduced DDS-induced apoptosis and neutrophil infiltration.[11]

In a paper in this issue of *Gene Therapy*, Professor Cho's group reports two novel, important findings: one pertaining to the function of mCRAMP in colonic protection in mice, and the second, a successful prevention of experimental, DSS-induced colitis by local gene therapy with intrarectal administration of a mCRAMP-encoding plasmid.[12] The authors demonstrated that cathelicidin-knockout (*Cnlp−/−*) mice have significantly increased and exaggerated responses to DDS challenge (vs wild-type mice).[12] These included more severe colitis symptoms, more extensive mucosal injury, higher levels of interleukin-1β and tumor necrosis factor-α, increased number of neutrophils and apoptotic cells; and reduced mucus secretion and impaired mucin gene expression in the colon of DSS-challenged *Cnlp−/−* mice vs wild-type mice.[12] Importantly, all these abnormalities were significantly reversed by the intrarectal administration of mCRAMP or gene therapy using the mCRAMP expression plasmid.[12] The latter represents the first successful use of cathelicidin gene therapy for ulcerative colitis. These studies are important findings that provide a new mechanistic insight into colitis and pioneer a novel therapeutic approach to the healing of experimental ulcerative colitis. Moreover, the importance of these findings is further underscored by the fact that the pathogenesis and molecular mechanisms of ulcerative colitis are not fully understood and the current anti-inflammatory and biological therapies do not cure the disease and induce a long-term remission only in $<34\%$ of the patients. This indicates that other factors, for example, dysregula-

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tion of cathelicidin expression/function, may have important roles in the pathomechanism of ulcerative colitis.[13,14]

PERSPECTIVES AND FUTURE DIRECTIONS

Since cathelicidins are natural peptides expressed in human tissues, cathelicidin gene and/or recombinant protein therapy for the healing of ulcerative colitis in humans seems to be a very appealing approach. Theoretically, such therapy could also be used for chronic skin infection, chronic non-healing dermal ulcers, and chronic lung and urinary tract infections, especially those caused by antibiotic-resistant bacteria. The broad spectrum of cathelicidin antimicrobial activity, the low incidence of bacterial resistance and their function as immunomodulatory agents are attractive features of cathelicidins for their potential clinical use.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This paper was supported in part by VA Merit Review to AST.

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