Background

Innate Defense Regulators (IDRs) are a novel class of synthetic peptides with no antimicrobial activity that enhance the control of microbial infections while attenuating tissue damage and suppressing inflammation. The ability of IDRs to modulate the innate defense system renders them attractive drug candidates in therapeutic areas where harnessing the innate defenses would be beneficial.

IDRs have been shown to transiently increase local chemokine levels (CCL5 and TNFα) and to recruit neutrophils in a murine model of oral mucositis due to immunosuppression. Binding of IDRs to their intracellular protein target, p62 (sequestosome-1), is less effective in animals depleted of neutrophils, but abolished in animals depleted of macrophages/monocytes. Recently, the enhanced survival benefit conferred by IDR treatment has been shown in clinically relevant animal models of neutropenic sepsis after cyclophosphamide treatment. Simultaneously, protection of the gastrointestinal mucosal barrier due to IDR treatment was also demonstrated. Further investigations in animal models of mucositis, where pathogenesis is linked to the response of the innate defense system, have demonstrated that IDRs have significant efficacy in both oral and gut mucositis.

Innate immune responses are triggered in sentinel cells via TLR or NOD receptor sensing of pathogen or damage-associated molecular patterns. Binding of IDRs to its intracellular protein target, p62 (sequestosome-1), alters the signaling downstream of TLRs and NODs. IDRs have been shown to transiently increase local chemokine levels (CCL5 and TNFα), enhance macrophage recruitment to the site of infection and improve the resolution of bacterial infection alone or in conjunction with antibiotics. The anti-inflammatory effect of IDRs was maintained in annexin depleted of neutrophils, but abolished in animals depleted of macrophages/monocytes, indicating an important role for macrophages in IDR mediated host protection at the site of infection.

Results

IMX942 attenuates chemotheraphy-induced oral and gut mucositis

Expt 1: Duration of Severe Mucositis

Expt 1: Endoscopy (Colitis) Score

Expt 1: % Body Weight Each Day

-IMX942 has a beneficial effect on multiple modalities of oral and gastrointestinal mucositis; IMX942 treatment is dose proportional, and effective after damage is initiated.

-IMX942 attenuates gastrointestinal damage in a colitis model

-IMX942 attenuates colitis without the increased weight loss associated with steroid treatment; IMX942 treatment is effective after damage is initiated.

-IMX942 does not enhance tumor growth or interfere with tumor treatment

Cellular Mechanism of IMX942

-IMX942 protects against febrile neutropenia caused by infection.

-IMX942 protects against oral mucositis after chemotherapy or radiation treatment.

-IMX942 protects against gastrointestinal damage in models of chemotherapy-induced mucositis and DSS-induced colitis.

-IMX942 does not enhance tumor growth or interfere with tumor treatment.

Conclusions

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