Candidalysin: Anti-fungal target and immunotherapeutic candidate

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Technology description

The Problem

Candida albicans is an opportunistic fungal pathogen, which normally exists as a commensal of the oral cavity and gastrointestinal tracts and frequently causes of superficial vaginitis infections. Moreover, common clinical procedures, such as gastrointestinal surgery, implantation of a central venous catheter or antibiotic treatment are major risk factors for life-threatening systemic candidiasis. Systemic candidiasis is now the third most common cause of hospital-acquired bloodstream infections and is often fatal, having 30–50% mortality which equates to ~100,000 deaths/year. Damage of host cells and uncontrolled immune activation are the hallmarks of several diseases caused by C. albicans. In the USA, yearly healthcare costs for fungal infections are $3 billion, of which Candida infections account for $2 billion. EU healthcare costs are estimated to be similar. Therefore, Candida pathogens carry an immense health burden and represent a major socio-economic challenge for worldwide communities.

The Solution

It is known that expression of the Candida gene ECE1 (extent of cell elongation 1) is upregulated during hypha formation and that the gene’ s product, Ece1, can be proteolytically processed by Kex2 into eight peptide fragments. The inventors have now found that a single 31 amino acid proteolytic fragment of Ece1 (fragment 3; termed Candidalysin) acts both as a novel peptide pore-forming toxin and as an immunostimulant. No truncations have been found that produce cell lysis or inflammatory responses in epithelial cells, although the fragment’ s carboxy-terminal K residue appear to be important for membrane interactions and damage induction, but not its immunostimulatory function. This opens a therapeutic window in which protective immunity may be generated without triggering damage.

To conclude, neutralisation of Candidalysin has the strong potential to prevent not only host damage during C. albicans infections but also deleterious inflammatory responses. Data obtained using multiple approaches supports Candidalysin representing a very promising new therapeutic target to treat C. albicans infections. Additionally, a modified fragment can form the basis of an antigen or adjuvant to provide mucosal protection against C. albicans and related infectious agents. Finally there are a range of diagnostic applications for the peptide and the specific binding partners for it.

Keywords:

Candida

C. alibicans
candidiasis
fungal infection
Candidalysin
vaginitis
sepsis
systemic infection
anti-fungal
drug target
therapeutic
mucosal immunity
immunomodulation
vaccine
peptide fragment
antibody

Advantages

Candidalysinrepresents a very promising new therapeutic target to treat C. albicans infections, overcoming growing resistance to existing anti-fungals. As a vaccine candidate peptide 3 can be delivered via a number of routes; oral or vaginal delivery would be favoured if mucosal immunity was required and intravenous or intraperitoneal delivery might be preferred for systemic protection. Additionally, antibodies against Candidalysin might be used therapeutically to produce passive immunity. Application may be topical or, in the case or septicaemia, systemic.

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