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Andrei GUDKOV
Flagellin vs Radiation

http://www.theaustralian.news.com.au/story/0%2C25197%2C25797329-15084%2C00.html
The Australian **(July 18, 2009)**

New Drug Shields Against Radiation by Rabinovich

A medication that can protect people exposed to normally lethal doses of radiation from a nuclear or a "dirty" bomb has been developed, reports say.

In tests involving 650 monkeys exposed to radiation equivalent to that recorded during the Chernobyl nuclear reactor disaster in 1986, 70 per cent died while the rest suffered serious maladies, the newspaper *Yediot Achronot* said yesterday.

Of the group given anti-radiation shots, almost all survived and had no side effects. A test on humans not exposed to radiation showed none suffered side effects from the medication.

The medication was developed by Andrei Gudkov, chief scientific officer at Cleveland BioLabs in the US. Also involved was Israel's Elena Feinstein.

"We made a breakthrough that may save the lives of millions," Dr Gudkov was quoted as saying.

The medication has important implications in the treatment of cancer, the report said, since it permits use of more powerful radiation.

If the medication is given final approval by the Food and Drug Administration, which Dr Gudkov said would happen within two years, it could have a strategic impact, particularly for nations threatened with nuclear attack. Among the major fears in the West is not nuclear attack but "dirty bombs", which kill mostly by radiation.

Dr Gudkov conceived the idea in 2003 of using protein produced in bacteria found in the intestine to protect cells from radiation. "The medication works by suppressing the 'suicide mechanism' of cells hit by radiation," the newspaper said, "while enabling them to recover from the radiation-induced damages that prompted them to activate the suicide mechanism in the first place."

The medication is a preventative drug administered by one or several doses.

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http://en.wikipedia.org/wiki/Flagellin

Flagellin

Flagellin is a protein that arranges itself in a hollow cylinder to form the filament in bacterial flagellum. It has a mass of about 30,000 to 60,000 daltons. Flagellin is the principal substituent of bacterial flagellum, and is present in large amounts on nearly all flagellated bacteria.

Structure

The structure of flagellin is responsible for the helical shape of the flagellar filament, which is important for its proper function.

The N- and C-termini of flagellin form the inner core of the flagellin protein, and is responsible for flagellin's ability to polymerize into a filament. The central portion of the protein makes up the outer surface of the flagellar filament. While the termini of the protein is quite similar between all bacterial flagellins, the central portion is wildly variable.

Immune response

In mammals

Mammals often have acquired immune responses (T-cell and antibody responses) to flagellated bacterium occurs frequently to flagellar antigens. Some bacteria are able to switch between multiple flagellin genes in order to evade this response.

The propensity of the immune response to flagellin may be explained by two facts:

First, flagellin is an extremely abundant protein in flagellated bacteria.
Secondly, there exists a specific innate immune receptor that recognizes flagellin, Toll-like receptor 5 (TLR5).

In plants

In addition a 22 amino acid sequence (flg22) of the conserved N-terminal part of flagellin is known to activate plant defence mechanisms. Flagellin perception in Arabidopsis thaliana functions via the receptor-like-kinase, FLS2 (flagellin-sensitive-2)). Mitogen-activated-protein-kinases (MAPK) acts as signalling compounds and more than 900 genes are affected upon flg22 treatment.

Pre-stimulation with a synthetic flg22-peptide led to enhanced resistance against bacterial invaders.

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http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Flagellin

MeSH Heading -- Flagellin
Tree Number -- D12.776.097.380
Annotation - a bact protein
Scope Note -- A protein with a molecular weight of 40,000 isolated from bacterial flagella. At appropriate pH and salt concentration, three flagellin monomers can spontaneously reaggregate to form structures which appear identical to intact flagella.

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http://www.ncbi.nlm.nih.gov/pubmed/11489966
J Immunol. 2001 Aug 15;167(4):1882-5

Bacterial flagellin activates basolaterally expressed TLR5 to induce epithelial proinflammatory gene expression.

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Flagellin, the structural component of bacterial flagella, is secreted by pathogenic and commensal bacteria. Flagellin activates proinflammatory gene expression in intestinal epithelia. However, only flagellin that contacts basolateral epithelial surfaces is proinflammatory; apical flagellin has no effect. Pathogenic Salmonella, but not commensal Escherichia coli, translocate flagellin across epithelia, thus activating epithelial proinflammatory gene expression. Investigating how epithelia detect flagellin revealed that cell surface expression of Toll-like receptor 5 (TLR5) conferred NF-kappaB gene expression in response to flagellin. The response depended on both extracellular leucine-rich repeats and intracellular Toll/IL-1R homology region of TLR5 as well as the adaptor protein MyD88. Furthermore, immunolocalization and cell surface-selective biotinylation revealed that TLR5 is expressed exclusively on the basolateral surface of intestinal epithelia, thus providing a molecular basis for the polarity of this innate immune response. Thus, detection of flagellin by basolateral TLR5 mediates epithelial-driven inflammatory responses to Salmonella.

WO2005056042
METHODS OF PROTECTING AGAINST RADIATION USING FLAGELLIN

Abstract --The invention relates to a method of protecting a mammal against radiation comprising administering said mammal a composition containing flagellin.

Also published as: WO2005056042 // WO2005056055 // WO2005056055 // WO2005057218
