UNIVERSITAT DE BARCELONA

SOLEMNE INVESTIDURA DE
DOCTOR *HONORIS CAUSA*
al professor

Roland Benz

Discurs de presentació del professor
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DISCURS DEL PROFESSOR
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Bacterial Protein Toxins and Humans, Status and Perspectives

Rector Magnífic de la Universitat de Barcelona,
dignissimes autoritats,
professors i professores,
alumnes,
senyores i senyors,

La meva ignorància de la vostra llengua m'impedeix fer el meu parlament en català; tampoc no puc fer-lo en castellà i, per tant, m'ha semblat oportú triar l'anglès, que és una llengua més universalment coneguda que l'alemany.

Bacterial protein toxins represent virulence factors of bacteria. They are delivered to mammals, including humans, during the process of bacterial infection in the eukaryotic host. Bacterial toxins are the cause of many different diseases. Prominent examples are plague, typhoid fever, cholera and others, which over history have caused epidemics that have killed thousands of humans. These diseases should not be confused with viral infections such as smallpox or measles, which have also caused epidemics over the centuries, killing thousands of human beings. In the 17th century, bacterial epidemics killed more humans than the Thirty Years' War, which involved not only Germany, France and Sweden but also Spain and other European countries. This war laid waste to areas throughout Europe but particularly in Germany. But this was not the only century with thousands of people killed by plague or Black Death, caused by *Yersinia pestis*. The first plague pandemic probably began in Central Asia and spread to Europe by the middle of the 14th century. The infection was transmitted by rodents and fleas but also by direct contact between humans. The total number of deaths in Europe alone from the first pandemic is estimated at 20 million people. This means that the Black Death is estimated to have killed between a third and two-thirds of Europe's population. It is noteworthy that the first pandemic resulted in widespread persecution of minorities, in particular of the Jews, and pogroms were frequent. Throughout history we have knowledge of more than 100 plague epidemics sweeping across Europe until the 1700s. The strains that caused the different epidemics have been iden-

tified. After the 1700s the infections became rarer although even nowadays certain cases have been recorded, caused by close contact between humans and rodents. Virulence factors of *Yersinia* strains are the Yops, a class of bacterial protein toxins that are delivered from bacterial cells to eukaryotic cells during close contact by a special type of export system. This type III secretion/translocation system mediates secretion and injection of anti-host factors into eukaryotic cells via a contact dependent mechanism.

A bacterial infection of more modern times is Typhoid fever, also known as enteric fever. This is a disease caused by the bacterium *Salmonella enterica serovar typhi*. The infection is transmitted by the fecal-oral route, by food or water contaminated with feces from infected people. The bacteria reside first in the blood stream and then in the digestive tract, causing violent diarrhea that can lead to death. Although typhoid fever became more frequent after the accumulation of humans in big cities, combined with the lack of hygiene, it probably had a great impact in historical times as well. The Golden Age of Pericles and Athens ended around 430–426 B.C. because of an epidemic, a devastating plague, probably typhoid fever. This epidemic killed one third of the population of Athens, including their leader Pericles. Sparta became the master of Greece and Athens' dominance of the ancient world ended. The ancient historian Thucydides also suffered from the disease, but he survived to write about it. His writings describe this outbreak, which, according to medical scientists, was probably epidemic typhus. This supposition is supported by the poor public health conditions of the time, because the whole population of Attica was besieged inside the Long Walls. In the 19th century typhoid fever was, as already mentioned, very frequent because of the accumulation of humans in the big cities and the poor hygiene. There was a high mortality rate in big cities: for example in 1891 the typhoid death rate was 174 per 100,000 persons in Chicago. Other cities in Spain and Germany reported similar rates.

Another modern infectious disease is cholera, caused by the Gram-negative bacteria *Vibrio cholerae*. The virulence factor is cholera toxin, a bacterial protein, whose action on the small intestine is responsible for the characteristic massive diarrhea caused by the disease. In its most severe forms, cholera is one of the most rapidly fatal illnesses known: healthy persons may become hypotensive within an hour of the onset of symptoms and may die within 2-3 hours if no treatment is provided. Rehydration treatment is essential; other-

wise, the disease progresses from the first liquid stool to shock in 4-12 hours, with death following within days, sometimes within 18 hours. The origin of cholera is believed to be the Indian subcontinent, where rivers such as the Ganges as a contamination reservoir. In the 19th century it spread by trade routes (both land and sea) to Russia, then to Western Europe, and from Europe to North America. As many as 5 cholera pandemics occurred in the 19th century and routinely killed thousands of people in Europe, Russia and North America. The pandemic in the early 20th century had little effect in Europe and North America because of advances in public health, but Russia was badly affected again. Cholera is now no longer considered an issue in Europe and North America, due to the filtering and chlorination of the water supply.

Bacillus anthracis is a Gram-positive, facultatively anaerobic, rod-shaped bacterium of the genus *Bacillus*. This natural soil-dwelling organism is able to form endospores. Under conditions of environmental stress, *B. anthracis* bacteria naturally produce endospores which remain in the soil and can survive for decades in this state. When ingested by cattle, sheep, or other herbivores, the bacteria begin to reproduce inside the animal and eventually kill it, and then continue to reproduce in its carcass. Once the nutrients are exhausted, new endospores are produced and the cycle repeats itself. This means that *B. anthracis* was originally an animal disease. *B. anthracis* was the first bacterium conclusively demonstrated to cause disease, by Robert Koch in 1877. The species name *anthracis* is from the Greek *anthrakis*, meaning *coal* and referring to the most common form of the disease, cutaneous Anthrax, in which large black skin lesions are formed. Anthrax can be highly lethal for animals and human beings when they come into contact with endospores. The main virulence factor of *Bacillus anthracis* is the Anthrax toxin complex. The plasmid-encoded tripartite Anthrax toxin comprises a receptor-binding moiety termed protective antigen (PA), because antibodies against PA inhibit intoxication by Anthrax and two enzymatically active components, edema factor (EF) and lethal factor (LF). EF and LF act on intracellular targets. EF is a calcium and calmodulin-dependent adenylate-cyclase (89 kDa) which causes a dramatic increase in the intracellular cAMP level, altering water homeostasis and intracellular signaling. In addition, EF is believed to be responsible for the edema found in cutaneous Anthrax. LF is a highly specific zinc metalloprotease (90 kDa) which removes the N-terminal tail of mitogen-activated protein kinase kinases (MAPKKs).