Laudatio
von
Prof. Dr. Hans Wigzell

anlässlich der Verleihung
des Paul Ehrlich- und Ludwig Darmstaedter-
Preises 2010 an

Prof. Dr. Charles Dinarello

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Es gilt das gesprochene Wort.

Charles Dinarello has received the prize of 2010 for his pioneering activities in defining the molecule Interleukin-1 and its role in regulation of inflammation and fever.

Fever is a reaction of the human body that we have all experienced.It is frequently an unpleasant reaction linked to infections.Certain diseases like malaria are well known to induce very high body temperatures.Certain forms of cancer are also linked to febrile stages.Long term febrile diseases are cause weight loss and other dysfunctions of the body.However,the consequences of fever with regard to fighting an acute infection are mostly considered to be of benefit to the host.For several infectious diseases this has also been verified under experimental conditions.In support for this beneficial effect poikilothermic animals ,like reptiles,which cannot regulate temperature by themselves try actively to increase their body temperatures when infected..Mant snakes try to hide themselves from being observed i.e. by preybirds.However,if you infect such a snake with a bacterial infection it will rapidly try to increase its body temperature by putting itself at the sunniest position possible even if this will bring the snake on top of a stone and thus in imminent danger of being taken by a preybird.In clinical situations reasonable levels of fever during an acute infection should thus be allowed or recommended to be maintained whereas very high temperatures causing potential harm by putting the host under too much stress should be reduced.The phenomen of inflammation is frequently observed as a heating of localized tissue,often associated with pain.There exist a multitude of more or less serious inflammatory diseases in man,many of which are chronic in nature.

When trying to understand what was inducing fever during infection scientists started in the 19th century to be able grow bacteria in vitro. and inject the bacteria or their soluble products into animals.Rabbits was the favourite animal species at the time.These animals also turned out to be particular sensitive to induction of fever by products produced by bacteria,for instance by a very common bacteria, E.coli.The soluble product(s) in the bacterial culture capable of inducing such fever attacks were subsequently given the name pyrogens,from the Greek word pyretos meaning fire.Intensive research over long periods of time was carried out to further purify and characterize the various pyrogens.We now know that there exist a number of various molecules produced by bacteria which when introduced into animals (and humans)will induce fever plus sometimes additional symtoms associated with normal infections by this bacterium.Significant success was made in particular in identifying pyrogenic molecules from E.coli and related bacteria. Highly purified lipopolysacharides,LPS,also called endotoxins, turned out to be extremely efficient pyrogens when introduced into animals .As such LPS molecules are quite widespread in nature,are sticky and resistant to destruction by various protocols including heating they are very common contaminants in various biological materia.The problem of contamination and the extremely low amounts of endotoxin required to induce fever required extensively sterile conditions if one wanted to study conditions of fever or inflammation in the absence of pyrogens coming from the outside of the body. .Using a technology to induce sterile inflammation in the absence of endotoxins it was possible to generate a local accumulation of certain white blood cells,s.c. granulocytes.When these granulocytes were collected they were shown to in

vitro release molecules which when injected back to other rabbits induced fever.It was thus clear the granulocytes can produce their own pyrogen ,subsequently called endogenous(=generated from within) pyrogens in contrast to LPS and other microbial exogenous (coming from outside) pyrogens.The pyrogren produced by granulocytes was called leukocytic endogenous pyrogen or LP.It was in defining the nature of this pyrogen as to structure(s) and function(s) in multiple pathological conditions that Charles Dinarello made his pioneering discoveries.

Leucocytic pyrogen,LP, is nowadays called interleukin-1 or IL-1.The interleukins belong to a group of proteins called cytokines.Cytokines are soluble proteins,mostly produced by cells of the immune system and endowed with strong pharmalogical activites activating or inacting immune and inflammatory cells as well as serving as growth factors for many cell types. Interleukins constitute the dominating group of cytokines and were initially given the name as being produced by various white blood cells but can be produced by other cells as well.

Charles Dinarell is a leading pioneer in the field of cytokines. He is renowned around the world for his outstanding work on solving some of the basic elements underlying the causes of fever and inflammation.Dinarello´s doctoral thesis in 1969 was on fever looking for how fever was produced by something produced within the body,the endogenous leukocytic pyrogen,or LP.In 1974 he was able to show that LP could be separated into two groups of molecules with pyrogenic activities,in modern terminology representing IL-1alpha and IL-1beta molecules.Working hard on the purification of the LP molecules to exclude contamination with exogenous pyrogenic endotoxins he was finally able to showin 1977 that indeed pure human LP by itself could induce high fever in rabbits even when used in such extremely low doses as 25 ng/kg of bodyweight.1 ng is one thousandmillion part of 1 g!Several activities reported by other research groups on endogenous pyrogens given unique names could during the late 70-ties be shown by Dinarello to in fact be generated by LP by using this purified human LÅ .In 1979 a meeting to introduce a global terminology for interleukins determined that LP should be called interleukin-1,IL-1,thus showing it to be the first of its kind.

However,,Dinarello and other research groups had during the 70-ties attributed a very wide variety of functions to LP/ IL-1 such as induction of fever,sleep,anorexia, muscle wasting,injury to the insulin-producing beta-cells of the pancreas ,lymphocyte activation and the hematological and hemodynamic changes typical of septic chock.Many scientists were still in 1979 highly skeptical that a a single molecule,IL-1,could really execute all these diverse biological activities.Dinarello thus decided to try to genetically clone the gene for IL-1.The work started in 1982 at a time when genetic cloning was quite new and difficult..Two years later,1984, Dinarello had cloned the gene for human IL-1 beta and was now starting to produce the single protein in recombinant form.The IL-1 beta protein could be shown to produce each of the biological properties that had previously been attributed to purified IL-1.Recombinant IL-1 was also injected into human beings showing that humans are extremely sensitive to the capacity of IL-1 to induce inflammatory reactions.These results did initiate a search for anti-IL-1 reagents to try to block pathological conditions in man attributed to IL-1.The article in 1984 by Dinarello describing the cloning of IL-1 beta andits

function was rightly considered by a review in the American leading journal Science 20 years later to have been ″the final point in establishing the identity of these long-sought pyrogenic substances causing the typical symtoms of septic chock-The results published did also provide encouragement for the development of cytokine inhibitors now in use in therapy of rheumatological disorders″.

Charles Dinarello has besides truely identifying IL-1 as the single causative agent for many important biological reactions also been the first to describe some of its unique activities.He was the first to describe that IL-1 beta is selectively cytotoxic for insulin-producing beta cells of the pancreas which has lead to a most a most active research area in the field of etiology of diabetes.Dinarello suggested that IL-1 blocking should protect the insulin-producing cells.This has now been found to be true in diabetes type II patients in some recent,most exciting clinical trials.Another of Dinarello´s pioneering findings was the demonstration that IL-1beta (which is induced by endotoxins from i.e..E.coli bacteria)also can function as a growtht factor for E.coli,a finding with great potential relevance.

Dinarello was also early involved in studies of another very active cytokine.,tumor necrosis-alpha,TNF.and could show that TNF-alpha is an efficient inducer of IL-1,with synergies between the activities of the two cytokines..The functions of IL-1 as a catalyst for generating inflammatory reactions and the close connection with TNF-alpha were all activities that made IL-1 an interesting target when trying to treat rheumatoid arthritis.Dinarello had himself been early in showing the presence of IL-1 in increased amounts in the joints from rheumatoid arthritis patients.Another research group had presented data showing that in humans there eixst a natural inhibitor protein of IL-1 function called anakinra.Dinarello was here involved in clinical trials showing that injections of anakinra to rheumatoid patients indeed had a beneficial curative effect.Anakinra is now a registered drug for the treatment of this disease.Akinra has recently also been shown by Dinarello to have an extraordinary therapeutic effect in a Still´s disease,mainly affecting children like a juvenile onset rheumatoid arthritis.The IL-1 inhibitor has now also proven to allow excellent and rapid treatment of aggressive gout and further expansion of diseases where blockage of IL-1by anakinra is reported to function is forthcoming.

Besides being directly involved in cytokine work Dinarello has also established himself as an authority in many other aspects of inflammation.Not known to many scientists are for instance the original works of Dinarello showing the function and capacity of unsaturated omega-3 fatty acids to function as anti-inflammatory substances in vivo in man.These findings and ramifications in relation to not only rheumatoid diseases but also atherosclerosis are considerable.

Charles Dinarello was born 1943.He is at present a most active Professor of Medicine at University of Colorado School of Medicine in Denver,Colorado,USA.
Amongst his latest findings are the observation that blockage of IL-1 would seem to cause a significant improval in the outcome after myocardial infarction.He continues to find new interleukins and interleukin-binding proteins.One of these,the IL-18 binding protein is already in clinical

trials.Recently,a new cytokine denoted IL-32,was discovered by Dinarello´s group.This cytokine is now under active research to further understand its activities and it looks like a potential target in the treatment of several pulmonary and autoimmune diseases.