



The evolutionary origins of inflammation

Leo Pruimboom MSc psychoneuroimmunologist, physiotherapist and physiologist

Inflammatory responses in humans are remarkably similar to those in other animals. Snakes, worms, rats and also non-human primates such as anthropoid apes are all subject to inflammatory responses. Nearly all animals, except for those who hibernate, react in an identical manner to both tissue damage and a lack of oxygen. This probably means that this response, which has been around for millions of years, must have conferred evolutionary benefits. In other words: the inflammatory response as we know it today has developed during an unimaginably long period of time, has therefore been put to the test extensively, and, as a result, has slowly been optimised. In fact, it is one of the main reasons animals - including humans - are still around today.

There are only a few medical problems that evolution has not 'resolved' and inflammation is one of them. Its mechanisms of action, which have an evolutionary origin, can therefore not be said to be either 'good' or 'bad'. It is much more fruitful to make a cost-benefit analysis of the different processes involved in an inflammatory response. When the benefits exceed the costs, the response will have to proceed unhampered. This is exactly what happens in a physiological inflammatory response. Only when this response transgresses the boundaries of the ingrained evolutionary response, is it advisable to take medical action, in particular with interventions that properly resolve the inflammatory process. This process of resolution is called 'resoleomics'. Evolution has made sure that the initiation of an inflammatory response to tissue damage is at the same time the beginning of its end. Evolution slowly polishes our genes, and

these genes are 'stubborn'. The genes that are responsible for a healthy inflammatory response have come into existence in specific environmental conditions that existed millions of years ago. These genes have not changed - it is the conditions in which they have to operate which have been revolutionised. Our 'stubborn' genes hardly take any notice of anti-inflammatory agents, bad nutrition, lack of physical exercise and other modern lifestyle changes introduced by man and consequently do not adapt to them. In fact, there is nothing wrong with inflammation; it is just that human beings no longer live in an environment that is optimally suited to their genes. In other words: to make sure inflammatory processes run as smoothly as they should, human beings should become more like they once were!

"I have called this principle, by which each slight variation, if useful, is preserved, by the term Natural Selection"

Charles Darwin, *The Origin of Species*

"Nature encourages no looseness, pardons no errors"

Ralph Waldo Emerson

Natural Selection

Natural selection is the process of filtering possibilities such that the fittest organisms survive rather than those most aesthetically pleasing. Natural selection is not a theory, it is a practical process taking place every day. A metaphor will suffice as an example: you arrive at your holiday home and you find unbreakable glasses, chairs you can dance on and beds as hard as steel. It is not pleasing to the eye,

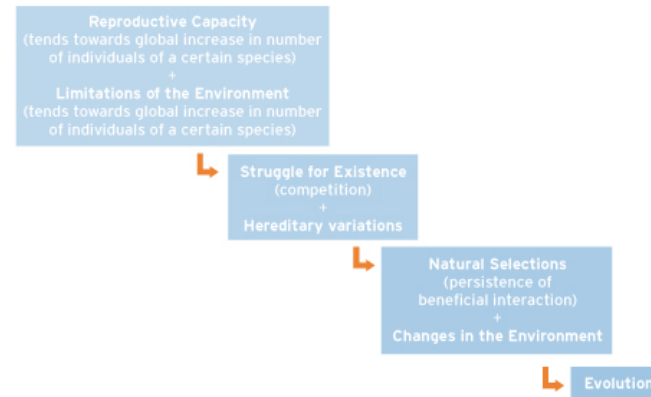


Figure 1. The mechanism of action of natural selection within the process of optimum functioning as an evolutionary trait

maybe you are not looking forward to living there for a few weeks, but the home is indestructible.

Natural selection has definitely been responsible for the specific inflammatory response in modern human beings. When this response proceeds well, it is able to heal every wound, but not without some unpleasant side effects. (the hard steel bed in the holiday home). Lack of oxygen (hypoxia), mechanical or chemical traumas, but also viral and bacterial activity elicit an inflammatory response that, firstly, has to make sure that the host is being protected from infections (which may be lethal) and, secondly, has to repair the damage.

The inflammatory response

During the first phase of inflammation the cytotoxic neutrophils are activated. The main goal of this phase is to exterminate any harmful microorganisms. However, there is also a possibility that more tissue becomes damaged. Cytotoxic responses are responsible for releasing substances that cause unpleasant sensations of pain.

However, this pain does have a function in that it protects damaged tissue from further damage (you cannot have one without the other). Within 12 - 36 hours following the inflammatory response, the cytotoxic cells disappear to make room for tissue repair cells.

When the body is 'allowed' to carry out the full inflammatory response, this will lead to optimum recovery of the damaged tissues, though be it not painless. This optimum response - repairing damage through an often unpleasant repair process - is what the science of resoleomics studies.

Resoleomics

Resoleomics may well be the oldest evolutionary response of all mechanisms of action currently known within the medical sciences. Even single-celled organisms have at their disposal a response that resembles the inflammatory response in humans. Therefore, it is inferred that resoleomics is at least 500 million years old. Resoleomics is carried out by a series of genes that has been preserved during those 500 million years - an impressive example of natural selection.

The inflammatory response consists of three phases that have been universally (and therefore evolutionarily) passed on to all humans:

Acute inflammatory response: initiated by the production of leukotriene B4 (figure 2). LtB4 activates migration of neutrophils towards the wound area to fight sepsis. Pain, heat, swelling and redness accompany this phase and are unpleasant side effects of an evolutionarily determined protective response.

Plateau phase: production of prostaglandin E2 inhibits the further production of LtB4-2 (see figure 2).

Neutrophils are not called upon anymore and are even slowly inhibited. Monocytes and macrophages infiltrate the wound to cytostatically phagocytose necrotic tissue. Pain sensation decreases somewhat and minimal physical movement is allowed.

End of inflammation: the eicosanoid switch (PgE2 has prevailed against LtB4) induces the production of lipoxins that stop the inflammatory response and activate tissue repair processes (evolution has prevailed). This optimum response originated during a time in evolution in which the preconditions were set for wound healing. These preconditions have taken shape under a specific intensity of physical movement (metabolic exhaustion), brief inflammatory situations and specific feeding habits. This means that mild stress responses have trained the human body to survive severe stress such as bacterial infections or major wounds. Nutrition used to be rich in salicylic acid' (especially common in tuberous plants) and essential fatty acids such as linoleic and linolenic acid (in the right proportions). Arachidonic acid from offal and eggs, as well as DHA and EPA from fish were also abundant. In addition, as a result of frequent exposure to sunlight, human beings experienced no lack of vitamin D. All these factors helped the human body support the eicosanoid switch (signalling the end of inflammation). This switch is vital to resoleomics (figure 2).

Frits Muskiet (Muskiet 2007) put it this way: "We are what we eat, but to become what we once were we will have to start eating again what we have been eating". However, evolution is not influenced exclusively by our nutrition. Also physical exercise, social interaction (safety and security), a certain amount of 'dirt and the need for reproduction (both direct and indirect reproduction — having children, but also caring for grandchildren, nephews, nieces, etc.) have made humans into the very adaptive Homo

sapiens they are today.- However, even though modern man adapts more quickly than scientists have ever thought possible, the rate of change in the environment of the past fifty years makes everybody more vulnerable to disease.

"Systemic unrest impacts repair processes, causing the inflammatory response to no longer proceed physiologically"

Local inflammatory responses are influenced by central stress axes such as the sympathetic stress axis (noradrenalin) and the hypothalamus-hypophysis-adrenal axis (cortisol). Normally, these axes aid in the optimisation of the local inflammatory response. After the response has been initiated, a large number of substances is produced that inform the central organs about the degree of success or failure of the response. Positive feedback here means that there was an optimum response (in accordance with evolution) and that the axes can be switched off. Now, resoleomics can do its work and can make the inflammatory response last as long as is necessary. Resoleomics are disturbed when the axes remain active — this is exactly what happens in circumstances that have little or no precedent in evolution.

Too little physical exercise, overabundant intake of food, eating too frequently, mobile phones and many other new stressors (including overabundant use of medicines, alcohol abuse, smoking and individualism) cause the said stress axes to become chronically activated. The systemic unrest this causes is an evolutionary newcomer; evolution has clearly selected in favour of stress axes that remain largely at rest and against those that are permanently activated. Subsequently, systemic unrest impacts repair processes at a cellular level (including resoleomics), causing the inflammatory response to stop proceeding physiologically. It may seem the response was wrong, but this is not at all the case. The response would have proceeded smoothly

if no alarm had been raised (unrest). In other words: to make the inflammatory response proceed smoothly, humans should exercise more, eat less often and eat different foods, as well as invest their time in building up a large social network. Or:

"To experience inflammation the way it once was experienced, we have to become who we were, eat what we used to eat and exercise how we used to exercise"

Summary and conclusion

Resoleomics is the physiological response to (possible) damage to the human body, including wound healing, microbial intruders and situations of hypoxia (including thrombosis). The physiological response consists of a primary inflammatory response that causes certain substances to be produced

which, in their turn, initiate the production of so-called stopping substances. Wound healing and microbial intruders are some of the oldest 'medical' problems of Homo sapiens; these problems have long since been solved by the process of natural selection during human evolution. Resoleomics is a universal process ingrained on both a genetic and epigenetic level. Resoleomics genes and gene activity have developed in circumstances that do no longer exist today. In people with chronic diseases it may seem as if the inflammatory response proceeds pathologically, which is far from the truth. The real problem with the inflammatory response is that it does not come to an end, as central stress axes are permanently active as a result of new environmental conditions. The solution is to create rest in the central axes, which requires humans to start eating what they used to eat, exercise how they used to exercise and live how they used to live.

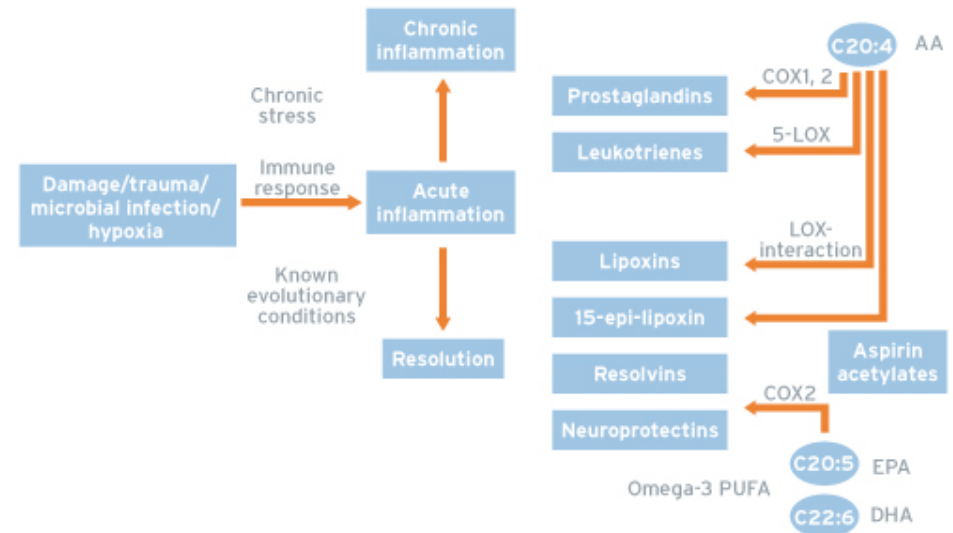


Figure 2. Resoleomics -resolution of inflammation succeeds when the environmental conditions have a precedent in evolution. Chronic stress is here taken to be the sum of unknown environmental conditions in which modern man lives.

"The inflammatory response does not come to an end because central stress axes are permanently activated"