DNA damage causes immune reaction and inflammation, linked to cancer development

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Nelson Gekara, Laboratory for Molecular Infection Medicine Sweden (MIMS), Credit: Umeå University

For the first time scientists from Umeå University show the importance of DNA damage in fine tuning of our innate immune system and hence the ability to mount the optimal inflammatory response to infections and other biological dangers. The study is published on 17th February in the very prestigious international journal *Immunity* (CellPress).

The research group of Nelson Gekara within the Laboratory for Molecular Infection Medicine Sweden (MIMS) at Umeå University is interested in understanding how the innate immune system, our first line of defense is regulated and how defects in the immune system contribute to infectious and inflammatory diseases. Our immune system does not lie idle waiting to be attacked before it responds. Even in the absence of infections, our immune system is in a constant state of alert. Among the immune mediators that are constantly produced at low levels and which keep our immune system awake are a group of factors called type I interferon. A very delicate balance in the production of type I interferons is essential for health: insufficient production results in susceptibility to viral infections, while excessive production normally leads to autoimmune/inflammatory diseases.

One of the questions Gekara´s lab has been studying is aimed to understand the signaling processes that control type I interferon production and in particular to identify the endogenous "danger signals" that constantly trigger basal production of interferons and therefore keep our immune system in a "ready to attack" state? The clue to this question came from a rare but complex disease called Ataxia telangiectasia (AT). This disease is characterized by multiple features including neurodegeneration, increased cancer risk, sterility and accelerated aging. Furthermore, AT patients are prone to various autoimmune/inflammatory syndromes. Currently there is no cure or specific treatment for this disease.

While studying immune cells from AT patients, in collaboration with

Torben Ek, medical doctor at Hallands hospital Halmstad, scientists in Gekara´s lab observed that AT patients cells produced abnormally high type I interferons spontaneously even in the absence of infections. Such cells were therefore able to mount a stronger and hence protective response against viruses, compared to those from healthy subjects which could not survive the infection. This very surprising observation gave the MIMS scientists inspiration to study the underlying processes on the molecular level. With the help of studies in genetically engineered mouse models, the researchers were able to decipher the immune signaling mechanisms more in detail. And they show for the first time that DNA breaks are the "endogenous danger signals" that trigger the basal type I interferon response that keeps our immune system alert.

DNA damage - Infection – Inflammation - Cancer

Our DNA, the home to ca 23.000 genes that control all aspects of our physiology is the most precious content in our body. DNA is under constant threat of damage from otherwise normal cellular events such as DNA replication, endogenous metabolic mutagens or damaging agents such as irradiation, UV light or environmental chemicals. Furthermore, many microbes are known to cause damage to DNA such as by directly inserting their DNA into the host DNA or by releasing mutagens which can react with and damage DNA. To mitigate this continuing threat, considerable amount of the housekeeping maintenance activities of the cell are devoted to DNA safety and integrity. Indeed one of the most ancient and highly conserved signaling molecules in eukaryotic life are those dedicated to the repair of DNA breaks. However, in the event of major DNA damages, such signaling molecules trigger a cell death program thus ensuring that damaged DNA is not passed on to daughter cells. Defects in DNA repair machinery normally increases chances that mutations in genes that control cells death will occur. And when that happens this often leads to uncontrolled cells growth and hence cancer development.

In AT patients, a central component in the DNA repair, the molecule ATM, is defective. Nelson Gekara and his colleagues were able to show that small DNA fragments generated from the DNA-breaks accumulate in the cytoplasm of AT patients' cells where they are recognized by innate immune receptors that normally detect viral DNA. This "false alarm" of viral invasion results in the production of type I interferon which in turn drives the innate immune system into an agitated state ready for a rapid and amplified response to danger signal. The upside of this chain of events is an enhanced and hence protective response to viral infections. The downside however is that such an agitated immune system is often hyper reactive and may account for severe inflammatory disease observed in AT patients.

This discovery of an unexpected link showing how genomic instability impacts our innate immune system provides a new perspective on the interconnection between infection, inflammatory disease and cancer development that may aid further clinical studies and eventually influence the management of these disease types.

"Our project is an example of how studies of relatively rare diseases can result in astonishing findings and discoveries that have impact on general understanding of cell regulation and signaling, in this case how DNA damage influences our innate immune system", continues Gekara who is grateful for the support from medical doctors and AT patients.

"Without the interest and support of medical doctors and the AT patients this study would not have been possible."

Dr Torben Ek, Hallands hospital Halmstad, supported the findings in the Gekara lab with clinical studies.

"Whereas no cure or specific treatment exists for AT, it has been observed that AT patients often exhibit hyperinflammatory features that

are suspected to contribute to the morbidity of the disease. In fact, some clinical studies have indicated that the progression of neurodegeneration one of the features of AT can be slowed down by anti-inflammatory therapy. The mechanisms behind such effect have however been unclear. These findings therefore provide us with vital mechanistic insights that may lead to better management of the disease", Torben Ek continues.

Nelson Gekara explains why he became interested in AT for his studies of the immune system.

"I think that immunity is not just a system designed to combat infections. This definition unfairly credits microbes as the sole source of biological danger that has driven the evolution of our immune system into what we know it to be today. A more inclusive definition of Immunity is a system evolved to recognize and respond to 'biological danger'. And this make danger from pathogenesis/parasitism quite a recent one in the evolutionary clock. The most persistent danger which predates parasitism and which our ancestors had to grapple with since the beginning of time is DNA damage. DNA´s troubled past is particularly evident from the fact that our DNA is littered with many retroviruses - endogenous viruses that invaded our genome and probably continue to influence various aspects of our physiology including the immune system in ways we still do not understand. Thus the need to recognize and respond to DNA damage could probably be one of the ancient immune reactions."

"To me it was just logical that in order to understand how the immune system functions it is important to go down to the roots: DNA damage, how is it recognized? What signaling molecules are involved and how defects in such molecules influence our immune system", Gekara explains.

And in the future Gekara and his group will now study in more detail the

link between inflammation and cancer.

"Inflammation is thought to play a key function for all stages of cancer development i e initiation, progression and dissemination. However the endogenous signals that trigger associated inflammation have been unclear. With this new information on how DNA breaks (as a result of genomic instability) triggers inflammation, the plan is to study the role of specific immune signaling pathways in cancer development and to explore how manipulation of such pathways could be translated into the management of cancer", the MIMS group leader says about his future plans.

More information: "DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity." *Immunity* Volume 42, Issue 2, p1–12, February 17, 2015. DOI: dx.doi.org/10.1016/j.immuni.2015.01.012

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