Researchers probe the enigma of healing element that is also the enemy

April 3 2013

The same factor in our immune system that is instrumental in enabling us to fight off severe and dangerous inflammatory ailments is also a player in doing the opposite at a later stage, causing the suppression of our immune response.

Why and how this happens and what can be done to mediate this process for the benefit of mankind is the subject of an article published online in the journal *Immunity* by Ph.D. student Moshe Sade-Feldman and Prof. Michal Baniyash of the Lautenberg Center for General and Tumor Immunology at the Institute for Medical Research Israel-Canada at the Hebrew University Faculty of Medicine.

Chronic inflammation poses a major global health problem and is common to different pathologies—such as autoimmune diseases (diabetes, rheumatoid arthritis, lupus and Crohn's), chronic inflammatory disorders, chronic infections (HIV, leprosy, leishmaniasis) and cancer. Cumulative data indicate that at a certain stage of each of these diseases, the immune system becomes suppressed and results in disease progression.

In their previous work, the Hebrew University researchers had shown that in the course of chronic inflammation, unique immune system cells with suppressive features termed myeloid derived suppressor cells (MDSCs) are generated in the bone marrow and migrate into the body's organs and blood, imposing a general immune suppression.

A complex network of inflammatory compounds persistently secreted by the body's normal or cancerous cells support MDSC accumulation, activation and suppressive functions. One of these compounds is tumor necrosis factor-a (TNF-a), which under acute immune responses (short episodes), displays beneficial effects in the initiation of immune responses directed against invading pathogens and tumor cells.

However, TNF-a also displays harmful features under chronic responses, as described in pathologies such as rheumatoid arthritis, psoriasis, type II diabetes, Crohn's disease and cancer, leading to complications and disease progression. Therefore, today several FDA- approved TNF-a blocking reagents are used in the clinic for the treatment of such pathologies.

What has remained unclear until now, however, is just how TNF-a plays its deleterious role in manipulating the host's immune system towards the generation of a suppressive environment.

In their work, the Hebrew University researchers discovered the mechanisms underlying the TNF-a function, a key to controlling this factor and manipulating it, perhaps, for the benefit of humans. Using experimental mouse models, they showed unequivocally how TNF-a is critical in the induction of immune suppression generated during chronic inflammation. The TNF-a was seen to directly affect the accumulation and suppressive function of MDSCs, leading to an impaired host's immune responses as reflected by the inability to respond against invading pathogens or against developing tumors.

Further, the direct role of how TNF-a works in humans was mimicked by injecting the FDA-approved anti-TNF-a drug, etanercept, into mice at the exacerbated stage of an inflammatory response, when MDSC accumulation was observed in the blood. The etanercept treatment changed the features of MDSCs and abolished their suppressive activity,

leading to the restoration of the host's immune function.

Taken together, the results show clearly how the TNF-a-mediated inflammatory response, whether acute or chronic, will dictate its beneficial or harmful consequence on the immune system. While during acute inflammation TNF-a is vital for immediate immune defense against pathogens and clearance of tumor cells, during chronic inflammation—under conditions where the host is unable to clear the pathogen or the tumor cells—TNF-a is harmful due to the induction of immune suppression.

These results, providing new insight into the relationship between TNF-a and the development of an immune suppression during chronic inflammation, may aid in the generation of better therapeutic strategies against various pathologies when elevated TNF-a and MDSC levels are detected, as seen, for example, in tumor growths.

More information: Sade-Feldman, M. et al. Tumor Necrosis Factor-α Blocks Differentiation and Enhances Suppressive Activity of Immature Myeloid Cells during Chronic Inflammation, *Immunity*, Volume 38, Issue 3, 541-554, 07 March 2013.

Provided by Hebrew University of Jerusalem