Autoimmune diseases are globally regarded as a consequence of the loss of tolerance against self-antigens. This view has guided our therapeutic efforts to increase the auto-reactive threshold using immunosuppressive drugs. This editorial aims at discussing the strategies to treat autoimmune flares from a different perspective, and in the light of recent molecular insights.

At present, the capacity of immunosuppressive drugs to maintain remission in autoimmune conditions is unquestioned. However, during flares of activity there is a completely different scenario, under which our first goal should probably be to kill over-reactive cells. This is because positive selected immune cells cannot easily be switched off, unless they are forced to die. It is, therefore, understandable that cytostatic agents, typically cyclophosphamide, yield so good results dampening severe flares, even when used at low dose to reduce toxicity. In contrast, doses of “selective” immunosuppressive drugs required to kill cells can get unacceptably high, in many occasions failing to provide a safer alternative.

On the other hand, too much killing could be dangerous. As it happens, not all patients show a good response to the so-called induction therapies, and the line between success and toxicity is very thin. In addition, drug regimens are frequently applied according to fixed protocols, e.g. during an established period of time, although sometimes we really do not know at which point the patient ceases to benefit from the therapy and if it can be safely withdrawn. On the whole, it seems clear that there are two distinct stages of disease that need different approaches, but still we need to decipher mechanisms concurrent during flares and find out when to stop cytostatic strategies.

The more we learn about the innate defence system, the more it looks that it greatly contributes to spark the flares of autoimmune diseases. My colleagues at the clinic usually remind me that not all autoimmune deregulation can be explained by germs. However, these provide a fine model to learn what can be going on in our patients during flares. Furthermore, the pathways triggered by the engagement of innate receptors help understand the importance of cell death in shutting down the activation process. Essentially, the debate about presence or absence of inductor pathogens is not so relevant in itself, as far as we accept that the activation of immune cells closely resembles the one evoked by intracellular microorganisms.

In order not to argue with my colleagues, let us consider that not germs in particular, but “perturbations inside immune cells” come to be detected by innate receptors. The latter will then trigger three types of responses: (1) the production of NF-kappaB driven pro-inflammatory genes, (2) the induction of type I interferons, and (3) the initiation of self-destruction programmes. These are straightforward mechanisms intended to erase the disturbing agent, create specific memory against future attacks and eliminate the igniting cell. In this regard, the self-destruction programmes of the immune system are a most effective way to terminate the activating signals emitted by disturbed cells. In addition, they eradicate germs that have made a shelter out of the intracellular environment, which the immune cell confers. As a matter of fact, many intracellular pathogens have ideated the so-called immune evasion mechanisms to protect this shelter and remain in latency. If the auto-destruction programmes fail, the carrier cell continues to struggle to get rid of the invader, in this manner adding more wood to the fire.

This rationale challenges the concept of loss of tolerance, suggesting instead that patients with autoimmune diseases probably bear a paradoxical excessive tolerance to own cell internal perturbations. In other words, they could have problems to carry out the programmes designed to erase intracellular pathogens, or to alternatively get the carrier cells killed. All indicates that in autoimmune diseases, the perturbed cells live abnormally long, and so does the invader as well. In this setting, application of cytostatic drugs helps eradicate the niche and break the vicious circle.

Of course, the solution provided by cytostatic strategies is transient, as it is thereafter the immune system from the host, which should add up for a favourable outcome. In this regard, the ability of phagocytes to clear dead cells needs to be intact. Also to consider is the leakage of germs upon cell death and their capacity to resist at the extracellular space until they can find another niche. This means that lymphocytes should be ready to battle an overt infection. Hence, the importance to carefully design our therapies, in order to avoid increasing the patient’s vulnerability. At this point, we should acknowledge the drawbacks of selective immunosuppressive drugs. If along with killing cells we add alterations

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to the normal function of lymphocytes, mechanisms of fighting microorganisms will be at stake. Perhaps, we should reconsider the use of therapies that potentially decrease natural killer (NK) functions, since in fact NK cells are trying to eliminate over-reactive cells and restore the balance. In this sense, it is attractive to suggest that actual targets during flares are over- rather than auto-reactive cells, both populations being not necessarily coincident. Also to bear in mind is that therapies decreasing levels of secreted IgM could hamper the removal of apoptotic cells. Thus, not only our strategy might favour overt infections, but also the formation of autoantibodies to epitopes showing up during apoptosis.

Since we need to implement mechanisms that are failing and try not to touch those that are working well, we have to learn how and which cell death processes are taking place in a particular setting. Globally, death can be classified into necrosis, heterophagy, and autophagy. The two latter terms imply digestion of the cell components, which can result from apoptosis (first case) or from own programmed destruction, while necrosis is associated to changes in permeability, and cell swelling. All these processes take place in a tightly regulated manner, and an expanding family of death-related terms has emerged as a result of the identification of killing machinery. Among them, RIP-mediated necroptosis, parthanatos, oxtosis, ferroptosis, NETosis, pyro necrosis, or pyroptosis have been coined to underline particular aspects characterising the deadly pathways, as recently reviewed by Vande Berghe. The surface receptor MHC class I related chain A (MICA) is induced by stress and intracellular pathogens and makes the cell visible for NK cells. Through the binding of MICA, NK cells help flagged cells undergo apoptosis. This pathway is up-regulated by retinoid acid, a fact that has been advantageously translated to treat cancer. Inactivation of MICA is used as immune evasion system by some pathogens, such as cytomegalovirus, which thus make sterile the efforts of NK cells to erase the infected cell. Interestingly, we have recently observed a suppression of MICA gene expression in peripheral blood mononuclear cells from a subgroup of patients with lupus. We are currently trying to decipher the underlying mechanism, but it appears that these patients show some kind of evasion strategy to NK surveillance, promoting the survival of perturbed mononuclear cells.

Autophagy is a homeostatic cell program that has attracted attention because of its participation in the elimination of intracellular altered products – or sources of intracellular disturbances. Autophagy involves fusion of late phagosomes with lysosomes and endosomal vesicles, and consists in a sequential process of digestion/degradation of unfolded proteins, microbiota, and stress-dependent organelles. The vitamin D receptor pathway and the activation of IL-1β contribute to the successful progression of autophagy. It turns out that an efficient autophagy usually prolongs cell survival, arrests cell growth at G1, and protects cells from apoptosis. Studies conducted with rapamycin – an activator of autophagy – have shown that the cell growth arrest is responsible both for its antifungal activity and the tolerogenic effect on lymphocytes. In this sense, the integrity of this homeostatic process may not only make the over-activation subside, but rescue the cell as well, a fact that makes it look as a very promising pathway to modulate in autoimmunity. Intriguingly, some available therapeu tic compounds can directly or indirectly affect the progression of autophagy, including estrogens and chloroquine, as well as drugs of common use, such as metformin.

It will take time to take full advantage of these processes at the bedside. First we would need to work out how the pieces fit together in each patient, so it would be necessary to find sensitive markers of the ongoing death pathways. We have already mentioned several candidates, although their utility in clinical practice has not been established so far. Between them, IL-1β appears as a master regulator of cytotoxicity and bactericidal activity. Soluble MICA has been found to act as a decoy receptor, so that its circulating levels could point to deficient NK functions. Important is the awareness of vitamin deficiencies since, as we have mentioned, both vitamin A deriva tives and 25-hydroxy vitamin D3 fuel regulatory death mechanisms. Our patients are especially prone to deficiencies of these vitamins, because they have been instructed into low-fat diets, the dread of intoxication, and sun protection. Finally, we could more frequently measure serum IgM levels, particularly in patients under B cell depleting strategies, to assess capacity of removal of apoptotic bodies.

In summary, all through these pages, I have argued for killing instead of disarming the immune system. However, not to forget is the fact that cell death is a principal source of inflammation related accrued damage. Killing and rescue should be, therefore, conveniently mixed to protect cells from indirect inflammation-derived injury. I would like to stress the need to consider adjuvant therapies such as the aforementioned vitamins and antimicrobial prophylaxis, whenever we use pure immunosuppressive drugs.

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**References**