A renaissance of interest in innate immunity: will new treatments for rheumatoid arthritis emerge?

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'…will the new insights being gained in innate immunity allow for further progress in the development of new treatments for diseases such as RA?'

As the old adage goes, if you think you know what's going on in any given situation, you haven't got a clue. The uncovering of the molecular and cellular basis of a disease such as rheumatoid arthritis (RA) has had many false dawns. When it seemed that prostaglandins held the answer to the question of what the central inflammatory mediators were, cytokines came along as important and bewilderingly complex drivers of disease. A clear pathogenic role for T lymphocytes suggested that the answer would be found in dysregulated adaptive immunity, with breakdown in tolerance to self antigens being blamed. This was also suggested from the genetic associations involving the MHC, whose role is to present processed antigens to T lymphocytes. The role of the B lymphocyte was also explored for a number of years, and has undergone a revival with the therapeutic effect of the B-lymphocyte-targeted agent rituximab [1]. However, those investigators whose primary interest lay in inflammation always felt that the answer would lie in innate immunity.

Innate immunity was usually seen as the poor relation of adaptive immunity [2]. Immunologists saw it as primitive (lowly creatures such as fruit flies and sea urchins only have innate immunity), crude (the mechanisms involve processes such as coagulation to trap the infectious agent or proteins such as lysozyme that burst open bacteria) and unsophisticated (no memory response, unlike the elegant and complex genetic rearrangements that give rise to memory T and B lymphocytes). Immunologists working on innate immunity were the Cinderellas of the field, staying at home whilst those interested in T and B cells went to the ball (or international conferences). However, the past 8 years or so have seen a remarkable renaissance in the study of innate immunity and, as we might expect, more and more complexities are being revealed [2–4]. Even more excitingly, the role of innate immunity in the pathogenesis of a multitude of inflammatory diseases continues to be determined. Insights from innate immunity give us what is effectively a 'step up' from cytokines and adaptive immunity, since the evidence so far indicates that it is the driver of all that comes next in both host defence and in the chronicity that is a signature of diseases such as RA. Receptors involved in innate immunity, when activated, are responsible for induction of all inflammatory mediators from cells such as macrophages. As we unravel this system, will the new insights being gained allow for further progress in the development of new treatments for diseases such as RA?

Where does innate immunity fit into the immune system and immune-mediated disease? Despite recent substantial clinical advances in the treatment of diseases such as RA, with the advent of biologics to target cytokines (notably TNF), B cells (the aforementioned rituximab) and T cells (with agents such as abatacept), there remains a major unmet need. This is owing to the lack of patient responsiveness (as many as 50% in some studies fail to respond to anti-TNF [5]), difficulties associated with administration (since biologics have to be injected), and inflammatory diseases (in which these newer treatments have been shown to have limited efficacy [6]). A clear picture of what is driving the cytokines, T and B cells has yet to emerge, and this is where innate immunity plays its role. Starting in the late 1990s, new families of receptors were uncovered, largely in macrophages, which sense microbial products and then provoke production of pro-inflammatory cytokines and also, and very importantly, the costimulatory molecules CD80 and CD86, which are required for T-cell activation [4]. Toll-like receptors (TLRs) were the first class and these provide a repertoire to respond to all pathogens [2]. Equally importantly, however, is that certain TLRs respond to host factors released during tissue and cellular injury, such as host DNA, which is sensed by TLR9 in the context of immune complexes [7], or hyaluronic acid

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fragments released during damage to the extracellular matrix, which is sensed by TLR4 [8]. The other major class are the NOD-like receptors (NLRs) [3,9]. They too respond to various microbial ligands, but also to host-derived factors such as uric acid, the causative agent of gout, which binds the NLR Nalp3 [10]. It can therefore be hypothesized that these receptors arose, in terms of evolution, to respond to 'danger', either exogenous (e.g., microbial) or endogenous (damaged tissue) [11]. That a given receptor can respond to either a microbial factor or an endogenous factor is challenging since, similar to autoimmunity, it raises the prospect of inappropriate responses to our own tissues. However, the response to the host is strictly controlled since it appears to only occur when there is injury. The job of the inflammatory response that results is to help clear infection and also, and highly importantly, repair the damaged tissue.

Why would this system go out of control and give rise to an inflammatory disease such as RA? These new insights allow us to hypothesize why. All inflammatory diseases probably have an infectious origin – something from outside the body that is dangerous and needs to be dealt with. These microbes will be sensed by the innate receptors, which in turn cause inflammation. This will give rise to the production of endogenous inflammatory factors, which feed back on the receptors and amplify the whole process. Autoantigens will be released from tissues to provoke T and B cells via antigen-presenting cells. The cytokines that result from these cells, or the antibodies from the B cells acting via complement fixation, will cause further inflammation. This could pivot into chronicity, but in all likelihood this will only occur with a certain genetic background. Variants in receptors or signaling proteins might provide too strong a response, or alternatively, since we now know that there are widespread inhibitory mechanisms to keep this dangerous system in check, variants in proteins involved in inhibition that limit their activity might also allow for an overactivation.

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Two excellent examples will suffice. TLR4 will sense lipopolysaccharide from bacteria but also hyaluronic acid fragments or other endogenous factors [8]. TLR4 induces TNF production very strongly. Two inhibitory pathways have recently been found for TLR4. One of these involves three tyrosine kinase receptors termed Tyro, Axl and Myr, and the other a phosphatase termed SHP-1 [12,13]. If either of these TLR4 inhibitors are deficient or mutated in mice, systemic autoimmunity results. We also have clear evidence that inhibiting TLR4 in a spontaneous murine model of RA – the IL-1 receptor-deficient mouse – prevents the arthritis phenotype [14]. Arthritis in these mice is probably driven by bacteria, but will spin out of control because of the lack of the inhibitory protein IL-1 receptor antagonist. A second example concerns Nalp3. Mutations in this protein in humans give rise to autoinflammatory diseases with joint involvement, such as Muckle–Wells syndrome [14]. The complex clinical features of this syndrome can all be blamed on the Nalp3 mutation, since it is a key driver of IL-1 production, and the IL-1 receptor antagonist (whose production requires Nalp3) is showing remarkable clinical efficacy [15]. These advances would not have been possible without the fundamental research that uncovered receptors that are key for innate immunity.

'The new targets being revealed in innate immunity are all worthy of further analysis…'

Can we therefore exploit these findings to break the vicious cycle that is evident in a chronic inflammatory disease such as RA? Luck will be needed. The success of anti-TNF, although in retrospect seemingly predictable, was still a surprise to the investigators involved, since there was always a chance that it would be too immunosuppressive, or because TNF was not as important a target in humans as had been indicated from the preclinical studies. At that time, IL-1 was seen as a much more likely target, and the resurgence of clinical interest in targeting IL-1 is a testament to the researchers who continued to pursue it in the face of the success of anti-TNF [16]. The new targets being revealed in innate immunity are all worthy of further analysis but ultimately we will need to await clinical trials on the targeting of these newly found processes to test their importance for a disease such as RA. We also have to confront the sobering reality of current research, where there is a constant deluge of new information appearing. A good example here is the recent description of miRNAs in RA [17].

miRNAs are a recently discovered class of small RNA molecules that are believed to regulate the expression of many genes. Their dysregulation has been linked to specific human diseases, notably cancer and viral infections. miRNAs could be seen as the cytokines for the new millennium – some, termed immunoMiRs, are key regulators of immune cell function and their role must now be superimposed on our knowledge of RA. They are yet another set of inflammation-regulating factors that could turn out to be excellent drug targets [101].

Will new treatments therefore emerge from this renaissance of interest in innate immunity? Government agencies, charities and drug companies who fund the research, and, most of all, patients afflicted with debilitating inflammatory diseases and the clinicians who treat them, certainly hope so.

Financial & competing interests disclosure

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