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EDITORIAL

Inflammation and multiple myeloma: the Toll connection

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Multiple myeloma (MM) is a B-cell malignancy critically dependent for survival and proliferation on signals coming from the microenvironment.[1] These include most prominently the inflammatory cytokine IL-6 as well as other cytokines and growth factors such as TNFα and IL-13. Two articles in the Journal, now report that MM express a vast repertoire of Toll-like receptors (TLR) and that TLR ligands potently promote the proliferation and survival of these malignant cells (Jego G *et al*. and Bohnhorst J *et al*.). These results provide a fresh new perspective on the interaction between an inflammatory microenvironment and MM.

Human Toll-like receptors (TLR) include at least 10 type-I transmembrane proteins and form a larger superfamily with members of the IL-1 receptor family.[2] TLR recognize diverse ligands ranging from microbial moieties (lipopeptide, lipopolysaccharides, nucleic acids) to, possibly, endogenous molecules. The ligand recognized by TLR10 remains elusive. Frequently, optimal recognition involves cooperation with a ligand recognizing molecules such as CD14, members of the scavenger receptor family or dectin-1.[3,4] TLR are differentially expressed in leukocyte populations and B cells express substantial amounts of selected TLR, in particular TLR9 and 10. Activation by B-cell receptor engagement augments TLR levels in B cells, with high expression of TLR9 and TLR10 in activated and memory B cells (Figure 1).[5,6]

Engagement of TLR in B cells, for instance TLR9 by CpG oligonucleotides, stimulates proliferation, immunoglobulin release and chemokine production (Figure 1).[5,6] TLR-mediated activation of B cells has been suggested to play a role in the generation of T cell-dependent antibody responses,[7] in systemic autoimmunity[8] and in the maintenance of memory.[9]

The two articles in the Journal (Jego G *et al*. and Bohnhorst J *et al*.) now report that unlike normal plasma cells, MM express a wide and variable repertoire of TLR. Interestingly, while MM cells generally have high levels of a set of TLR (e.g. the nucleic acid recognizing TLR7, 8 and 9), TLR10, high on activated B cells,[6] is absent. TLR agonists such as CpG oligos induce MM proliferation and protect from dexamethasome-induced apoptosis. Strikingly, in both studies TLR agonists can substitute for IL-6 in the maintenance of MM cell lines. TLR-mediated induction of IL-6 plays an important role in the effect of TLR agonists on MM cells, but does not explain their action completely.

These reports raise several issues related to the biology and clinics of MM. TLR signalling is kept under check by multiple pathways of negative regulation including surface receptors (e.g. TIR8/SIGIRR[10,11]) and intracellular inhibitors.[12,13] Are these pathways operative in MM? Do they account for observed dissociations between TLR expression and cell responsiveness in MM or for divergent effects of CpG oligos on B cell (apoptosis)[14,15] versus MM (protection from apoptosis)? Understanding the balance is key to therapeutic targeting of TLR in B-cell malignancy.

The actual *in vivo* relevance of TLR in MM is critically dependent on provision of appropriate ligands. Endogenous ligands (for a critical appraisal see[8]), such as nucleic acids from damaged tissues may provide an amplification loop in MM progression (Figure 1). Similarly, MM is associated with immunosuppression and infection[1] and a vicious circuit may ensue involving MM, suppression of B cell responses, infection, promotion of MM. It will be important to ascertain whether reactive plasmacytosis, an expansion of plasma blasts and monoclonal gammopathy of undetermined significance express TLR and their function (Figure 1). Finally, the central question whether acquisition of a TLR repertoire actually contributes to the acquisition or maintenance of malignancy in MM or is a mere epiphenomenon remains unanswered. At this stage, TLR expression in MM appears yet another molecular link between inflammatory reactions and malignancy.[16–18]

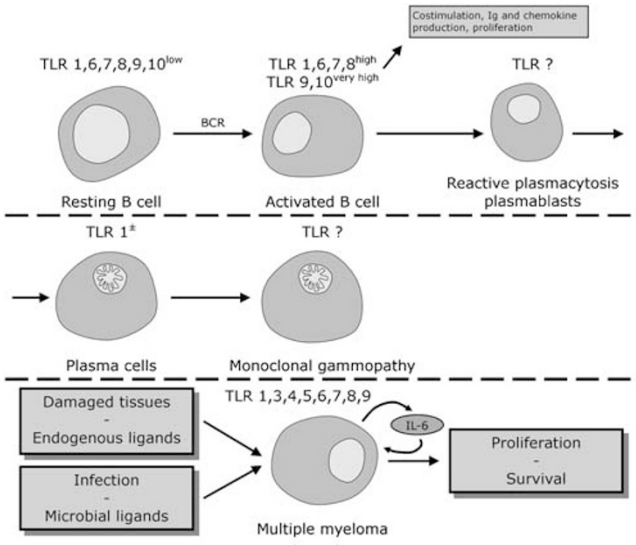

Figure 1 A schematic view of TLR in multiple myeloma. By way of comparison, normal B cells are shown. Question mark, unknown. Rp105 is not shown as it is expressed on all B cells and MM.

The results reported in the Journal should not be over interpreted to imply a general protumor function of TLR in the cancer microenvironment. Indeed, in a butylated hydroxytoluene-model of lung carcinogenesis, TLR4 dampens inflammation and cancer.[19] Elucidation of the role of the TLR system will require an accurate dissection in different tumors.

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