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# Modulation of dendritic cell function by zoledronate

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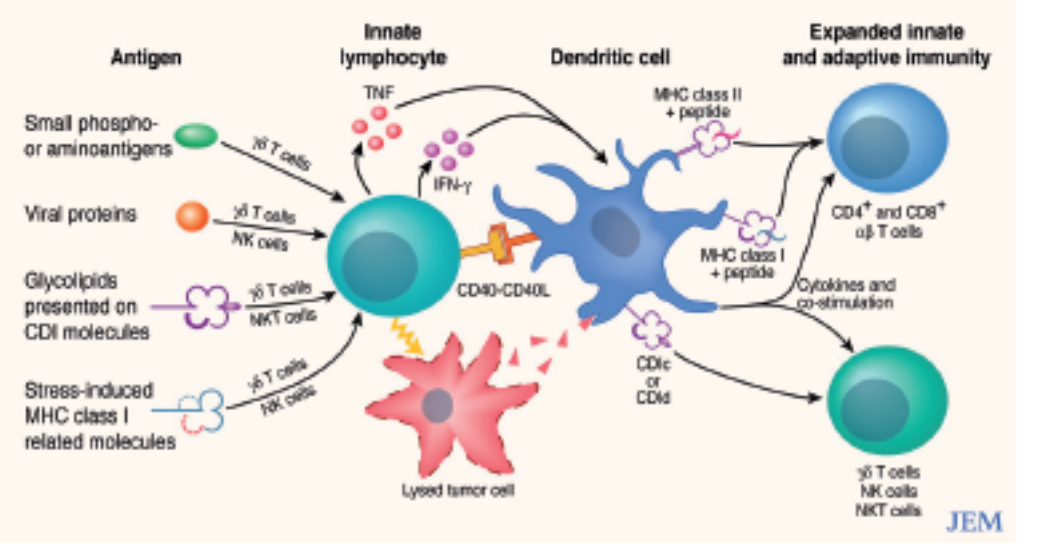
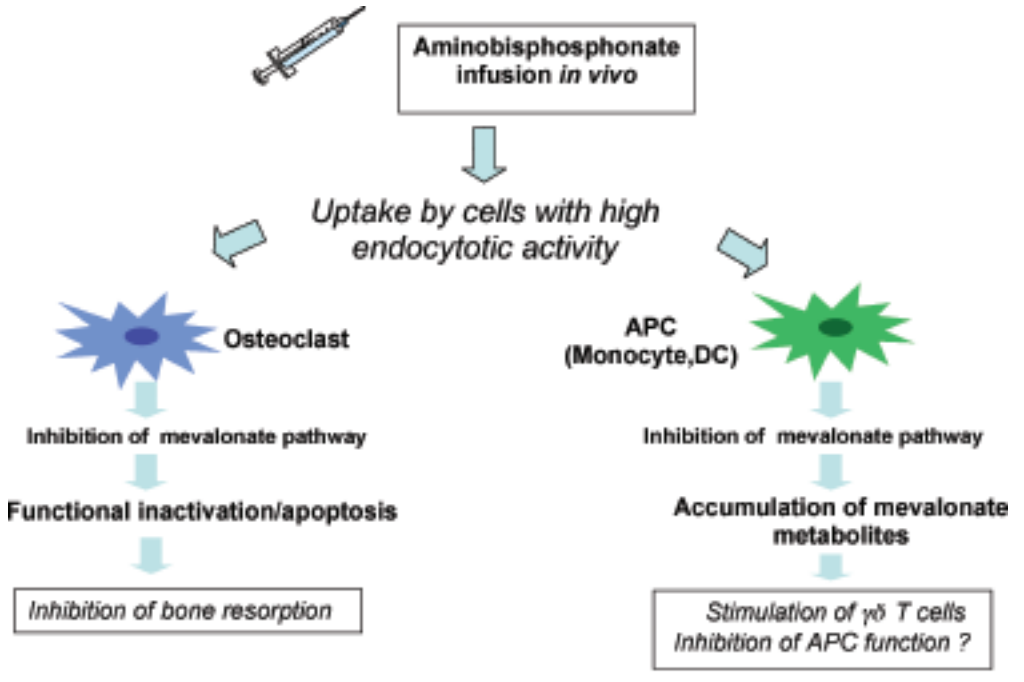
Dendritic cells (DC) as professional antigen presenting cells (APC) play a central role in initiating an effective immune response. However, activation and maturation of DCs is critical for induction of an immune response. Activated innate lymphocytes (NK cells, NKT cells or γδ T cells) have been shown to mediate the most potent activation/maturation signals to DCs by cytokines (TNF-α, IFN-γ) and by cell-cell contact dependent signals (e.g. CD40-C40L interaction). In addition, microbial products known as pathogen-associated molecular patterns (PAMPs; e.g. LPS, viral dsRNA, bacterial CPG-OGN) can directly contribute to DC activation. On the other hand, activated DCs can stimulate innate lymphocytes, predominantly by producing cytokines (such as type I Interferons) and cell-cell contact dependent co-stimulation indicating reciprocal interactions between DCs and innate lymphocytes.[1]

Our recent work focused on different activation modalities for human γδ T cells (Vγ9Vδ2 subset) and their contribution to DC activation. Besides TCR-mediated stimulation of γδ T cells by phosphoantigens we could recently demonstrate that NKG2D ligation alone induces functional activation (cytokine production and cytotoxicity) of Vγ9Vδ2 T cells.[2] NKG2D ligands (e.g. MICA/B) are stress-induced molecules which are rapidly expressed on infected or transformed cells enabling γδ T cells to sense directly infections and malignant cells, respectively. Phosphoantigen- or NKG2DL-activated γδ T cells have the capacity to induce DC activation/maturation by secretion of proinflammatory cytokines and cell-cell contact dependent mechanisms. In addition, we have shown that DC-derived Type I IFNs produced after stimulation with PAMPs (e.g. viral dsRNA mimicked by poly(I:C)) activate γδ T cells and mediate potent co-stimulatory effects on posphoantigen-induced gd T cell proliferation.[3] These results and observations from other groups[4] confirm the concept of reciprocal interactions between γδ T cells and DCs supporting the important role of these cells during early immune response.

In contrast to natural or synthetic phosphoantigens, stimulation of γδ T cells by aminobisphosphonates (ABP) is strictly




*Adapted from Münz C et al., JEM 2005, 202:203-7.*




dependent on the uptake of these compounds by cells with high endocytotic activity (such as DCs or monocytes). Stimulation of γδ T cells by ABP is mediated by inhibition of the mevalonate pathway in APC which leads to accumulation of stimulating mevalonate metabolites such isopentenylpyrophosphate (IPP).[5,6] However, inhibition of the mevalonate pathway in APC might also influence the survival and function of APC as demonstrated for ABP effects in osteoclasts.[7]

This hypothesis has been recently addressed in our group by evaluating the effects of ABP (Zoledronate) on DC function. First results indicate that PAMP-mediated TNF-α secretion by DCs when DC where generated in presence of Zoledronate. In addition, induction of antigen-specific $CD4^+$ and $CD8^+$ αβ T cell response is reduced by Zoledronate-generated DC compared with untreated DC.

These results support the recent clinical observation that ABP can mediate immunosuppressive effects in vivo since the acute rejection rate after renal transplantation is significantly lower in patients treated with an ABP as compared to placebo.[7] Thus, ABP can mediate either immunostimulatory effects (activation of Vγ9Vδ2 T cells) or immunosuppressive effects (inhibition of APC function). These dual immunmodulatory effects of ABP must be considered in subsequent clinical trials with these compounds.

## References

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