DEC-205 is a cell surface receptor for CpG oligonucleotides

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Keywords: dendritic cells, CpG, TLR9, vaccines, adjuvants

Dendritic cells (DCs) detect pathogens and their products using a gamut of receptors,1 including Toll-like receptor 9 (TLR9), which recognizes non-methylated cytosine-guanosine (CpG) motifs found in bacterial DNA.1,2 Synthetic CpG oligonucleotide (ODN) TLR9 agonists are used as vaccine adjuvants.3 Although different classes of CpG ODNs have been developed, clinical trials predominantly utilize class B ODNs (B-ODNs),3 which are single stranded, fully phosphorothioated and activate B cells, plasmacytoid DC (pDCs) and, in the mouse, conventional DCs (cDCs). The phosphorothioate backbone confers resistance to nuclease degradation and facilitates uptake.4,5 The CpG ODN-mediated activation of DCs is known to require TLR9 but it has long remained unclear how extracellular CpG ODNs gain access to the intracellular compartments that house TLR9. We have recently demonstrated that synthetic CpG oligonucleotides (ODNs), which function as potent immunostimulators, bind to the multi-lectin receptor DEC-205, resulting in their internalization. DEC-205-deficient mice exhibit impaired dendritic-cell and B-cell maturation, impaired cytokine responses and suboptimal cytotoxic T-cell responses. As murine and human DEC-205 are highly conserved, CpG ODNs destined to clinical applications should be designed to maximize DEC-205 binding.
Together with a monoclonal antibody specific for Clec12A coupled to ovalbumin. Since Clec12A is expressed on DCs, this immunization regimen delivers ovalbumin to DCs, yet it requires the adjuvant effect of CpG ODNs for the successful priming of CTLs. With this approach, we have shown that the induction of robust CTL responses that depend on the adjuvant effect of CpG ODNs also requires DEC-205. Thus, DEC-205 is required for the induction of strong pro-inflammatory responses to CpG ODNs in mice. As this receptor is well conserved in humans, DEC-205 may also play an important role in promoting optimal responses to CpG ODNs in clinical settings. Since the inflammatory protein (MIP)-1α and MIP-1β, in response to CpG ODNs. Most strikingly though was the poor production of IL-12, a cytokine produced in large amounts by CD8+ DCs.

Given that CD8+ DCs play a key role in activating naïve CD8+ T cells and IL-12 promotes the acquisition of cytotoxic functions, and that DEC-205-deficient mice exhibited impaired CD8+ DC maturation and an impaired ability to produce IL-12 in response to CpG ODNs, we wondered whether DEC-205 is required for the induction of cytotoxic T lymphocytes (CTLs) in a model that depends on CpG ODNs for adjuvancy. To test this hypothesis, we immunized mice with CpG ODN together with a monoclonal antibody specific for Clec12A coupled to ovalbumin. Since Clec12A is expressed on DCs, this immunization regimen delivers ovalbumin to DCs, yet it requires the adjuvant effect of CpG ODNs for the successful priming of CTLs. With this approach, we have shown that the induction of robust CTL responses that depend on the adjuvant effect of CpG ODNs also requires DEC-205. Thus, DEC-205 is required for the induction of strong pro-inflammatory responses to CpG ODNs in mice. As this receptor is well conserved in humans, DEC-205 may also play an important role in promoting optimal responses to CpG ODNs in clinical settings. Since the capacity of human DEC-205 to bind CpG ODNs heavily depends on their DNA sequence, it will be important to identify the motifs that most efficiently bind DEC-205 so as to facilitate optimal uptake. In man, the main targets of CpG ODNs are B cells and pDCs, both of which express TLR9 and DEC-205. Thus, identifying the ideal sequence for human DEC-205 binding and coupling this to the ideal sequence for TLR9 activation should allow for the design of CpG ODNs with maximal stimulatory capacities.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
Author/s:
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Title:
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Date:
2013-03-01

Citation:

Persistent Link:
http://hdl.handle.net/11343/262823

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