INNATE IMMUNITY

HMGB proteins: universal sensors for nucleic acids

Several transmembrane and cytoplasmic receptors that specifically recognize distinct types of nucleic acid and activate innate immune responses have been described. Now, Taniguchi and colleagues show that high-mobility group box (HMGB) proteins act as universal sensors of nucleic acids upstream of these receptors and are required for the subsequent induction of innate immune responses.

To gain new insights into the nucleic-acid-sensing system, the authors identified proteins that bind directly to the B-form DNA poly(dA:dT)–poly(dT:dA) (B-DNA) and found that the main binding proteins were HMGB1, HMGB2 and HMGB3. Extending these observations, the authors showed that, *in vitro,* recombinant HMGB1 bound other types of nucleic acid — including double-stranded RNA (polyinosinic–polycytidylic acid (polyI:C)), single-stranded RNA (polyU), CpG-containing B-type oligodeoxynucleotides and base-free phosphorothioate deoxyribose homopolymer — but did not bind to imiquimod, a non-nucleic acid recognized by Toll-like receptor 7 (TLR7; which also recognizes RNAs). Interestingly, strongly immunogenic nucleic acids bound HMGB1 with higher affinity than weakly immunogenic nucleic acids. HMGB2 bound B-DNA but not RNA, and HMGB3 bound both DNA and RNA.

Analysis of *Hmgb1*$^{-/-}$ mouse embryonic fibroblasts (MEFs) stimulated with cytoplasmically delivered B-DNA or polyI:C showed lower production of type I interferon (IFN) than by control MEFs. By contrast, the type I IFN response to lipopolysaccharide (LPS) was intact. Suppression of all three HMGB proteins using small interfering RNA resulted in a further decrease in the production of type I IFN (as well as several other cytokines and chemokines) in response to B-DNA or polyI:C. Again, responses to LPS were intact in these cells. In addition, activation of the transcription factors downstream of cytoplasmic nucleic-acid-sensing receptors — IFN-regulatory factor 3 and nuclear factor-κB — was suppressed in HMGB-deficient MEFs stimulated with B-DNA or polyI:C.

Furthermore, infection of HMGB-deficient MEFs with vesicular stomatitis virus or herpes simplex virus resulted in lower type I IFN production and higher viral replication than in control MEFs. Finally, activation of TLR3, TLR7 and TLR9 by their nucleic acid agonists in dendritic cells was impaired in the absence of HMGB1.

These results indicate that nucleic acids are promiscuously sensed by HMGB proteins and that this step is required for the activation of their specific nucleic-acid-sensing receptors. The authors suggest that the evolutionarily ancient HMGB proteins are remnants of an ancient nucleic-acid-sensing system that has evolved along with and in support of specific nucleic-acid-sensing receptors. Therefore, HMGB proteins could be potential targets for the general inhibition of nucleic-acid-mediated pathological immune responses.

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