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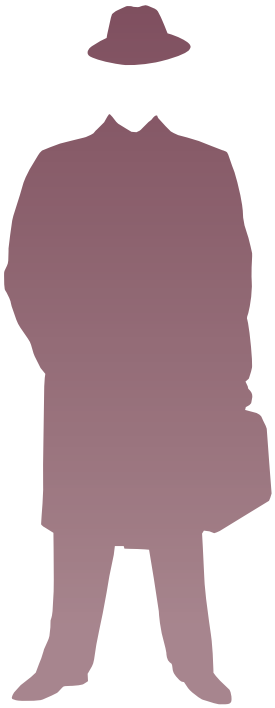
IMMUNE EVASION

Gm18, a bacterial 'invisibility cloak'



Eukaryotic RNA, including both ribosomal RNA and tRNA, is more heavily modified post-transcriptionally than bacterial RNA, and it had been suggested that these differences facilitate the discrimination of self and non-self by the immune system. In agreement with this idea, two studies now reveal that 2′-*O*-methylation of G18 (Gm18) on bacterial tRNA suppresses activation of the immune response.

Both groups began by screening a panel of native bacterial tRNA species for immunostimulatory activity towards peripheral blood mononuclear cells. Most of these tRNAs triggered the secretion of interferon-α (IFNα) in a manner that was dependent on stimulation of Toll-like receptor 7 (TLR7). Interestingly, Jöckel *et al.* found that total tRNA from distinct bacterial species (*Escherichia coli* str. Nissle 1917 and *Thermus thermophilus*) did not promote the secretion of IFNα. Moreover, Gehrig *et al.* pinpointed $tRNA^{Tyr}$ as one specific *E. coli* tRNA that did not trigger immune activation.

But what is the feature of these tRNAs that prevents their recognition by TLR7? By comparing $tRNA^{Tyr}$ with an unmodified, *in vitro*-transcribed version, Gehrig *et al.* identified seven post-transcriptional modifications that might have a role in this process. Further analysis showed that alteration of an otherwise immunostimulatory tRNA with just one of these modifications, Gm18, was necessary and sufficient to prevent immune activation. Consistent with this, both groups found that bacteria lacking the 2′-*O*-methyltransferase TrmH, and therefore Gm18, had greater immunostimulatory ability than wild-type bacteria. Importantly, Jöckel *et al.* showed that the immunostimulatory capacity of these mutant bacteria was abolished following G18 methylation *in vitro*.

Synthetic 2′-*O*-methylated tRNA had previously been shown to act as an antagonist for TLR7, so both groups sought to determine whether Gm18 on native tRNA also has this effect. Jöckel *et al.* observed that, when incubated together with stimulatory bacterial tRNA, tRNAs from *E. coli* str. Nissle 1917 and *T. thermophilus* inhibited the immunostimulatory ability of the total preparation in a concentration-dependent manner. Similarly, Gehrig *et al.* found that Gm18-containing $tRNA^{Tyr}$ abrogated IFNα secretion induced by unmethylated tRNA. These findings indicate that Gm18-containing tRNA acts as an antagonist for TLR7 and decreases the immunostimulatory activities of total bacterial tRNA.

So, these two studies reveal that post-transcriptional modification of a single residue on bacterial tRNA can suppress immune activation via TLR7. By examining the presence of Gm18 in different species, it might be possible to determine whether increased levels of this modification correspond with increased virulence and/or whether Gm18 is responsible for the beneficial, immune-dampening effects of probiotic bacteria by acting as an antagonist.

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ORIGINAL RESEARCH PAPERS Gehrig, S. *et al.* Identification of modifications in microbial, native tRNA that suppress immunostimulatory activity. *J. Exp. Med.* **209**, 225–233 (2012) | Jöckel, S. *et al.* The 2′-*O*-methylation status of a single guanosine controls transfer RNA–mediated Toll-like receptor 7 activation or inhibition. *J. Exp. Med.* **209**, 235–241 (2012)