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Commentary

Micro(RNAs)managing Macrophage Polarization During Schistosomiasis

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Infections with parasitic helminths of the genus *Schistosoma* are considered one of the most socioeconomically devastating parasitic diseases, with hundreds of millions of people infected worldwide. These infections can result in significant morbidity primarily due to parasite-derived eggs that accumulate in tissues, such as the liver (in the case of *S. mansoni* and *S. japonicum* infection), where they drive inflammation, tissue damage and fibrosis (Pearce and MacDonald, 2002). Macrophages have been shown to play a key modulatory role in this egg-induced immunopathology. Before the onset of egg-laying by the adult worms, the host immune response is characterized by a T helper 1 (Th1) response, which through the secretion of IFN-γ promotes the differentiation of macrophages towards a more pro-inflammatory classically activated phenotype ('M1'). Upon egg deposition a potent type 2 immune response is triggered, in which Th2 cells and Type 2 cytokine-driven alternatively activated macrophages ('M2') predominate. This M2 phenotype of macrophages is crucial for the host to survive acute schistosomiasis, by keeping Type 1 inflammatory responses, including those mediated by M1 macrophages, in check that would otherwise result in potentially lethal tissue-damage. Moreover, M2 macrophages are involved in granuloma formation and induction of fibrosis around eggs trapped in tissues, which is thought to be an important host protective mechanism against egg-driven pathology (Barron and Wynn, 2011). This illustrates the importance of a tight regulation of macrophage polarization during schistosomiasis and disease outcome. However, the molecular mechanisms that control macrophage polarization in egg-affected tissues are still not fully understood. In the current issue He and coworkers provide for the first time support for an important role for a specific microRNA (miRNA), miRNA-146, in regulating the balance between M2 and M1 macrophage polarization during *S. japonicum*-induced hepatic schistosomiasis (He et al., 2016).

miRNAs are small ubiquitously expressed non-coding RNAs, that regulate gene expression at the post-transcriptional level through RNA silencing and thereby play important roles in various aspects of cell biology, including regulation of the functional properties of immune cells (Bartel, 2004). While the role for miRNAs in schistosome biology and development has become an intense area of research (Zhu et al., 2014), the role of host miRNAs in shaping immune responses against these parasites has been poorly characterized. In a previous study He and coworkers performed a miRNA microarray on livers from *S. japonicum*-infected mice and identified miRNA-146 as one of several strongly upregulated miRNAs in response to infection (He et al., 2015). This prompted them to study this miRNA species in more detail in the current study. They found two miRNA-146 family members, miRNA-146a and b, to be highly induced in liver resident macrophages, the Kupffer cells, from around day 42 after infection, which coincides with the start of egg deposition in the liver. Using complementary *ex vivo* and *in vitro* approaches, they went on to show that the promotor region of the gene sequence encoding miRNA-146b contains response elements for transcription factors STAT3 and -6 and that as result Th2-associated cytokines IL-10, IL-4 and IL-13 could promote expression of this miRNA in macrophages. Importantly, He and coworkers identified STAT1, a critical component of IFN-γ signaling, as a direct target of miRNA-146a/b and as a result found IFN-γ-induced expression of M1 markers could be suppressed by these miRNAs.

Another group has recently found that miRNA-146a, by targeting of TRAF6, could suppress of M1 marker expression in the context of tuberculosis (Li et al., 2016). The current work from He and colleagues extend these findings by showing that miRNA-146 expression by macrophages can be regulated by type 2 cytokines and by identifying STAT1 as a novel additional target of the miRNA-146 family that results in inhibition of polarization towards a pro-inflammatory M1 phenotype. As the mechanistic data from the study performed by He and coworkers were primarily generated in *in vitro* macrophage models, an important next step will be to validate these findings *in vivo* and to study the functional relevance of miRNA-146 induced suppression of M1 polarization during schistosomiasis. One could speculate that since macrophages in the liver will be exposed to both IFN-γ and Type 2 cytokines during acute schistosomiasis, induction of miRNA-146 expression may be important to enforce and sustain M2 polarization to control immunopathology. Another question that arises from this work is to what extent this mechanism plays a role in the M1/M2 balance in other contexts. A recent study found that IL-4-polarized M2 macrophages can be repolarized to an M1 phenotype by IFN-γ just as efficiently as unpolarized 'M0' control macrophages (Van den Bossche et al., 2016), indicating that type 2 cytokine-driven limitation in M1 polarization through miRNA-146 may not be operating in that experimental model and suggests that the importance of miRNA-146 in regulation of M1/M2 polarization is context

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dependent. Nonetheless, studies such as the one performed by He and colleagues illustrate how multilayered and complex the regulation of macrophage biology is and what role miRNAs can play in this. A better understanding of how and which miRNAs regulate macrophage differentiation may help to identify potential new therapeutic targets to ultimately treat diseases that are characterized by misbalanced macrophage polarization.

Disclosure

The author declares no conflict of interest.

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