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Cancer Science 2020: MiRNAs, Vital regulators in tumor immunity: With a focus on innate immunity - Shi-Jun Xu - Henan Cancer Hospital

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The tumor microenvironment (TME) is the primary arena where tumor cells and the host immune system interact. Bidirectional communication between tumor cells and the associated stromal cell types within the TME influences disease initiation and progression, as well as tumor immunity. There are multiple types of stromal cells and among them, macrophages and natural killer (NK) cells are the most prevalent. They not only are key players in innate immunity which serves as the first barrier against pathogen infection and as the bridge to connect adaptive immunity, but also play important roles in tumor immunity. Besides, epithelial cells, such as hepatocytes in liver, perform robust innate immune response against pathogen infection and tumor initiation. More importantly, these cells display either pro- or anti-tumor properties, depending on the expression of key regulators. MicroRNAs (miRNAs) are emerging as such regulators. miRNAs are a large family of small (23nt) endogenous non-coding RNAs, which negatively regulate gene expression at the post-transcriptional level by binding to the 3'-untranslated region (UTR) of target mRNAs, thus degrading the mRNAs or repressing their translation. Decades of research have demonstrated that miRNAs affect not only immune cells but also epithelial cells whose functions closely related to pathogen infection, tumor initiation and tumor evasion of the immune system. In this review we will discuss the role of miRNAs in tumor immunity, focusing particularly on innate immunity related cells such as macrophages, NK cells and hepatocytes.

Macrophages, the best known innate immune cells, are essentially present in all tissues, and crucial effectors of wound healing, homeostasis, cancer and immune responses. In the TME, diversity and plasticity are the foremost characteristics of tumor-associated macrophages (TAMs). According to the polarization states, macrophages are divided into two types, classically activated (M1) macrophages and alternatively activated (M2) macrophages. M1 macrophages display anti-tumorigenic activities by producing type I pro-inflammatory cytokines and participating in antigen presentation. However, M2 macrophages secret type II cytokines, which improve anti-inflammatory responses and display pro-tumorigenic activities. Nowadays, more than 100 miRNAs are reported to involve in macrophages functioning in the TME. Firstly, 30 miRNAs work in the development and maturation of macrophages. Of note, miR-146a, miR-21, and miR-196b promote human and mouse macrophages development and maturation. Secondly, 31 miRNAs in human macrophages while 36 miRNAs in mouse macrophages participate in the polarization of macrophages, and half of these miRNAs affect the transition between M1 and M2 macrophages. For example, hsa/mmu-miR-146a/b and hsa/mmu-miR-181a increase the alteration from M1 to M2 macrophages; while hsa/mmu-miR-27a/b, hsa/mmu-miR-125a and hsa/mmu-miR-155 decrease the alternation from M1 to M2 macrophages. Besides, human miRNA and mouse miRNA has the opposite role in macrophages polarization. For example, hsa-miR-9 inhibits while mmu-miR-9 assists M1 macrophages. Thirdly, tumor-derived miRNAs also play crucial roles in macrophage functions and tumor immunity. mmu-miR-155 is up-regulated in CD11c+ pro-inflammatory TAMs and activately mediated tumor immunity in a mouse breast cancer model. Fourthly, virus-encoded or virus infection-induced miRNAs also regulate macrophages activities. miR-H1, miR-K12-3p and EBV-miR-BART11, are incorporated into macrophages to alter cellular gene expression then convert M1 macrophages into M2 macrophages, which facilitate tumor development and metastasis. Finally, some miRNAs also suppress tumor immunity by blocking the expression of key regulators in the innate immune pathways. For example, rhabdovirus infection significantly induced miR-3750 expression in macrophages by targeting MAVS, an adaptor gene involved in RIG-I pathway activation.

Natural killer (NK) cells are cytotoxic innate lymphoid cells and are critical mediators of early host defense against pathogen infection, immune homeostasis, and tumor surveillance. Based on the number of CD56 and CD16 surface markers, human NK cells are divided into two subsets: CD56bright/CD16-/dim and CD56dim/CD16bright, the latter is the main form of circulating NK cells. CD56bright cells regulate the activation and function of NK cells, as well as other immune cells, by secreting cytokines such as IFN-γ and TNF-α. CD56dim cells, however, release lytic molecules like perforin and granzyme B to exert highly cytotoxic effects. By far, only 6 miRNAs take part in the development and maturation of NK cells, 14 miRNAs influence IFN-γ production, 26 miRNAs affect cytotoxicity, and 36 miRNAs involve in tumor immunity. Mechanistically, miRNAs directly repress the translation of key factors in NK cells. For example, mmu-miRs-15/16 and mmu-miR-29 directly target IFN-γ 3'UTR, and mmu-miR-233 directly binds to the 3'UTR of granzyme B, and hsa-miR-150 targets the perforin 3'UTR. Besides, miRNAs regulate IFN-γ production or cytotoxicity by modulating inflammation-related signaling pathways. miR-155 regulates IFN-γ production in human and mouse NK cells by decreasing the activation of PI3K and NF-κB pathways. Furthermore, Pathogen- and tumor-induced miRNAs also regulate NK cell activities. HCV infection down-regulates hsa-miR-155 in NK cells, thus releasing T-bet/Tim-3, which

suppresses IFN-γ production and leads to HCV evading immune clearance. Importantly, TGF-β, a key mediator in the TME, post-transcriptionally increases hsa-miRNA-1245 expression, suppresses NKG2D expression then blocks NKG2D-mediated immune responses and supports the TME.

Hepatocytes, the most important somatic cells in the liver, have the intrinsic innate immunity and serve as the first line of immune defense against hepatitis virus infection. MiR-122 is the most abundant miRNAs in hepatocytes and a central player in liver biology and disease. But whether miR-122 functions in the antiviral innate immunity within hepatocytes is largely unknown. Our research demonstrate that restoration of miR-122 level in hepatocytes significantly increased the activation of IFNs in response to hepatitis C virus (HCV) and poly (I:C). Mechanistically, miR-122 down-regulated the phosphorylation (Tyr 705) of STAT3, thereby removing the negative regulation of STAT3 on IFN-signaling. miR-122 targets MERTK, FGFR1 and IGF1R, three receptor tyrosine kinases (RTKs) that directly promote STAT3 phosphorylation. STAT3 inhibits interferon regulatory factor 1 (IRF1) to repress IFN expression. Our work identifies miR-122–RTKs/STAT3–IRF1–IFNs regulatory circuitry, which may play a pivotal role in regulating hepatocyte innate immunity