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Modulation of Cancer Progression by Tumor Microenvironmental Leukocyte-Expressed microRNAs

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1. Introduction

microRNAs (miRNAs) have rapidly emerged as a widespread and important regulatory layer of gene expression (Ambros, 2004; Bartel & Chen, 2004). miRNAs can coordinately modulate the expression of hundreds of target genes, mainly by negatively affecting mRNA stability and/or protein output (Baek et al., 2008; Bentwich et al., 2005; Kozomara & Griffiths-Jones, 2011; Lim et al., 2005; Selbach et al., 2008). With this mode of gene expression control, a single miRNA can concomitantly influence multiple cellular programs under physiological and pathological conditions. Examples abound in which perturbation of miRNA functions can have catastrophic consequences for proper execution of developmental programs, for maintenance of cellular homeostasis, and for optimal performance of cellular processes (De Smaele et al., 2010; Garzon et al., 2010; Saba & Schratt, 2010; Sempere & Kauppinen, 2009; Ventura & Jacks, 2009).

Only one year after the discovery of miRNAs in 2001, Croce and colleagues found the first association between miRNAs and cancer when they noted the frequent occurrence of chromosomal deletion and the concurrent downregulation of two miRNA genes, miR-15a and miR-16-1, in B-cell chronic lymphocytic leukemia patients (Calin et al., 2002). Since that time, progress towards understanding the basic molecular and biological mechanisms of miRNA biogenesis, their normal patterns of temporal and spatial expression, and their roles in development and physiology has unfolded slowly compared to the rapid path towards translational and clinical applications of miRNAs, especially in cancer.

A particular active area of research has been high-throughput expression profiling of miRNAs in a variety of cancer types (Barbarotto et al., 2008; Sempere, 2011). The general interpretation of these expression profiling experiments has been to assign altered miRNA expression to the cancer cells and promptly labelled the implicated miRNA as having tumor suppressive or oncogenic properties depending on whether miRNA levels were detected a lower or higher levels, respectively, in tumor tissues compared to normal. However, the cancer cell compartment of many of the most aggressive types of solid tumors represents a minority of the variety of cell types in cancer lesions (Sempere, 2011). A tumor microenvironmental (TME) cell type invariably associated with cancer progression is the

leukocyte. Immune cells are the site of cancer origin in leukemias and lymphomas, whereas epithelial cells are the site of cancer origin in carcinomas and the immune cells constitute the inflammatory component of TME. Thus, inflammation and infiltrating leukocytes present as co-disease or co-morbidity in solid tumors and are a major confounding factor to correctly interpret expression profiling experiments. A salient example to illustrate this dichotomy between cancer cell and immune cell infiltrate is miR-155 in solid tumors. miR-155 resides in non-protein coding B-cell integration cluster (*BIC*) gene (Faraoni et al., 2009; Tili et al., 2009). miR-155 is frequently detected at high levels in leukemias, lymphomas and solid tumors (e.g., carcinomas) and overexpression of miR-155 causes rapid and aggressive disease progression in a mouse model of B cell lymphoma (Faraoni et al., 2009; Tili et al., 2009). Thus, miR-155 has been regarded as a master oncogenic miRNA in hematological and solid tumors. However, a large body of evidence also attributes important roles to miR-155 as a mediator of lymphoid and myeloid cell responses to infection and inflammation, which is further supported by immunological deficiency exhibited by mir-155 knockout mouse models (Faraoni et al., 2009; Tili et al., 2009). We recently showed that expression of miR-155 was confined to a subpopulation of infiltrating immune cells in breast, colorectal, lung, pancreas and prostate tumor lesions (Sempere et al., 2010). Importantly, these results indicated that the majority of miR-155 signal detected by RT-PCR assays in whole tissue biopsies or blood samples likely emanates from TME cells, drawing into question whether miR-155 plays any role within the cancer cells in these carcinomas. In the light of these findings, we revisit here altered expression of miR-155 and other leukocyte-expressed miRNAs (e.g., miR-17-5p, miR-20a, miR-21, miR-25, miR-29a, miR-142-3p, miR-146a, miR-150, miR-181a, miR-221, miR-223) in solid tumors, which are likely to reflect, at least in part, immune cell responses in the TME rather than molecular aberrations within the cancer cells per se. We review the emerging roles of these leukocyte-expressed miRNAs in the immune system with an especial emphasis on myelomonocytic-derived cells, and discuss their implications in the modulation of cancer initiation and progression in the context of a reactive and/or permissive TME.

2. Physiological roles of microRNAs in the immune system

In the bone marrow, pluripotent hematopoietic stem cells give rise to common progenitors of the lymphoid and myeloid lineages. In the blood, these progenitors will continue distinct differentiation paths to produce the principal cell types of the immune system: B and T lymphocytes and natural killer (NK) cells in the lymphoid branch, and basophils, neutrophils, eosinophils, mast cells and monocytes in the myeloid branch; other non-immune cell types such as erythrocytes and thrombocytes are also produced in the myeloid branch. In tissues, further maturation awaits for lymphoid and myeloid lineages to mount innate and adaptive responses against bacterial, viral and other pathogens as well as against cancer cells and other aberrant cells not recognized as self. These differentiation programs are crucial to establish a fully functional immune system. Expression profiling and functional studies have implicated miRNAs as key regulators of specific stages of differentiation and maturation of specific immune cell lineages, which in general have overt deleterious consequences at the organismal level.

Mature and biologically active miRNAs, ~21-23 nucleotides-long, function as guides to recognize and bind partially complementary elements (miRNA recognition element; MRE)

on the 3′ untranslated region (UTR) of target mRNAs. miRNA biogenesis and processing determine the total levels of mature miRNA and to a large extent miRNA function (however see these reviews for cooperative and competitive effects of RNA binding proteins (Van Kouwenhove et al., 2011) and competing endogenous RNAs (Salmena et al., 2011) on miRNA activity). Most miRNA genes are transcribed by RNA polymerase II, which produces a long primary transcript (pri-miRNA) with a 5′ cap and a 3′ poly(A) tail (Ketting, 2011; van et al., 2011). In the nucleus the pri-miRNA is recognized by the microprocessor, a multiprotein complex that cleaves off a 70 nts-long precursor miRNA hairpin (pre-miRNA). The catalyzes this cleavage as DGCR8 recognizes structural features of the hairpin and accordingly position the pre-miRNA for cleavage by RNAse III endonuclease Drosha. The pre-miRNA is exported to the cytoplasm by Exportin-5 in a RAN-GTP dependent manner. Then, the pre-miRNA is cleaved by another RNAse III endonuclease Dicer in association with TARBP2 or PACT and the mature miRNA strand (guide) is loaded in Argonaute-containing RNA-induced silencing complexes (Ketting, 2011; van et al., 2011).

The expression of key components of the miRNA processing machinery such Dicer can be inhibited under physiological stress and disease states, including cancer (Tomasi et al., 2010). Moreover, Dicer expression is affected by cortisone, interferon and other pharmacological agents prescribed for the treatment of immune disorders (Tomasi et al., 2010). Thus, perturbation of global miRNA activity can have undesirable clinical implications. In mouse models, deleterious effects of global miRNA impairment by conditional removal of Dicer or DGCR8 in specific immune cell lineage using the Cre/LoxP system has pinpointed important roles of miRNAs in production of antibody diversity, terminal differentiation and survival of B cells (Belver et al., 2010; Koralov et al., 2008), function of regulatory T (Treg) cells and Treg-mediated control of autoimmunity (Liston et al., 2008; Zhou et al., 2008), the development and function of invariant natural killer T cells (Bezman et al., 2010; Seo et al., 2010; Zhou et al., 2009), and terminal differentiation, activation, migration and survival of CD8+ T cell (Muljo et al., 2005; Zhang & Bevan, 2010). Subsequent studies have uncovered a major role of a single or small subset of miRNAs for immunological phenotypes observed in animals deficient in miRNA processing machinery (see below). As we describe in the next subsections, high-throughput expression profiling has been a useful discovery tool to correlate expression with function and thereby highlight specific miRNAs for further mechanistic characterization.

2.1 Dynamic expression of microRNAs during hematopoietic lineage differentiation

Using primarily the mouse as a model system, several groups have characterized in detail changes of miRNA expression during immune cell lineage differentiation as a means to infer from this a functional involvement of specific miRNAs at key steps of these processes (Malumbres & Lossos, 2010; O'Connell et al., 2010b; O'Neill et al., 2011).

2.1.1 microRNA expression in granulocyte differentiation and maturation

There are several well-defined differentiation stages that mature granulocytes (PB-N) undergo from a common myeloid progenitor (CMP): granulocyte-monocyte progenitor (GMP), immature bone marrow neutrophils (BM-N). Expression of miR-223 gradually increases from CMP to BM-N stages, reaching the highest level of expression in PB-N cells

(Johnnidis et al., 2008). This differentiation pathway is crucial for the mobilization of the massive amount of immature myeloid leukocytes typically found in cancer patients.

2.1.2 microRNA expression in monocytic-macrophage differentiation and maturation

There are several well-defined differentiation stages that mature macrophages (Mϕs) undergo from a CMP cell: GMP, monocyte. Using similar strategies, several groups independently profiled miRNA expression in *in vitro* cell culture systems that induce monocytic differentiation and maturation into Mϕs (Fontana et al., 2007; Ghani et al., 2011). Expression of miR-17-5p, miR-20a, miR-106a was downregulated during differentiation and maturation of unilineage monocytic cell culture (Fontana et al., 2007). Expression of miR-99, miR-146a, miR-155, miR-342 and others was upregulated and that of miR-20a, miR-25, miR-26a, miR-223 and others was downregulated during differentiation and maturation of PU.1-expressing PUER cells (Ghani et al., 2011). Downregualtion of miR-223 in monoctyes had been previously noticed (Johnnidis et al., 2008).

2.1.3 microRNA expression in dendritic cell differentiation and maturation

There are several well-defined differentiation stages that mature dendritic cells (DCs) undergo from a CMP cell: GMP, monocyte. Expression of miR-99a, miR-193b was exclusively upregulated during induced differentiation and maturation into DC of *ex vivo* culture of human blood-derived monocytes, whereas upregulation of miR-34a, miR-125a-5p, miR-99b, miR-511 expression was observed in both DC and Mϕs (Tserel et al., 2011). These results are in good, but not in complete, agreement with similar studies in which relative miRNA expression levels were compared between monocytes, immature and mature DCs (Hashimi et al., 2009; Lu et al., 2011a). Upregulation of miR-21, miR-342 expression and downregulation of miR-17-5p, miR-25, miR-93, miR-106a expression in immature and/or mature DCs was observed in both studies (Hashimi et al., 2009; Lu et al., 2011a). Upregulation of miR-146a and miR-155 expression in mature DC upon activation by various pro-inflammatory stimuli, including bacterial lipopolysaccharide (LPS) and interleukin (IL) 1β, has been consistently observed by independent groups (Turner et al., 2011).

2.1.4 microRNA expression in B cell differentiation and maturation

There are several well-defined differentiation stages that mature memory B cell or plasma cells undergo from a common lymphoid progenitor cell (CLP): Pro-B, Pre-B, IM-B, Naive B and germinal center (GC) cell. When comparing relative expression levels between pro-B and naive B cells (Monticelli et al., 2005), expression of the following miRNAs was enriched at a specific stage: miR-24, miR-93, miR-101, miR-107, miR-324 in pro-B cells; miR-26, miR-29a, miR-142-3p, miR-142-5p, miR-150 in naive B cells. When comparing relative expression levels between naive, GC and memory B cells (Malumbres et al., 2009; Tan et al., 2009), expression of the following miRNAs was enriched at a specific stage: let-7a, miR-92, miR-95, miR-142-3p, miR-142-5p, miR-193 and others in naive cells; miR-15b, miR-16, miR-17-3p, miR-17-5p, miR-20, miR-25, miR-93, miR-106a, miR-181a, miR-181b and others in GC cells; miR-21, miR-23a, miR-24, miR-29c, miR-30b, miR-146, miR-150 and others in memory cells.

2.1.5 microRNA expression in T cell differentiation and maturation

There are several well-defined differentiation stages that naive CD4+ or CD8+ T cells undergo from a CLP cell: double negative (DN) 1, DN2, DN3, DN4, double positive (DP). When comparing relative expression levels between DN1-DP to CD4+ or CD8+ cells (Neilson et al., 2007), expression of the following miRNAs was enriched at a specific stage: miR-21, miR-29b, miR-221, miR-223, miR-342 in DN1 cells; miR-191 in DN3 cells, miR-16, miR-20a miR-128b, miR142-5p in DN4; miR-92, miR-181a, miR-181b, miR-350 in DP cells; miR-297 and miR-669c in CD4+ cells; and miR-15b, mir-24, miR-27a, miR-150 in CD8+ cells. When comparing relative expression levels between antigen-specific naive, effector and memory CD8+ T cells (Wu et al., 2007), expression of the following miRNAs was enriched at a specific stage: let-7f, miR-16, miR-142-3p, miR-142-5p, miR-150 in naive cells; miR-21, miR-221, miR-222 in both effector and memory cells; miR-18, miR-31, miR-146a, miR-146b in memory cells.

2.2 Roles of microRNAs in cellular components of the innate immune system

Inflammation is now recognized as a hallmark of established tumors (Hanahan & Weinberg, 2011). Over the last years, multiple independent lines of research have identified inflammation as a promoter of both cancer initiation and malignant progression. The secretion of inflammatory cytokines and chemokines that drive inflammatory responses by cells of the innate immune system are primarily elicited by the recognition of common structures shared by many microorganisms by receptors that activate complex transcriptional programs. Toll-like receptors (TLR) are an important component of inflammatory responses in this context. They are present in various myeloid cell lineages and serve as sensor to pathogenic RNA and other molecules from parasites. However, TLRs can also recognize certain cellular components and promote inflammation under sterile conditions. For instance, HMGB1 (Tang et al., 2010) and several S100 proteins (Ehrchen et al., 2009; Hiratsuka et al., 2008) have been associated with TLR-dependent carcinogenic inflammation. TLRs have also been shown to regulate expression of specific miRNAs in Mϕs, DCs and other myeloid-derived cell types (O'Neill et al., 2011). Transcription and expression of miR-21, miR-146a and miR-155 among other miRNAs is regulated by several TLRs in different cellular contexts that we discuss in more detail below. In turn, miRNAs regulate TLR-dependent signalling by targeting mRNAs of TRLs, of downstream signalling proteins and/or of effector transcriptional factors (O'Neill et al., 2011).

2.2.1 microRNA-mediated neutrophil responses

Transcriptional repression of miR-21 and miR-196a expression by zinc finger factor independent-1 (Ggi1) is required for granulocytic development and differentiation as persistent high levels of these miRNAs in CMP cells block this program (Velu et al., 2009). Similarly, overexpression of miR-125b blocks granulocytic differentiation induced by granulocyte colony stimulating factor (G-CSF) in 32D cell lines (Surdziel et al., 2011). Conversely, upregulation of miR-27 expression by G-CSF3-induced C/EBPα transcriptional factor enhances granulocytic differentiation (Feng et al., 2009). High levels of miR-27 post-transcriptionally repress expression of Runx1 transcriptional factor, which antagonizes differentiation of CMPs or myoblast cell lines into granulocytes (Feng et al., 2009).

Unlike these previous examples of miRNA-mediated granulocyte differentiation which primarily affect the overall number, but not function, of available neutrophils, miR-223 controls differentiation and activation of neutrophils (Johnnidis et al., 2008). *mir-223* knockout mice have an increased number of neutrophils as a result of an abnormal expansion of the GMP cells due to dysregulation of transcriptional factor Mef2c (Johnnidis et al., 2008). Moreover, these miR-223-deficient neutrophils are hypermature and hyperactive causing spontaneous pulmonary inflammation and excessive tissue damage upon endotoxin challenge (Johnnidis et al., 2008).

2.2.2 microRNA-mediated Mϕ responses

Several pro-inflammatory mediators such as LPS, polyriboinosinic–polyribocytidylic acid (poly IC), Tumor Necrosis Factor (TNF) α, interferon (IFN) β, have been shown to induce miR-155 expression in monocyte and/or Mϕs (Faraoni et al., 2009). miR-155 enhances type I IFN signaling-mediated Mϕ responses against viral infection, mainly by downregulating expression of suppressor of cytokine signaling 1 (SOCS1) (Wang et al., 2010). miR-155 is also an important player in the interleukin (IL) 13-dependent fate determination between M1 (classical, pro-Th1, tumoricidal) and M2 (alternative, pro-Th2, tumorigenic) Mϕs. As IL-13 signalling via its cognate receptor IL13Rα1 and consequent phosphorylation of STAT6 favors M2 programs, miR-155 antagonizes this process by directly repressing expression of IL13Rα1 mRNA as well as by repressing expression of IL-13 responsive genes such as SOCS1, DC-SIGN, CCL18, CD23, and SERPINE (Martinez-Nunez et al., 2011).

Induction of miR-146a/b expression by IL-1β, LPS, TNF-α in monocytes is an NF-κB-dependent process (Taganov et al., 2006). miR-146 is engaged in a negative feedback loop with TLR and cytokine signalling via downregulation of IL-1 receptor-associated kinase 1 (IRAK1) and TNF receptor-associated factor 6 (TRAF6) mRNA levels, which are transducers of these signals (Taganov et al., 2006). Several studies indicate the importance of miR-146 regulatory role in Mϕs. *mir-146a* knockout mice develop lymphoid and myeloid malignancies as well as myeoloproliferation and myelofibrosis; dysregulated and increased activation of NF-κB-mediated transcription is a major contributing factor to the observed phenotypes (Zhao et al., 2011). Some viruses such as vesicular stomatitis virus (VSV) can disrupt the miR-146 regulatory loop as a means to dampen IFN-β (Hou et al., 2009). Mice infected with VSV upregulate miR-146 expression in Mϕs in a TRL-independent, but NF-κB-dependent manner, and thereby triggers miR-146-mediated downregulation of TRAF6, IRAK1 and IRAK2 target genes (Hou et al., 2009).

In contrast, high levels of miR-125b expression potentiate IFN-γ-mediated Mϕ responses (Chaudhuri et al., 2011). Enforced miR-125b expression enhances Mϕ activation and antigen presentation to T cells (Chaudhuri et al., 2011). miR-125b-mediated downregulation of IFN regulatory factor 4 (IRF4) explained in great part the observed phenotypes and the enhanced ability of miR-125b-overexpressing Mϕs to elicit more effective cancer cell rejection (Chaudhuri et al., 2011).

2.2.3 microRNA-mediated DC responses

mir-155 knockout mice exhibit impaired B cell, T cell, and DC immune responses (Rodriguez et al., 2007; Thai et al., 2007). Several evidences indicate that impaired B cell

responses result from disruption of intrinsic miR-155-mediated processes (Turner & Vigorito, 2008; Vigorito et al., 2007). However, impaired T cell responses may reflect functional defects in miR-155-deficient DCs, which have a decreased capacity to present antigens to T cells (Rodriguez et al., 2007), rather than intrinsic T cell proceses. Intriguingly, *in vitro* studies suggest that high levels of miR-155 interfere with antigen binding ability of DC, and therery antigen presentation to and activation of T cells (Mao et al., 2011; Martinez-Nunez et al., 2009). miR-155 has been shown to promote pro-inflammatory or anti-inflammatory responses in DCs via downregulation, along with other targets genes, of SH2-containing inositol 5-phosphatase (SHIP) and SOCS1 or IL-1β and TAK1-binding protein 2 (TAB2), respectively (Ceppi et al., 2009; Lu et al., 2008; O'Connell et al., 2008; O'Connell et al., 2009). Thus, miR-155 may exert different roles in DCs that are context-dependent such as physiological resolution of viral infection or pathological interaction with cancer cells in solid tumors.

As miR-146a/b and miR-155, expression of miR-148 family members (miR-148a, miR-148b, miR-152) is induced by TLR signalling in DCs (Liu et al., 2010b). By targeting expression of calcium/calmodulin-dependent protein kinase II (CaMKII), these miRNAs diminished antigen presenting capacity of DCs (Liu et al., 2010b).

2.2.4 microRNA-mediated NK cell reponses

NK mediate contact-dependent cytotoxicity and produce immunostimulatory cytokines that activate other immune cells. Cytotoxic granules contain perforin (Prf1) and granzymes (Gmzs), which are delivered by exocytosis into the target cells. miR-27a* modulates cytotoxic NK cell responses by regulating expression levels of both Prf1 and GzmB in resting and activated NK cells (Kim et al., 2011). Similarly, miR-29 dampens interferon (IFN) γ-mediate responses in NK and other lymphocyte lineages as observed in animals infected with intracellular bacterial pathogens such as *Listeria monocytogenes* (Ma et al., 2011).

2.3 Roles of microRNAs in cellular components of the adaptive immune system

The adaptive immune system comprises lymphocytes and their products (e.g., antibodies). Although the role of innate immune cells (e.g., NK cells) may be crucial to prevent tumor initiation, adaptive immune responses, particularly those mediated by effector T cells, are responsible for exerting spontaneous (and clinically relevant) immune pressure against the progression of many established cancers (Dunn et al., 2005; Yu & Fu, 2006). While the role of miRNAs in the development and functions of T and B cells has only started emerging very recently, it is becoming increasingly clear that B and T cell responses are tightly regulated by a network of miRNAs (O'Connell et al., 2010b).

2.3.1 microRNA-mediated B cell responses

Genetic manipulation of miR-150 expression and activity indicate an important role of this miRNA in B cell development and function (Malumbres & Lossos, 2010). Unimmunized *mir-150* knockout mice exhibit an expansion in splenic and peritoneal B1 cells and enhanced humoral responses as determined by increased serum immunoglobulin levels (Xiao et al., 2007). Conversely, enforced expression of miR-150 in B cell lineages caused arrested development at the pro-B to pre-B transition. miR-150-mediated processes largely impinge

on negative regulation of c-Myb transcriptional factor involved at multiple steps of lymphocyte development (Xiao et al., 2007).

Similar to miR-150 enforced expression, mice deficient in the *mir-17~mir-92* gene cluster (miR-17-5p, miR-18a, miR-19a, miR-19b-1 miR-20a, miR-92-1) also exhibit a disrupted B cell development at the pro-B to pre-B transition (Ventura et al., 2008). Dysregulated and increased levels of pro-apoptotic protein Bim are a key molecular alteration responsible for this defect (Ventura et al., 2008).

2.3.2 microRNA-mediated T cell responses

The importance of miRNAs in controlling T cell-mediated responses was first illustrated by the demonstration that specific deletion of Dicer in the T cell lineage resulted in impaired T cell development and aberrant T helper cell differentiation and cytokine production (Muljo et al., 2005). Subsequent studies have confirmed that Dicer controls CD8+ T-cell activation, migration, and survival (Zhang & Bevan, 2010). More recently, a unique signature of 71 miRNAs has been identified in activated T cells (Grigoryev et al., 2011). In an independent study, seven miRNAs (let-7f, miR-15b, miR-16, miR-21, miR-142-3p, miR-142-5p, miR-150) alone were shown to account for approximately 60% of all miRNAs in naive, effector and memory $CD8^+$ T cells. Among the multiple miRNAs modulated by T cell activation, miR-155 appears to be particularly important. miR-155 enhances inflammatory T cell development (O'Connell et al., 2010a), and it is known to be essential for the T cell-mediated control of *Helicobacter pylori* infection and for the induction of chronic gastritis and colitis (Oertli et al., 2011). miR-155 is also crucial for T helper cell differentiation and generating optimal T cell-dependent antibody responses (Thai et al., 2007).

Robust T cell responses require the up-regulation of anti-apoptotic pathways, accelerated cell cycle progression, and efficient antigen presentation. miR-181a modulates these processes by regulating expression levels of anti-apoptotic protein BCL2, transmembrane C-type lectin protein CD69 and T cell receptor (TCR) α during T cell binding to an antigen (Neilson et al., 2007). miR-181a exerts an important role for antigen sensitivity and selection during T cell development imparted by downregulation of TCR and phosphatases relaying TCR signalling (Li et al., 2007). These effects, however, have been mainly investigated in thymocytes, and further studies are needed to conclusively extend these results to peripheral T lymphocytes.

CD69 is upregulated by antigen-specific T cells following acute infection, but CD69 expression returns to basal levels after 72 hrs. CD69 regulates sphingosine 1-phosphate (S1P1) and controls the release and migration of activated T cell from central lymphoid organs (lymph nodes and spleen) to infection site (Shiow et al., 2006). Expression of miR-130 and miR-301 is dramatically upregulated following CD8+ T cells activation *in vitro* by TCR stimuli. miR-130 and miR-301, in addition to miR-181a, inhibit CD69 expression via binding to an MRE in the 3'UTR of CD69 mRNA (Zhang & Bevan, 2010). These results suggest that this miR-130/mir-301-mediated process is important to establish the timing of activated T cells into circulation.

Finally, miR-182 has been recently found to be induced by IL-2 to promote clonal expansion of activated helper T lymphocytes (Stittrich et al., 2010).

3. Pathological roles of microRNAs in cancer-related inflammation and immunity

Twenty-five years ago Dvorak compared tumors with wounds that do not heal for the first time in a seminal paper (Dvorak, 1986). As in wounds, inflammatory cells are present in the microenvironment of virtually all solid tumors. In addition, chronic inflammation increases the risk of developing cancers in certain organs (e.g., in the digestive tract). Most importantly, inflammation is a hallmark of cancer (Hanahan & Weinberg, 2011), including those tumors that are not associated with chronic inflammatory conditions (Colotta et al., 2009). Over the last years, the crucial role of TME inflammatory cells such as MDSCs, Mϕs and Tregs to the survival and proliferation of cancer cells, angiogenesis, metastasis, and, especially, immnosuppression, has been progressively unveiled.

miRNA-mediated regulation is required for optimal functioning of the immune system. Impairment of global or specific miRNA activity in leukocyte subsets can lead a broad spectrum of diseases and pathological conditions from autoimmune disorders (destruction of normal self cells) to cancer (protection of abnormal non-self cells). We focus here on the emerging roles in initiation and progression of cancer of leukocyte-expressed miRNAs in the TME of most solid tumors.

3.1 microRNA roles in anti-tumor immune surveillance and modulation of cancer progression

The crucial role of immune surveillance in the prevention of cancer is today beyond question among immunologists (Zitvogel et al., 2006). However, we cannot detect the tumors that are rejected by the immune system during the course of our lives. This implies that tumors that become clinically noticeable are the result of failure of the immune system. Multiple mechanisms cooperate in the TME and at distal locations in tumor-bearing hosts to prevent the rejection of established cancers. Independent work from several laboratories has recently demonstrated that tolerance to tumor antigens in advanced malignancies is not a merely passive event but, rather, an active process whereby multiple immunosuppressive cell types confer immune privilege to tumors (Zou, 2005). How the phenotype and mobilization of these immunosuppressive leukocytes are regulated by miRNAs is only starting to be understood.

3.1.1 Role of microRNAs in Myeloid-Derived Suppressor Cell (MDSC)-mediated immunosuppression

MDSCs are one of the major components of the immune suppressive networks operating in cancer-bearing hosts (Gabrilovich & Nagaraj, 2009). Tumor-derived factors (e.g., S100, proteins) induce excessive myelopoiesis, resulting in the massive mobilization of immature myelomonocytic cells in virtually all solid tumor-bearing hosts (Sinha et al., 2008). These myeloid cells correspond to precursors of both monocytes and granulocytes, but are influenced by tumor-derived inflammatory signals that multiply their regular numbers and transform them into crucial contributors to immunosuppression. The specific abrogation of anti-tumor T cells in the absence of global immunosuppression in cancer patients has been elegantly explained via a mechanism of nitration of the T cell receptor on the T-cell surface (Nagaraj et al., 2007). How MDSCs specifically take up tumor antigen (thereby preventing

cancer patients from being severely immunodeficient) remains to be clarified, but this mechanism provides a framework to explain the unresponsiveness of tumor-specific T cells in established tumors. In addition, other mechanisms such as production of Arginase are relevant for T cell tolerogenic function.

These immature leukocytes migrate from the bone marrow where they are produced to the periphery, and differentiate into immunosuppressive Mϕs or regulatory DCs at tumor sites. This primarily occurs from cells of the monocytic lineage, as granulocytic MDSCs tend to disappear in the periphery. However, many tumors accumulate myeloid cells that, at least in terms of light scatter properties and phenotypic markers, show attributes of classical neutrophils (Rodriguez et al., 2009). A great deal of phenotypic overlap and heterogeneity among myeloid leukocytes is therefore typically found in the microenvironment of different tumors, and even within the same tumor specimen. What these cells have in common is a strong immunosuppressive activity and the production of angiogenic factors that are crucial for tumor neovascularization (Ahn & Brown, 2008; Conejo-Garcia et al., 2004; Huarte et al., 2008; Mantovani, 2010; Mazzieri et al., 2011). Together, this heterogeneous mix of MDSCs, Mϕs, regulatory DCs and monocytes also contributes to the promotion of tumor growth and metastasis.

Very little is known about how miRNAs regulate the mobilization and activities of this crucial and abundant tolerogenic population. The most compelling evidence for the contribution of miRNAs to MDSC-mediated immune suppression has recently arised from the demonstration that the expression of STAT3, which promotes the suppressive activity of MDSCs, is silenced by the combined activity of miR-17-5p and miR-20a. Correspondingly, ectopic expression of miR-17-5p or miR-20a significantly reduced the capacity of MDSCs to suppress antigen-specific CD4 and CD8 T cells, both *in vitro* and *in vivo* (Zhang et al., 2011). Further research is needed to understand the contribution of miRNAs to the activity of MDSCs, as well as to design potential therapeutic interventions based on delivery of miRNA mimetics to promote their differentiation into immunocompetent (or at least less immunosuppressive) cells types.

3.1.2 Role of microRNAs in the function of Antigen-Presenting Cells (APCs)

Another hallmark of adaptive immune responses against tumor antigens is the abrogation of the capacity of APCs to elicit strong T cell activation. Among the miRNAs that participate in this process, miR-155 appears to be particularly important, because miR-155-defficient DCs simply fail to activate T cells (Rodriguez et al., 2007). In addition, miR-155 expression in bone marrow-derived DCs increases upon LPS-induced maturation and miR-155 is the only miRNA substantially up-regulated in primary Mϕs stimulated with a TLR3 agonist plus IFN-β (O'Connell et al., 2007; Rodriguez et al., 2007). Furthermore, our results indicate that tumor-derived regulatory DCs express very low levels of miR-155, and that delivery of miR-155 mimetics (see **Section 5**) to these cells promotes their capacity to effectively present tumor antigens and elicit protective anti-tumor immunity (manuscript under consideration). Interestingly, DCs matured in the absence of miR-155 express levels of MHC–II and co-stimulatory molecules similar to those seen on identically treated matured wild-type DCs, but they fail to present antigens or co-stimulate T cells.

In contrast to miR-155, expression of miR-21 decreases Th1 responses by preventing IL-12 secretion in activated DCs (Lu et al., 2011b).

3.1.3 Role of microRNAs in Treg-mediated immunosuppression

One of the crucial cell players actively suppressing the anti-tumor activity of effector anti-tumor T cells are Foxp3$^+$ regulatory T cells (Treg). Treg are essential to prevent autoimmunity in healthy hosts by suppressing autoreactive T cells. Because most epitopes recognized by tumor-reactive T cells are self-antigens, advanced tumors co-opt their regulatory functions to suppress anti-tumor T cell responses, which specifically occurs in the TME (Curiel et al., 2004). Correspondingly, Treg infiltration is associated with accelerated tumor progression and reduced survival. Several miRNAs have been reported to contribute to the tolerogenic function of Treg, and therefore can only be important for immunosuppression in the TME. Among them, miR-146a, typically overexpressed in Treg, is critical for their suppressor function by controlling the expression of Stat1 (Lu et al., 2010). In addition, miR-155, miR-21 and miR-7, which are all targets of Foxp3, silence Satb1 and are also collectively required for the suppressive function of Treg (Beyer et al., 2011).

3.1.4 Tumor-infiltrating T cells

Infiltration of tumor islets by T cells has been associated with significantly improved outcomes in multiple histological types of cancer (Dunn et al., 2005; Yu & Fu, 2006). As many tumor-specific antigens have been identified and shown to induce the production of specific antibodies in cancer patients, the protective activity of these lymphocytes has provided a rationale for using them to treat cancer (Ertl et al., 2011). Over the last years, some authors have restricted the protective role of T cells to the activity of cytotoxic (CD8$^+$) lymphocytes (Hamanishi et al., 2007; Sato et al., 2005), primarily because CD4$^+$ T cells include significant proportions of Treg. The considerations about the immunostimulatory and immunosuppressive roles of the miRNAs described above are extensive to tumor-associated lymphocytes. Other miRNAs that deserve further investigation specifically in tumor-associated T cells are miR-29, which suppresses immune responses by targeting IFN-γ (Ma et al., 2011); and miR-125b, which prevents differentiation of naive lymphocytes into effector T cells (Rossi et al., 2011).

3.1.5 Antibody-mediated B cell/mast cell carcinogenic interactions

B cells are another leukocyte subset crucially associated with the progression of at least certain epithelial cancer models through the production of antibodies with the collaboration of CD4+ T cells (Andreu et al., 2010). These antibodies against extracellular matrix components engage mast cells via Fc receptors and trigger secretion of pro-angiogenic factors and chemokines by mast cells. This induces the recruitment of myelomonocytic cells, including alternatively activated Mϕs (M2). Then, these M2 cells promote tumorigenicity in a completely Fc-dependent fashion (Andreu et al., 2010). The observation that mast cells, which are known to accumulate in the periphery of tumors, can contribute to immunosuppression has been solidly documented by elegant studies (de Vries et al., 2011; Lu et al., 2006; Wasiuk et al., 2009). The role of miRNAs in mast cells is particularly important in this context because mast cells actively release microparticles that transfer miRNAs and mRNAs to other cells (Valadi et al., 2007). This exosome-mediated exchange of genetic materials between tumor-infiltrating leukocytes and cancer cells in the TME, remains a poorly understood mechanism (Brase et al., 2010; Mostert et al., 2011; Scholer et al., 2010; Schwarzenbach et al., 2011).

3.1.6 Role of microRNAs in immunosuppression-driven metastasis

To be able to metastasize, sprouted cancer cells need to evade multiple mechanisms of immune surveillance. The role of miRNAs in this active process of immunosuppression has been recently illustrated by studies focused on miR-30b and miR-30d. Ectopic expression of miR-30b/d was shown to promote the metastatic behavior of melanoma cells by silencing the GalNAc transferase GALNT7 (Gaziel-Sovran et al., 2011). This resulted in the up-regulation of the immunosuppressive cytokine IL-10, which impaired anti-tumor immunity and promote metastatic spreading at these locations.

4. microRNA signatures in cancer

Whole tissue profiling is a powerful discovery tool to identify differential expression of miRNAs in cancerous tissues. Changes of miRNA expression in tumor samples compared to normal samples or between groups of tumor samples with a favourable and poor clinical outcome have been used to generate miRNA signatures with potential prognostic and/or predictive value. Differential miRNA expression in tumor samples has also been used to infer molecular alterations in miRNA-mediated processes within cancer cells, but without carefully considering the contribution of other cellular components of the TME to these changes of miRNA levels.

Similar experimental designs, approaches, statistical analyses and data interpretations have been applied to the study of leukemias and lymphomas, in which immune cells are the site of cancer, and solid tumors such as carcinomas (e.g. breast and lung cancer), in which immune cells are the inflammatory component of TME and epithelial cells are the site of cancer. The techniques employed in the majority of these profiling experiments did not allow to identify specific cell type(s) as the source of altered miRNA expression. Altered expression of leukocyte-expressed miRNAs likely reflects the recruitment of inflammatory cells to the TME in solid tumors rather than molecular aberrations within the cancer cell per se. Nonetheless, most of these leukocyte-expressed miRNAs are also expressed to some extent in other cell types (including in some instances cancer cells) and consequently total contribution of each individual cell and cell type(s) to the overall RNA levels of these miRNAs cannot be ascertained with these experiments (see **section 4.3**). We review below cancer-associated miRNA signatures in hematological and solid tumors. It is apparent that many of these signatures contain leukocyte-expressed miRNAs.

Consistent with its upregulation in several hematological cancers, including B cell lymphomas and acute myeloid leukemia, miR-155 is a contributor to malignant hematological progression when it is overexpressed in cancer cells (Xiao & Rajewsky, 2009). In mice, retroviral expression of miR-155 in bone marrow progenitors causes a myeloproliferative disorder (O'Connell et al., 2008) and constitutive overexpression of miR-155 in the B cell lineage results in pre-B cell proliferation and eventually B cell malignancy (Costinean et al., 2006). Deletions and certain polymorphisms in BRCA1 promote carcinogensis by preventing epigenetic repression of miR-155 expression (Chang et al., 2011). The paradoxical association between oncogenesis and effective immunity is not surprising, because robust adaptive immune responses require rapid expansion of leukocytes. For instance, T cell expansion requires the upregulation of anti-apoptotic mediators, including Bcl-x. Therefore, miR-155 plays a tumorigenic role when it is up-

regulated in cancer cells of hematological origin and a protective, anti-tumor function when it is expressed by certain immune cell types, including APCs, in the TME of solid tumors.

4.1 Altered microRNA expression in hematological tumors

Altered miRNA expression has been reported in all studied hematological malignancies, including chronic lymphocytic leukemia (CLL), B cell lymphomas, acute myeloid leukemia (AML), multiple myeloma, acute lymphoblastic leukemia, myeloproliferative neoplasms and others (Calvo et al., 2011; Fabbri et al., 2009; Fabbri & Croce, 2011; Kotani et al., 2010; Marcucci et al., 2011b; Schotte et al., 2011; Wieser et al., 2010; Williams et al., 2011). It is common for many of these hematological malignancies to harbor recurrent chromosomal abnormalities that: serve to classify types and subtypes; affect specific molecular pathways; and have different disease progression dynamics, response to treatment and outcome.

4.1.1 Altered microRNA expression in chronic lymphocytic leukemia

CLL is the most common type of leukemia in the United States (Parker & Strout, 2011). Risk of contracting this clonal malignancy of immature/mature B cells increases exponentially with age, especially after age 50 (Parker & Strout, 2011). This heterogeneous disease has an indolent and an aggressive presentation. Patients afflicted with indolent disease will not progress clinical for years, but patient afflicted with aggressive disease can have rapid disease progression. Standard of care consists of chemotherapy-based treatment for patients with progressive or aggressive disease, with no obvious benefit of early treatment in patients with indolent disease. miRNA expression profiling has been used to improve prognostics based on expression of zeta-chain (TCR)–associated protein kinase 70kDa (ZAP70) and T-cell leukemia/lymphoma 1 (TCL1) as well as recurrent chromosomal abnormalities (Parker & Strout, 2011). As a matter of fact, decreased expression of miR-15a and miR-16-1 gene cluster as a consequence of 13q14.3 chromosomal deletion was the first link between miRNAs and cancer (Calin et al., 2002). Similarly, decrease of miR-34b and miR-34c gene cluster and TP53 expression is due to 11q and 17 p chromosomal deletions, respectively (Fabbri et al., 2011). This association between decreased miRNA expression and chromosomal deletion has uncovered a regulatory feedback loop between p53 that transcriptionally activates expression of miR-15a~miR-16-1 and miR-34b~miR-34c which in turn regulate post-transcriptionally the expression of p53 and ZAP70, respectively (Fabbri et al., 2011). This provides a mechanistic understanding for indolent CLL that could be applied as a prognostic tool and therapeutic target. Expression profiling experiments have also highlighted miRNA signatures that could be useful to separate indolent and aggressive CLL cases. Along with miR-15a, miR16-1, miR-34b/c, differential expression of miR-17-5p, miR-21, miR-29b, miR-29c, miR-34a, miR-103, miR-155, miR-181a, miR-181b, miR-223, miR-342-3p has been shown to have diagnostic and/or prognostic value (Asslaber et al., 2010; Calin et al., 2005; Fabbri et al., 2011; Li et al., 2011; Merkel et al., 2010; Mraz et al., 2009; Pekarsky et al., 2006; Rossi et al., 2010; Sampath et al., 2011; Stamatopoulos et al., 2009, 2010; Zhu et al., 2011). Several mechanistic links have been proposed between these miRNAs and oncogenic pathways. Briefly, miR-15a and miR-16-1 inhibit expression of TP53, Bcl2, Mcl1 (Fabbri et al., 2011), miR-29 and miR-181 family members inhibit Tcl-1 expression (Pekarsky et al., 2006), miR-34 family member inhibit expression of B-Myb, E2F1 and ZAP70 (Fabbri et al., 2011; Zauli et al., 2011).

4.1.2 Altered microRNA expression in B cell lymphomas

B cell lymphomas are a heterogeneous group of diseases that more frequently present in older individuals and immunocompromised patients. These five types of B cell lymphomas accounts for more than 75% of all cases: Diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma and mantle cell lymphoma (MCL) (Jemal et al., 2010). A 10-miRNA signature (miR-17-5p, miR-92, miR-125b, miR-126, miR-135a, miR-150, miR-213, miR-301, miR-330, miR-338) and a 26-miRNA signature (including miR-34a, miR-92, miR-93, miR-150, miR-199a, miR-200c, miR-634, miR-638) separed cases from the most common types of B cell lymphoma, DLBCL and FL (Lawrie et al., 2009; Roehle et al., 2008). Moreover, miRNA signatures with prognostic and/or predictive value in all or specific (sub)types of B cell lymphomas have been reported. An 8-miRNA signature (let-7g, miR-19a, miR-21, miR-23a, miR-27a, miR-34a, miR-127, miR-195) was associated with outcome in DLBCL cases (Roehle et al., 2008), a 21-miRNA signature (including miR-21, miR-23, miR-27a, miR-30e, miR-199b, miR-330) with outcome in *de novo* DLBCL cases (Lawrie et al., 2009), and a 23-miRNA signature (including let-7a, let-7f, miR-20a, miR-20b, miR-30b, miR-96, miR-195, miR-221*, miR-1260, miR-1274a) with treatment response to chemotherapy in FL cases (Wang et al., 2011b). Differential expression of individual miRNAs has enough power to predict outcome as is the case for miR-18a, miR181a and miR-222 in DLBCL (Alencar et al., 2011), for miR-29 family members in MCL (Zhao et al., 2010) and for miR-92a in plasma of patients afflicted with different types of non-Hodgkin's B cell lymphomas (Ohyashiki et al., 2011). Several mechanistic links have been proposed between these miRNAs and oncogenic pathways. Briefly, miR-29 family members inhibit CDK6 expression in MCL (Zhao et al., 2010), and miR-34a inhibits FoxP1 expression in DLBCL (Craig et al., 2011).

4.1.3 Altered microRNA expression in acute myeloid leukemia

AML is the most common acute leukemia affecting adults in the United States (Jemal et al., 2010). AML is a very heterogenous disease and different types have been tradictionally classified based on cytological and cytogenetic characteristics. Molecular studies have provided clinical useful prognostic and functional factors, including gene mutations in c-KIT, Fms-like tyrosine kinase 3 (FLT3), nucleophosmin 1 (NPM1), and CCAAT enhancer-binding protein-α (CEBPα) (Foran, 2010). A 27-miRNA signature (including let-7a, miR-21, miR-23a, miR-27a, miR-125a, miR-128a, miR-199b, miR-210, miR-221, miR-222, miR-223) separed AML cases from acute lymphoblastic leukemia (Mi et al., 2007). Moreover, miRNA signatures with diagnostic, prognostic and/or predictive value in all or specific (sub)types of AML have been reported (Marcucci et al., 2009, 2011a). A 57-miRNA signature (including let-7a, miR-29a, miR-15a, miR-16-1, miR-17-5p, miR-20a, miR-25, miR-92a) correlated with mutation status of NPM1 (Garzon et al., 2008a), a 3-miRNA signature (miR-1331a, miR-155, miR-302a) with mutation status of FTL3 (Garzon et al., 2008a), a 5-miRNA signature (miR-20a, miR-25, miR-191, miR-199a, miR-199b) and a 2-miRNA signature (miR-29a, miR-142-3p) were associated with outcome in AML cases (Garzon et al., 2008b; Wang et al., 2011a). Differenntial expression of individual miRNAs has enough power to predict outcome as is the case for miR-181a, miR-191 and miR-199a (Garzon et al., 2008b; Schwind et al., 2010), to predict response to decitabine treatment as is the case for miR-29b (Blum et al., 2010). Several mechanistic links have been proposed between these miRNAs and oncogenic pathways. Briefly, CEBPα-induced miR-29 family members inhibit expression of Mcl-1 and

Ski (Eyholzer et al., 2010; Garzon et al., 2009; Teichler et al., 2011; Xiong et al., 2011), CEBPα-induced miR-34a inhibits E2F3 (Pulikkan et al., 2010), miR-193b, miR-221 and miR-222 inhibit c-KIT expression (Gao et al., 2011; Isken et al., 2008).

4.2 Altered microRNA expression in solid tumors

Altered miRNA expression has been reported in all studied solid tumors, including breast, brain, colorectal, gastric, lung, ovarian, pancreatic, prostate, skin, and thyroid cancers (Barbarotto et al., 2008; Fabbri, 2010; Li et al., 2010; Liu et al., 2011; Pallante et al., 2010; Sempere, 2011). Carcinomas of the breast, colon and lung collectively account for more than 247,000 cancer-related deaths per year in the United States (Jemal et al., 2010). We will use these solid tumors to exemplify the etiological contribution of TME leukoctyes and to expose the enrichment of leukocyte-expressed miRNAs in reported diagnostic and prognostic miRNA-based signatures.

Immunohistochemical (IHC) characterization of cell type(s) present in the immune cell infiltrate in the TME can also be indicative of response to treatment. In breast cancer, the ratio of CD4+ T cells, CD8+ T cells and CD68+ monocytes/Mϕs is an independent prognostic indicator of recurrence-free and overall survival (DeNardo et al., 2011). A high number of infiltrating CD68+ cells, presumably with M2 attributes, in the TME is thought to decrease treatment response to chemotherapy (DeNardo et al., 2011). Recent gene ontology-annotated mRNA signatures has uncovered the important contribution and prognostic value of immune cell signatures in breast, colorectal and lung cancer (Finak et al., 2008; Kristensen et al., 2011; Roepman et al., 2009).

4.2.1 Altered microRNA expression in breast cancer

Breast cancer is the most prevalent and second most common cause for cancer-related death of women in the United States (Jemal et al., 2010). There are four major intrinsic subtypes based on mRNA expression profiles (Sims et al., 2006; Sorlie, 2004) which closely correlate with expression status of estrogen receptor (ER), progesterone (PR) and Human Epidermal growth factor Receptor-like 2 (HER2) (Carey et al., 2006). Targeted therapies exist to interfere with ER and HER2 oncogenic signalling pathways (Caskey, 2010). Several groups have reported prognostic miRNA signatures, which include multiple leukocyte-expressed miRNAs (miR-7, miR-21, miR-150, miR-221, miR-222, miR-342). A 4-miRNA signature (miR-7, miR-128a, miR-210, miR-516-3p), a 3-miRNA signature (miR-30a-3p, miR-30c, miR-182), and a 4-miRNA signature (miR-128a, miR-135a, miR-767-3p, miR-769-3p) were associated with outcome in ER+ cases (Buffa et al., 2011; Foekens et al., 2008; Rodriguez-Gonzalez et al., 2011), a 6-miRNA signature (miR-27b, miR-30c, miR-144, miR-150, miR-210, miR-342) with outcome in ER- cases (Buffa et al., 2011), a 4-miRNA signature (miR-21, miR-210, miR-221, miR-222) with outcome in ER-PR-HER2- cases (Radojicic et al., 2011), and a 2-miRNA signature (miR-21, miR-181a) with outcome in all comers (Ota et al., 2011).

4.2.2 Altered microRNA expression in colorectal cancer

Colorectal cancer is the third leading cause of cancer-related death for both men and women in the United States (Jemal et al., 2010). There are two major molecular subtypes: microsatellite stable (MSS) and microsatellite instable (MSI). MSI phenotype is observed in about 15% of

cases, is associated with a better prognosis and exhibits a different chemosensitivity profile to therapeutic agents (Pino & Chung, 2011; Vilar & Gruber, 2010). Several groups have reported diagnostic and prognostic miRNA signatures, which include multiple leukocyte-expressed miRNAs (miR-17-5p, miR-20, miR-25, miR-142-3p, miR-155, miR-223). A 8-miRNA signature (miR-92, miR-93, miR-106a, miR-125a, miR-142-3p, miR-144, miR-151, miR-212) and a 14-miRNA signature (miR-17-5p, miR-20, miR-25, miR-32, miR-92, miR-93, miR-106a, miR-125a, miR-155, miR-191, miR-192, miR-203, miR-215, miR-223) separated MSS and MSI cases (Lanza et al., 2007; Schepeler et al., 2008), a 2-miRNA signature (miR-320, miR-498) was associated with outcome in stage II MSS cases (Schepeler et al., 2008).

4.2.3 Altered microRNA expression in lung cancer

Lung cancer is the leading cause of cancer-related death for men and women in the United States (Jemal et al., 2010). There are two major histological subtypes: small-cell (SCLC) and non-small cell (NSCLC). NSCLC represent about 80% of all lung cancer cases and can be further divided in three histological groups: large cell carcinoma, squamous cell (SCC), adenocarcinoma (AdCa) (Wistuba & Gazdar, 2006). Several groups have reported diagnostic and prognostic miRNA signatures, which include multiple leukocyte-expressed miRNAs (miR-16, miR-17-5p, miR-20a, miR-20b, miR-29a, miR-29b, miR-29c, miR-106a, miR-106b, miR-146-5p, miR-146b, miR-155, miR-181a, miR-221). A 34-miRNA signature (including let-7a, let-7e, miR-16, miR-17-5p, miR-19b, miR-20a, miR-29a, miR-29b, miR-29c, miR-30b, miR-106a, miR-106b, miR-146-5p, miR-181a, miR-191, miR-195, miR-491-5p, miR-663) separated AdCa and SCC subtypes in male smokers (Landi et al., 2010), a 6-miRNA signature (let-7a, miR-221, miR-137, miR-182*, miR-372) was associated with outcome in NSCLC (Yu et al., 2008), a 19-miRNA signature (let-7e, miR-17-5p, miR-20a, miR-20b, miR-21, miR-93, miR-106a, miR-106b, miR-126, miR-146b, miR-155, miR-182, miR-183, miR-191, miR-200a, miR-200c, miR-210, miR-224) with outcome in SCC cases (Raponi et al., 2009), and a 5-miRNA signature (let-7e, miR-34a, miR-34-5p, miR-25, miR-191) with outcome in male smoker SCC cases (Landi et al., 2010).

4.3 Characterization of miRNA expression at single cell resolution in the TME

Solid tumor tissues are a complex and heterogeneous mixture of different cell types, in which cancer cell interact and intermingle with other cellular components of the TME. We and others have implemented similar *in situ* hybridization (ISH) methods to identify the cellular compartment(s) of altered miRNA expression in a variety of solid tumors, including brain, breast, colorectal, lung, pancreatic, and prostate cancer (Dillhoff et al., 2008; Donnem et al., 2011; Gupta & Mo, 2011; Habbe et al., 2009; Jorgensen et al., 2010; Liu et al., 2010a; Nelson et al., 2006, 2010; Nelson & Wilfred, 2009; Nielsen et al., 2011; Preis et al., 2011; Qian et al., 2011; Rask et al., 2011; Schepeler et al., 2008; Schneider et al., 2011; Sempere et al., 2007, 2010; Yamamichi et al., 2009). miR-21 and miR-155 are frequently detected at higher levels in solid tumors and their differential expression correlates with outcome (Barbarotto et al., 2008; Sempere, 2011). Using a combined ISH/IHC multiplex assay, we determined that miR-21 and miR-155 are expressed in different cellular compartments of the TME (Sempere et al., 2010). miR-21 was predominantly expressed within reactive stroma (tumor associated fibroblasts) in breast and colorectal tumors, and within cancer cells in lung, pancreatic and

prostate tumors. Cellular co-localization of miR-155 and CD45 (leukocyte marker) signals, but not that of CK19 (epithelial cell marker) indicated a predominant expression of miR-155 within a subset of immune cells in the TME (Sempere et al. 2010). Our unpublished observations suggest that miR-155 is predominantly expressed in a subset of myeloid-derived immune cells (MPO+CD68-) in the TME of breast and colorectal tumors as determined by co-staining with cell type-specific and functional markers of major immune cell types (e.g., CD4, CD8, CD19). Further contextual characterization to identify the immune cells that upregulate or downregulate miR-155 and other leukocyte-expressed miRNAs in the TME should shed light on their etiological contribution to modulate cancer aggressiveness and progression.

5. Manipulation of microRNA activity in the tumor microenvironment by non-viral synthetic compounds as a novel approach for cancer therapy

The crucial role of miRNAs in the immunobiology of cancer makes them attractive targets for the design of novel interventions to modulate their activity. Delivery of miRNAs that are lost in cancer cells has been accomplished using viral vectors, which results in impressive therapeutic benefits (Kota et al., 2009). However, direct administration of viral vectors to cancer patients represents a major challenge in terms of clinical implementation. Alternatively, synthetic miRNA oligonucleotides or antagonistic compounds could be delivered through nanoparticles or microparticles, complexed to polymers or liposomes. The caveat of this approach is that, as commented above, a myriad of phagocytic cells with enhanced endocytic pathways are present in the microenvironment of virtually all solid tumors. Overcoming endocytosis by these abundant leukocytes and reaching cancer cells represents a barrier that, at least in our hands, has proven impossible (Cubillos-Ruiz et al., 2009a, 2009b; Cubillos-Ruiz et al., 2010). Nevertheless, the myeloid leukocytes that spontaneously take up particulate materials are also optimal targets for miRNA mimetics-based interventions. Thus, the crucial role of these cells in promoting the survival and proliferation of cancer cells, angiogenesis, metastasis and immnosuppression, as well as their plasticity and preferential homing to tumor sites facilitates their targeting as "Trojan Horses". In proof-of-concept experiments, we have been able to deliver double-stranded RNA oligonucleotides specifically to myeloid leukocytes in TME of ovarian cancer mouse models, which transformed these myeloid leukocytes from an immunosuppressive to an immunostimulatory cell type, resulting in significant therapeutic activity (Cubillos-Ruiz et al., 2009a). More recently, taking advantage of this established delivery system, we have been able to deliver synthetic miRNAs to the same cells, which transformed more than a third of their transcriptional profile and turned them into effective antigen-presenting cells that elicit protective anti-tumor immunity (manuscript under consideration). Furthermore, synthetic miRNA mimetics, as double-stranded oligonucleotides, are recognized by TLR3 and TLR7, which results in an additional non-specific activation stimulus. Because TLR agonists are known to synergize with CD40 activating reagents (Scarlett et al., 2009), which have demonstrated impressive effectiveness against pancreatic cancer (Beatty et al., 2011), their combined activity could be even stronger. Consequently, the abundance of natural phagocytic cells that avidly take up nanoparticles, which has been traditionally a major hurdle for targeted delivery of systemically administered nanoparticles, represents an advantage for effectively reaching this immunological-based therapeutic target.

6. Conclusion

We have reviewed evidences of miRNA-mediated processes that modulate immune responses. The effects of miRNA-mediated regulation are cell type-, stage- and context-dependent. Thus, cautions should be exercised when observed effects of miRNAs on clearly demarcated and controlled set of experiments in animal models are to be extrapolated from a physiological to a pathological context such as cancer and are to be generalized to human physiology and disease. This is of great importance when fragmentary knowledge of altered miRNA expression in whole tumor tissue biopsies is used to infer etiological roles and functional consequences of this presumed miRNA dysregulation in cancer cells.

As commented above, hematological cells are the site of cancer origin in leukemias and lymphomas. Therefore, it is reasonable to assume that dysregulation of leukocyte-expressed miRNA-mediated developmental and differentiation programs can be exploited by the cancer cells to become malignantly transformed. However, immune cells are an inescapable and important component of the TME in solid tumors, in which epithelial cells or mesenchymal cells are the site of cancer origin, in carcinomas or sarcomas, respectively. Although it is possible that cancer cells dysregulate within themselves the activity of leukocyte-expressed miRNAs to hijack and stimulate tumorigenic immune responses in the TME of solid tumors, it is more parsimonious that cancer cells via cellular interactions and paracrine signals interfere with immunomodulatory properties of leukocyte expressed-miRNAs such as miR-29 and miR-155 within specific subsets of infiltrating immune cells.

Further investigations are needed to understand the role that miRNAs play in cancer, both in hematological and solid tumors. We hope that our reflections here serve to inform the experimental design of future pre-clinical and clinical studies, namely, that cell type-specific and context-dependent effects of miRNA-mediated immunomodulation are appropriately considered and distinguished from miRNA-mediated processes within cancer cells and other cellular compartments of the TME. This could have important clinical implications and applications since reprogramming a subset of immune cells to elicit anti-tumor responses is an appealing and potentially feasible approach for therapeutic intervention.

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Tumor microenvironment represents an extremely dynamic niche shaped by the interplay of different cell types (e.g. tumor cells, stromal cells), their soluble products (e.g.cytokines, chemokines and growth factors) and varied physico-chemical conditions (e.g low oxygen concentration or hypoxia). Recent studies have identified myelomonocytic cells as key players in regulating the tumor microenvironment and hence, tumor progression in a variety of cancers. In view of these findings, the present book attemps to provide a comprehensive account of the diversity of tumor microenvironment across different cancers and how myelomonocytic cells have taken the center-stage in regulating this niche to direct cancer progression. A better understanding of the myelomonocytic cells and the mechanisms by which they regulate cancer progression will open new vistas in cancer therapeutics.

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