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miR-148a weaves its thread into the plasma cell fate.

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Abstract

The plasma cells (PC) are characterized by their rarity, their formidable capacity to continuously secrete massive amounts of antibodies and the potential to live through the whole life span of the organism that houses them. Because of the potency of their effector function, their differentiation and survival are tightly regulated. The PC identity is implemented and maintained by a transcriptional program that allow them to face the challenges entailed by their longevity and high metabolic activity. The main transcription factors overseeing this transcriptional network have been identified (BLIMP1, IRF4, XBP1), but new players, like miRNA, continue to emerge and bring new layers of complexity to the regulatory loops.

In the current issue of the *European Journal of Immunology* [Eur. J. Immunol. 2021. 51: XXXX-XXXX], Pracht et al. identify miR-148a as a significant actor of the PC program that favors the differentiation through the inhibition of competitor fates, and supports the survival and fitness of the long-lived PC. In this commentary, we will discuss the place of miR-148a in the PC transcriptional network and its potential as a therapeutic target in PC-driven diseases.

Keywords: antibody-secreting cell, miRNA, transcription regulation. BLIMP1

See accompanying article by Pracht et al.

During differentiation, a cell transitions through successive states of decreasing potency to reach a determined fate. Each step of the way is characterized by significant changes of the gene expression profile. The implementation of transcriptional programs requires a timely control of vast numbers of genes, and development stages are thus marked by defined sets of transcription factors [1]. Because of the binding nature of the expression of these sets, transcription factors make unparalleled cell type markers and are an integral part of the identity of the cell. Each new wave of transcription factors switches on the genes underlying the capacities and function of a particular stage, but also suppresses obsolete, and more importantly, antagonist gene pathways. Therefore, silencing is as essential as activating gene expression in the differentiation process.

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A good example of the drastic evolution of a transcriptional landscape induced by fate decision is the plasma cell (PC), the terminal stage of the B cell lineage. As an antibody-secreting cell (ASC), it is a specialized cell that possesses a totally distinct function and transcriptional program from its direct precursor, the mature B cell (Figure 1) [2]. The ASCs, that regroup the cycling plasmablast and the post-mitotic long-lived PCs, are dedicated to the secretion of huge quantities of antibodies. A strong commitment that is reflected in its morphology, metabolism and transcriptome, as illustrated by the fact that close to 70 % of ASCs' transcripts are devoted to the immunoglobulins [3]. On the other end, the mature B cell roles are mainly to scout for foreign antigens, present them to T lymphocytes and differentiate into a memory B cell or an ASC. In a T-dependent response, the activated B cell will enter in a particular stage, the germinal center (GC) B cell, which allows a high level of affinity maturation and class switching of its immunoglobulin. The GC transcriptional program, led by BCL6, IRF8 and BACH2, by antagonizing the PC transcriptional program (Figure 1) and delaying the differentiation into ASC, allows the GC B cell to go through several rounds of affinity maturation and increases the rate of class switching [2].

The differentiation into ASC will occur only after several rounds of division [4] and is spearheaded by a triad of transcription factors, BLIMP1, IRF4 and XBP1, that orchestrates the PC transcriptional program (Figure 1). BLIMP1 in particular switches off several master regulators of the B cell fate (PAX5, BCL6, SPIB) and shuts down wide groups of canonical B cell genes [2]. The inhibitory function of BLIMP1 is mainly carried out through direct repression of the transcription and the recruitment of histone-modifying enzymes to induce epigenetic silencing [5]. However, Pracht et al. in this issue of *European Journal of Immunology* propose that BLIMP1 also achieves the silencing of some of the ASC fate antagonists (BACH2, MITF) through the expression of miR148a, a microRNA (miRNA) that regulates the differentiation and homeostasis of the ASCs [6].

miRNAs are small non-coding RNAs that exist in all animal cells and regulate gene expression. They act mainly as post-transcriptional inhibitors through mRNA silencing: they bind to target messengers and induce their degradation or block their translation [7]. Several miRNAs have been implicated in the GC response, ASC differentiation and/or homeostasis (Figure 1). miR155 was found to target PU.1, IRF8, AID and pro-apoptotic genes, thereby modulating GC B cell and plasmablast numbers, class switching and affinity maturation of the immunoglobulins [8-11]. BCL6, the master regulator of the GC in B and T cells, in addition of binding directly to its target genes, promote the GC program by repressing several miRNA, including miR155 and miR142 [9]. The miR142-KO mouse develops a hypogammaglobulinemia and a splenomegaly with hyper-proliferating B cells, notably due to the deregulation of BAFF-R, CD84 and SAP [12,13]. In turn, BCL6 is enhanced by miR-217, which shields it against the degradation induced by the DNA damage response in GC B cells [14]. In mice transgenic for miR217, GC B cell numbers, somatic hypermutation and BCL6 expression all increase.

Concerning the triad of transcription factors that governs ASC differentiation and function, few miRNAs have been identified to influence their expression. miR-125b can target both IRF4 and BLIMP1 in different cell types including B cells [15,16], and its over-expression affects cell survival. The miR-30 family can also modulate IRF4 and BLIMP1, as well as Ell2, a transcription elongation factor critical for the expression of secreted immunoglobulins [17] and XBP1, a regulator on the Unfolded Protein Response [18]. In a genome-wide study on *in vitro* differentiated human plasmablasts, Tsai *et al.* identified two opposite miRNA hubs: the first including miR-101, -125b and -223 was down-modulated during differentiation and synergistically inhibited BLIMP1, the second, containing miR-34, -148a and -183, was up-regulated and suppressed BCL6, BACH2 and FOXP1 [19]. These findings illustrate how miRNAs, like transcription factors work cooperatively in networks to regulate gene pathways. Interestingly, these two networks form regulatory loops; as for example BLIMP1 represses the expression of the hub miR-101, -125b and -223.

The report from Pracht *et al.* focuses on miR148a. In a previous study, this group identified miR148a as the most abundant miRNA in murine and human ASCs, and found that its expression was specific to this stage in the B cell lineage [20]. They determined that miR148a promoted ASC differentiation via the repression of BACH2, MITF (an inhibitor of IRF4), and promote survival through the down-regulation of BIM and PTEN. For their current study, they extended these data obtained on *ex vivo* or *in vitro* cultured cells, by generating a miR148a-floxed mouse. In the context of a B cell-specific deletion, the generation of ASC was reduced, in particular the switched cells, and the memory B population increased in parallel. This phenotype is the opposite of the BACH2-null mouse [21], and suggests that the absence of miR-148a leads to an extended expression of BACH2 that favors isotype switching and memory fate over the ASC generation. To identify additional targets of miR-148a, Pracht *et al.* performed an RNA-sequencing analysis on bone marrow PCs. In line with their previous work, the authors found that miR-148a inhibited PTEN and favored the expression of CD93 and BCMA, two receptors that sustain PC survival. The predominant loss of long-lived mature CD19⁺ PC in the bone marrow of the inducible miR148a KO mice also supports that miR-148a favors the survival of PCs. Notably, in addition to a shortened longevity, the bone marrow KO PC population could be crippled by a reduced capacity to hold to its niche, due to an increased expression of the chemokine receptor CXCR3 that could compete with CXCR4 and lead the migratory cells away from the medullar niche. In keeping with this hypothesis, PCs were detected in the circulation after the inducible deletion of miR148a.

A key feature of PC homeostasis is their particular metabolism that sustains the massive production of glycosylated antibodies. The glycoprotein synthesis requires large amounts of amino acids, glucose and energy in the form of nucleoside triphosphates, and the plasma cell metabolism is notably more demanding than that of plasmablasts, as their secretory abilities are superior. Importantly, beyond allowing the cell to reach full effector capacities, adopting and maintaining a specific combination of

high import of nutrients and oxidative respiration seems a prerequisite for a PC to strive and reach longevity [22,23]. Pracht et al. found that miR148a enhanced the expression of the main glucose transporter GLUT1 and of the oxidative phosphorylation pathway as a whole. In line with these findings, both glucose import and the mitochondrial respiration were diminished in ASCs in absence of miR148a. This deficient oxidative metabolism of the PC could impair both the function and the survival of long-lived PCs. It is noteworthy that the loss of miR148a also affected the expression of CD98, a crucial amino acid transporter regulating the mTOR pathway; as it could curb the proteosynthesis, resulting in a potential lower capacity of antibody generation. Additionally, the gene set enrichment analysis pinpointed to the protein translation processes as likely targets of miR148a. It would be of interest to further investigate the impact of miR148a on the proteosynthesis and the antibody secretion at the cellular level. Particularly as the regulation of this process is overseen by BLIMP1 in the ASC [24], and Pracht et al. made a correlation between the expression of BLIMP1 and miR148a. In this study, they observed that the BLIMP1 heterozygous cells expressed a lower amount of miR148a, and in their previous study, they noticed that the expression of the two genes followed similar kinetics during the ASC differentiation [20]. If miR148a was confirmed to be a direct target of BLIMP1, it would be interesting to understand which BLIMP1 indirect activity is attributable to miR148a. A cooperative action on some genes is also conceivable, as CD93 and CD98 are identified targets of both BLIMP1 and miR148a.

As regulators of gene expression, the miRNAs make prime oncogenes and tumor suppressors. An example of oncogene is miR-21, one of the most frequently deregulated miRNA in malignancies, including B cell lymphoma b[25]. miR-21 is a STAT3 target that can be induced by IL-21 in activated B cells, but is repressed by BLIMP1 during normal ASC differentiation. However, multiple myeloma cells can re-express it after stimulation by IL-6, where miR-21 contributes to the pro-survival effect of STAT3 [26]. Pracht et al. report that miR-148a is one of the three most abundant miRNA in human multiple myeloma. Its influence on both survival and niche retention confers to miR-148a a particular attractiveness as a therapeutic target as the bone marrow niche is well known to protect the multiple myeloma cells against chemotherapy [27]. Furthermore, it has been shown that the knockdown of miR-148a in a multiple myeloma cell line induces a cycle arrest [28]. Importantly, the effect of miR-148a on metabolism is not to be neglected as part of its therapeutic potential. In addition to contributing to the fitness of the cell, the modulation of the metabolism, if miR-148a impacts the secretory function will be of interest for numerous disorders, inflammatory or auto-immune, where an excessive production of antibodies contributes to the pathology. Finally, the deregulation of the immunoglobulin glycosylation can also have pathological consequences, as illustrated by the link established between the aberrant glycosylation of IgA in nephropathy and the abnormal expression of miR-148b [29].

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Conflict of interest:

The author declares no commercial or financial conflict of interest

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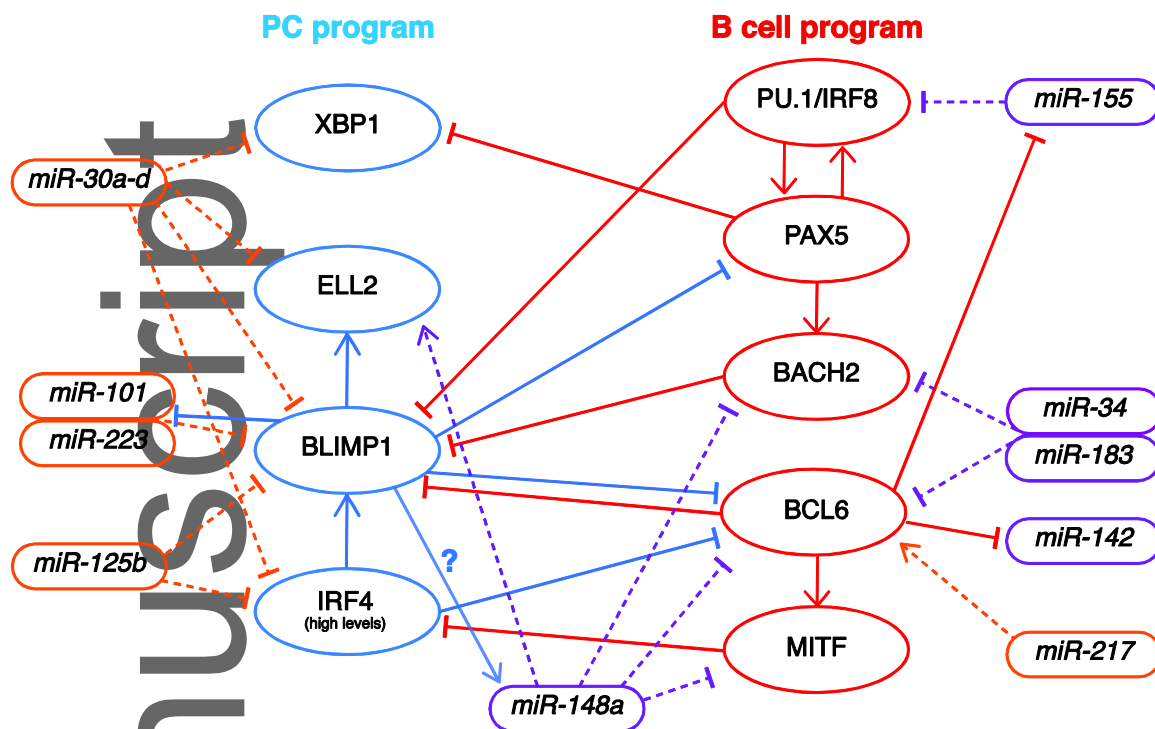
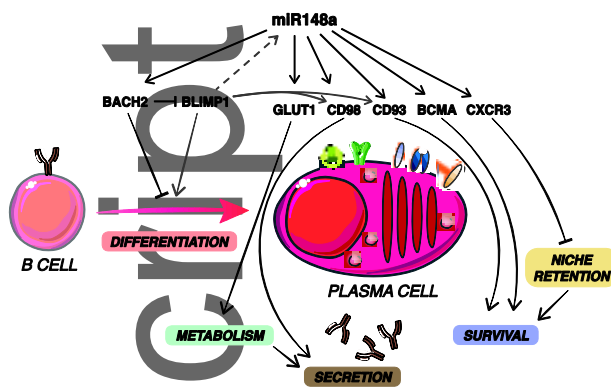


Figure 1. The gene regulatory networks of B and plasma cells.

This figure depicts model gene regulatory networks and shows the action of key transcription factors (ellipse) and miRNA (round rectangle). The lines indicate the direct regulation by binding of the transcription factor (solid line) or the miRNA (dashed line). The plasma cell network is colored in red/orange and the B cell network in blue/purple.

BACH2, BTB and CNC homologue 2; BCL6, B cell lymphoma 6; BLIMP1, B lymphocyte-induced maturation protein 1; ELL2, Elongation Factor For RNA Polymerase II 2; IRF, interferon-regulatory factor; miR, micro-RNA; MITF, Melanocyte Inducing Transcription Factor; PAX5, paired box protein 5; XBP1, X-box-binding protein 1 .

Graphic abstract



miRNA are key players of the transcriptional programs that define each cell type. miR148a supports the differentiation, metabolism and homeostasis of plasma cells through the regulation of multiple genes.