Editorial

A miR-20a/MAPK1 connection widens therapeutic perspectives in breast cancer

Lucas Philippe[1], Philippe Georgel[2,3]

[1]Department of Cellular and Molecular Physiology, Yale School of Medicine, New Haven, CT 06510, USA; [2]Université de Strasbourg, INSERM, ImmunoRhumatologie Moléculaire UMR_S 1109, Fédération de Médecine Translationnelle de Strasbourg, Faculté de Médecine, F-67000 Strasbourg, France; [3]Fédération Hospitalo-Universitaire, OMICARE, Centre de Recherche d'Immunologie et d'Hématologie, 67085 Strasbourg, France

Correspondence to: Philippe Georgel. Université de Strasbourg, INSERM, ImmunoRhumatologie Moléculaire UMR_S 1109, Fédération de Médecine Translationnelle de Strasbourg, Faculté de Médecine, F-67000 Strasbourg, France. Email: pgeorgel@unistra.fr.

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Over the past decade, microRNAs (miRNAs) have emerged as major players enabling accurate gene expression and regulation. As such, they participate in basic cellular processes, like apoptosis and proliferation which are often deregulated in cancer cells (1). This feature has been largely documented in the case of the miR-17~92 cluster, the overexpression of which is a key event in oncogenesis (2). This observation substantiated the concept of "oncomiRs" to describe the microRNAs encoded into this cluster (6 miRNAs, miR-17, miR-18a, miR-19a, miR-19b, miR-20a and miR-92a are encoded in this polycistron) or others distributed all over the genome and responsible for cancer initiation (3,4). On the other hand, mitogen-activated protein kinases (MAPK) are essential proteins involved in intracellular transduction of signals controlling important healthy cells decisions such as growth, survival, differentiation and development; in addition, MAPK are also involved in uncontrolled inflammation or apoptosis in various pathological settings (5), including cancer (6).

In a recent report, Si *et al*. explored the connection between these two important actors of tumorigenesis and observed an inverse correlation between miR-20a/b expression levels and chemoresistance in breast cancer-derived cell lines (7). *In vivo*, they showed that breast cancer patients with low miR-20a expression exhibited poorer survival compared to those characterized with higher miR-20a levels and a better prognostic. To analyze the underlying mechanism, miR-20a mimics were transfected in breast cancer cells. These experiments demonstrated that increased miR-20a expression inhibited cell proliferation and the occurrence of chemoresistance when paclitaxel (PTX) or other chemotherapeutic agents were added into the culture medium. In an animal model, in which cancer cells were grafted into immunodeficient mice, co-administration of cholesterol-conjugated miR-20a and PTX significantly reduced tumor growth and increased apoptosis. Almost 2,000 genes are bioinformatically predicted to be targeted by miR-20a, among which those participating in MAPK signaling and cancer-related pathways are significantly enriched. To reduce the list of potential miR-20a targets, Si *et al*. selected only those common to these pathways and known to regulate cell growth, proliferation or drug resistance. Interestingly, five genes exhibited miR-20a-dependent reduced expression in a luciferase-based assay, among which *MAPK1* appeared of high interest. Of note, both genetic ablation (using siRNA transfection) and pharmacological inhibition of MAPK1 reduced cancer cells proliferation and drug resistance. Drug resistance often require ATP binding cassette (ABC) transporters that efflux drugs out of cells, and indeed, Si *et al*. observed accumulation of *P-Gp/ABC1* expression in breast cancer-resistant cells, a phenomenon correlated with MAPK1 augmented expression and miR-20a reduction. Besides its action on drug resistance, miR-20a also promoted cancer

cells apoptosis through MAPK1-dependent regulation of the *Bcl-2* and *c-Myc* genes. Finally, the authors demonstrated that reduced miR-20a expression in cancer cells results from specific epigenetic modification of histones at the corresponding locus.

A first intriguing discovery in this paper is the negative impact of miR-20a on *c-MYC* expression. Indeed, c-MYC is a well-described transcription factor of the cluster miR-17~92 (8), and therefore, by negatively regulating the ERK signaling pathway, miR-20a-dependent decrease of c-MYC expression would decrease its own expression. However, low levels of miR-20a and high expression of c-MYC likely implies the deregulation of a negative feedback loop, potentially involving several factors participating in tumor progression.

Another interesting observation of this report is the fact that regulation of miR-20a in drug resistant breast cancer cell lines appears uncoupled from that of other members of the 17~92 cluster. Indeed, a microarray analysis of the BADS-200 cell line shows miR-20a downregulation, in contrast to miR-18a which is upregulated in the same dataset. As previously noted by others, the different members of the miR-17~92 cluster do not necessarily display a similar expression profile. Whether this is due to detection levels artefacts or to the specific dysregulation of a single miRNA within the cluster is an interesting issue which has not been mechanistically clarified yet.

In addition, this study provides evidence that miR-20a, possibly like many other microRNAs, exhibit multiple, sometime opposing activities. Many reports have evidenced a pro-tumorigenic role of miR-20a, which appears in sharp contrast with the data presented in this paper. This illustrates the pleiotropic roles of microRNAs, fine-tuners of the expression of multiple genes (9) as illustrated in the present study through the simultaneous effect of miR-20a on both drug resistance and apoptosis. One might regret that data presented in this paper keep demonstrating the connections between miRNAs and their likely target genes through bioinformatics predictions and the classical luciferase-based assay. More thorough and biologically relevant approaches, such as single cell joint miRome/transcriptome analysis and use of conditional or targeted knock-out mouse models should further document *in vivo* the complex interactions of the miR-20a/MAPK1/c-MYC pathway in cancer for a better prognostic and therapeutic management of patients in the future. Nevertheless, this study represents an important step forward to achieve this goal.

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Footnote

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