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## **Flick the cancer stem cells switch to turn cancer off**

Christophe Ginestier<sup>1</sup>, Daniel Birnbaum<sup>1</sup>, and Emmanuelle Charafe-Jauffret<sup>1</sup>

1. Aix Marseille Univ, CNRS, INSERM, Institut Paoli-Calmettes, CRCM, Molecular Oncology "Equipe labellisée Ligue Contre le Cancer", Marseille, France

### **Corresponding author:**

Christophe Ginestier, CRCM, U1068 Inserm, Department of Molecular Oncology, 27 Bd Leï Roure, BP 30059, 13273 Marseille. Tel: 33 (0)4 91 22 35 09. Fax: 33 (0)4 91 22 35 44. Email:

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## **Abstract**

Tumors are organized in a cellular hierarchy with a population of cancer stem cell (CSC) driving cancer progression and resistance to treatment. Recently, we identified miR-600 as a bimodal switcher that balances breast CSC-fate from a self-renewing to a differentiation state, with a direct impact on tumor progression.

## **Introduction**

Tumor cell heterogeneity has been pointed out as the main cause of therapeutic failure. Tumor cell organization is a complex ecosystem where several subpopulations of cancer stem cells (CSCs) maintain the long-term oligoclonal architecture of the tumor. Deciphering the multiple factors that can influence intratumoral evolution is a prerequisite to understand therapeutic resistance, tumor progression, and local or distant recurrence. The hierarchical organization of the cancer cell populations grandly contributes to the evolution of the tumor cell diversity. Moreover, experimental models and clinical studies indicate that CSCs are resistant to conventional therapies and initiate metastasis development. Thus, understanding the molecular mechanisms that regulate the switch of CSC-fate from a self-renewing state to a differentiating state is a key step in the development of new therapeutic strategies.

## **microRNA bimodal switch for CSC-fate decision**

Since 1940 and the Waddington's concept of "epigenetic landscape" we know that complex epigenetic networks regulate cell commitment.<sup>1</sup> Among these networks, microRNAs (miRNAs) play a central role in cell identity maintenance. Several studies clearly identified miRNAs as regulators of CSC-fate.<sup>2</sup> Bu et al. were the first to introduce the concept of miRNA-regulated bimodal switch for CSC-fate decision.<sup>3</sup> In this study, they demonstrated that miR-34a sequesters NOTCH1 mRNA to induce colon CSCs differentiation. In contrast, CSCs lacking miR-34a expression maintain their NOTCH signaling active and keep self-renewing. As a consequence, miR-34a expression directly impacts tumor progression and its restoration may represent an important therapeutic strategy for future colon cancer treatment. In our recent study, we proposed to develop an unbiased methodology for the systematic detection of miRNA bimodal switch in breast CSCs. We developed a miniaturized ALDEFLUOR-probed CSC detection assay to perform high throughput screening.<sup>4</sup> We performed two concurrent miRNome-wide loss- and gain-of-function screens using locked nucleic acid (LNA) and pre-miR libraries as miRNA inhibitors and mimics, respectively. We considered as a "hit" each miRNA that balanced the CSC/non-CSC ratio according to its expression level. Interestingly, our hit list was enriched in members of the miR-17-92 cluster known to regulate the CSC-fate in different cancers.<sup>2</sup> These observations could support the generalization of the concept of miRNA bimodal switch in CSCs

to a broader spectrum of tumors. In this context, our screening strategy may be a good tool to detect such miRNAs, which represent new therapeutic targets.

### **miR-600 balances breast CSC-fate through WNT signaling**

In our study, we focused on miR-600, which showed a reproducible switcher effect in all the cell models tested.<sup>4</sup> Using patient-derived xenografts (PDX) from primary breast tumors we demonstrated that miR-600 regulates tumor progression by controlling CSC-fate. miR-600 silencing resulted in breast CSC expansion with an increase of tumor growth kinetic, whereas CSCs overexpressing miR-600 had a markedly reduced tumor-initiating capacity in recipient mice compared to control. Because neither the target genes of miR-600 nor its function was known, we dissected the underlying molecular mechanisms of this switcher effect. Our findings highlighted a miR-600/SCD1/WNT axis in which miR-600 regulates the production of active lipid-modified WNT proteins. In the absence of miR-600, WNT signaling is maintained in an active state that promotes CSC self-renewal, whereas miR-600 expression inhibits SCD1 (steraoyl-coenzyme A desaturase) and the subsequent production of active WNT proteins. The clinical relevance of these observations was shown in a series of breast tumors in which patients with miR-600-expressing tumors had a better clinical outcome than patients without miR-600 expression. Interestingly, miR-600 was recently described to regulate colon cancer progression suggesting a role of this miRNA in other cancers.<sup>5</sup> Our study was the first to report a miRNA switcher in breast CSCs and it underlines the importance of identifying such master determinants of CSC-fate to develop new clinical tools.

### **What is the place of miRNA switches in clinic?**

Targeting CSCs has stirred a new hope in cancer management. Several clinical trials testing potential anti-CSC therapies are currently enrolling patients. miRNA switchers may represent a source of therapeutic targets to directly impaired CSC self-renewal and deplete the tumorigenic cell populations. Currently, several miRNA-targeted therapies are developed. Most of them are based on the use of oligonucleotides to either block the expression of an oncogenic miRNA or to substitute the loss of expression of a tumor suppressor miRNA. The efficacy of miRNA-targeted therapies is dependent on finding accurate nanovectors to deliver oligonucleotides in CSCs. However, challenges must be overcome to delive these non-small-molecules agents in an optimal way.<sup>6</sup> More recently, new strategies based on the use of antibiotics have been developed. These antibiotics (ribosome-targeting antibiotics) are able to bind the Dicer complex or pre-miRNAs and consequently inhibit specific miRNAs production.<sup>7</sup> This latter approach may be a good way to target miRNA switches. Beside the direct targeting of miRNA switchers, new strategies based on the targeting of miRNA-regulated pathways can be considered. As an example, an inhibitor of porcupine (a protein downstream of SCD1) is currently tested to inhibit the production of active lipid-modified WNT proteins in colon cancer stem cells.<sup>8</sup>

Beyond the control of CSC-fate, miRNA switches may be found as global determinant of cancer cell plasticity. Several studies described a potential reversion of non-CSCs into CSCs after chemo- or radio therapies, leading to therapeutic resistance.<sup>9</sup> Some miRNAs, such as miR-200, may play a role in this cell reprogramming and could be ideal therapeutic targets to block chemo- or radio-induced cell plasticity.

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