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Inhibition of the orphan nuclear receptor estrogen related receptor alpha sensitizes breast cancer cells to DNMT inhibitors

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Alterations in DNA methylation are implicated in the acquisition of malignant phenotype, and the use of epigenetic drugs is a promising strategy for anti-cancer therapy. In breast cancer, cell metabolism is tightly regulated by the oncogenic nuclear receptor estrogen-related receptor alpha (ERRa) and we wondered whether ERRa regulates SAM levels and DNA methylation. A gene signature designed to assess ERRa activity reveals that patients with high ERRa activity have a shorter free-disease survival. Interestingly, expression of the principal DNA methyltransferase DNMT1 follows the expression profile of ERRa gene signature. Further analysis of chromatin immunoprecipitation experiments followed by DNA sequencing (ChIP-seq) of ERRa conducted in breast cancer cell lines showed that ERRa is located on the promoter of DNMT1 and many genes implicated in one carbon metabolism. Inhibition of ERRa reduced DNMT1 expression at the mRNA and protein levels and induced changes in SAM levels. Therefore, treatment of breast cancer cells with the ERRa inhibitor C29 highly sensitized these cells to the DNMTi. Surprisingly, inhibition of DNMT1 reduced protein levels of ERRa, unraveling the existence of a feedback loop. Further investigations on mouse models will be conducted to validate these results in vivo. We propose that patients with high ERRa activity would respond well to a combined treatment of ERRa and DNMT inhibitors.

Biography

Mathieu Vernier has completed his PhD from Montréal University and and is currently achieving his postdoctoral studies from McGill University. He has authored more than 15 publication in the area of Molecular Biology and Cancer research during his doctoral studies

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