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Identifying structural determinants of microRNA primary transcripts for DROSHA cleavage using machine learning

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MicroRNA (miRNA) primary transcripts (pri -miRNAs) are cleaved by DROSHA into precursor miRNAs, which largely determine their fate. The precise sequence and structure allowing for DROSHA cleavage have only been briefly described and the loss of maturation of single-nucleotide polymorphic variants is yet to be understood. Our desire to engineer *de novo* small artificial miRNAs (saRNAs) prompted us to investigate these intriguing questions. Here, we show how we combined *in vitro* DROSHA cleavage efficiencies of more than 50,000 variants of human miRNAs 16-1, 30a and 125a to discover key pri-miRNA structural determinants. We predicted secondary (2D) structure sets of all sequence variants using the MC-FlashFold program developed in our laboratory. We extracted from these predictions dynamic signatures composed of six nucleotide states. These signatures were submitted to random forests to predict DROSHA cleavage efficiency scores. The use of dynamic signatures increased the correlation between predicted and measured scores (0.94 compared to 0.87 from sequence data alone), supporting dynamics is playing a role in miRNA maturation. Traversal of the random forests allowed us to confirm previously reported determinants, as well as to identify new ones. We developed an application that precisely predicts the efficiency of *in vitro* cleavage by DROSHA of any new variant of the three pri-miRNA used in the analysis. A comparison of the correlation obtained between predicted and measured cleavage efficiencies for a given family of miRNAs using the data of another or a mixture of others indicated that pri-miRNA cleavage by DROSHA is pri-miRNA- or family-dependent. Finally, we compared predicted efficiencies with measured DROSHA cleavage efficiencies *in vivo* (HEK293 cells) of sixteen miR-125a variants. Our results indicated that DROSHA cleavage *in vitro* and *in vivo* differ, suggesting a role for other possibly yet unidentified factors *in vivo*.

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