



分子病理学实验室

Laboratory for Molecular Pathology

The microRNA network and tumor metastasis

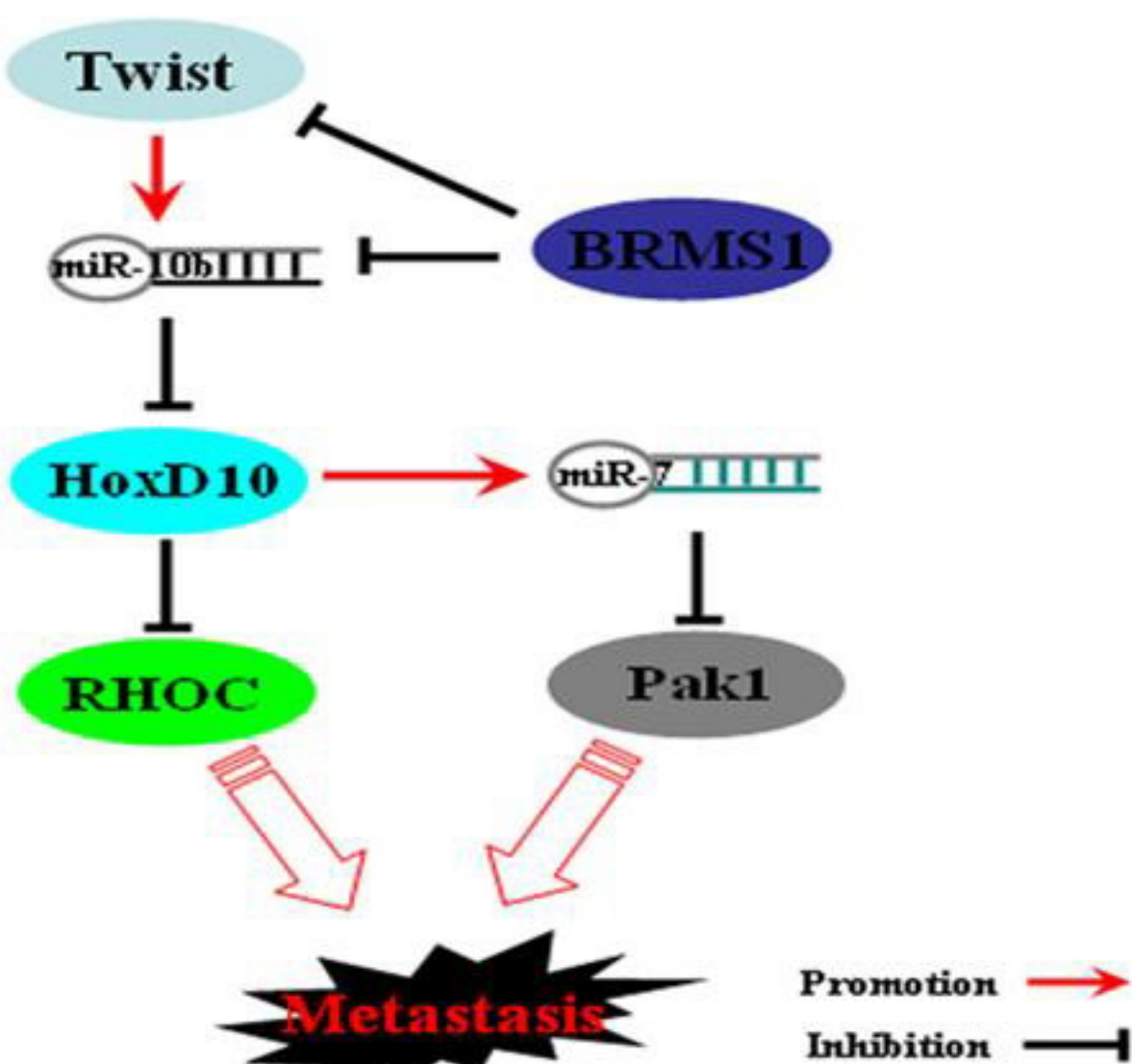
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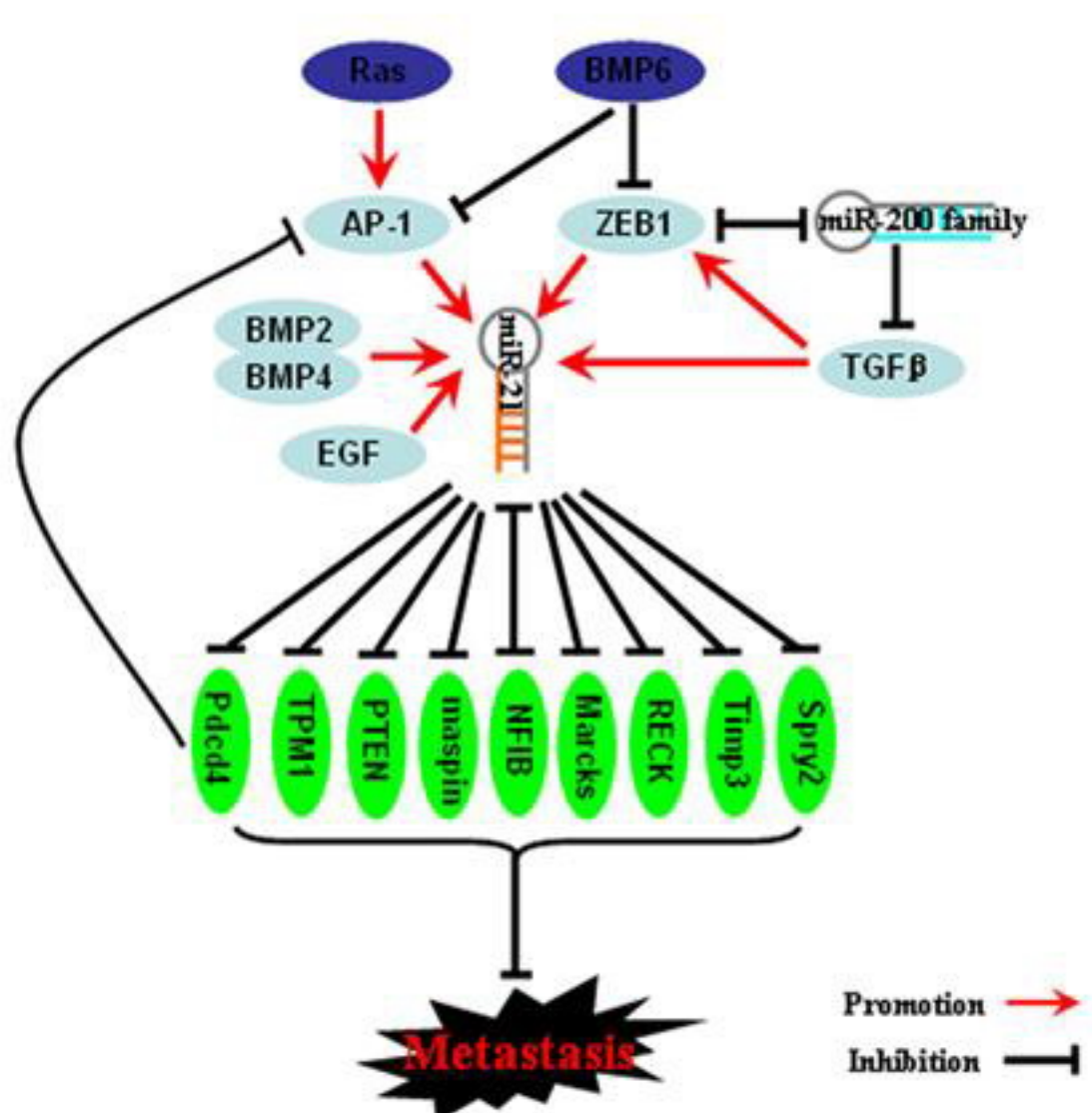
Oncogene.2009 Nov 23.[Epub ahead of print].

IF:7.216

Pro-metastatic miRNAs

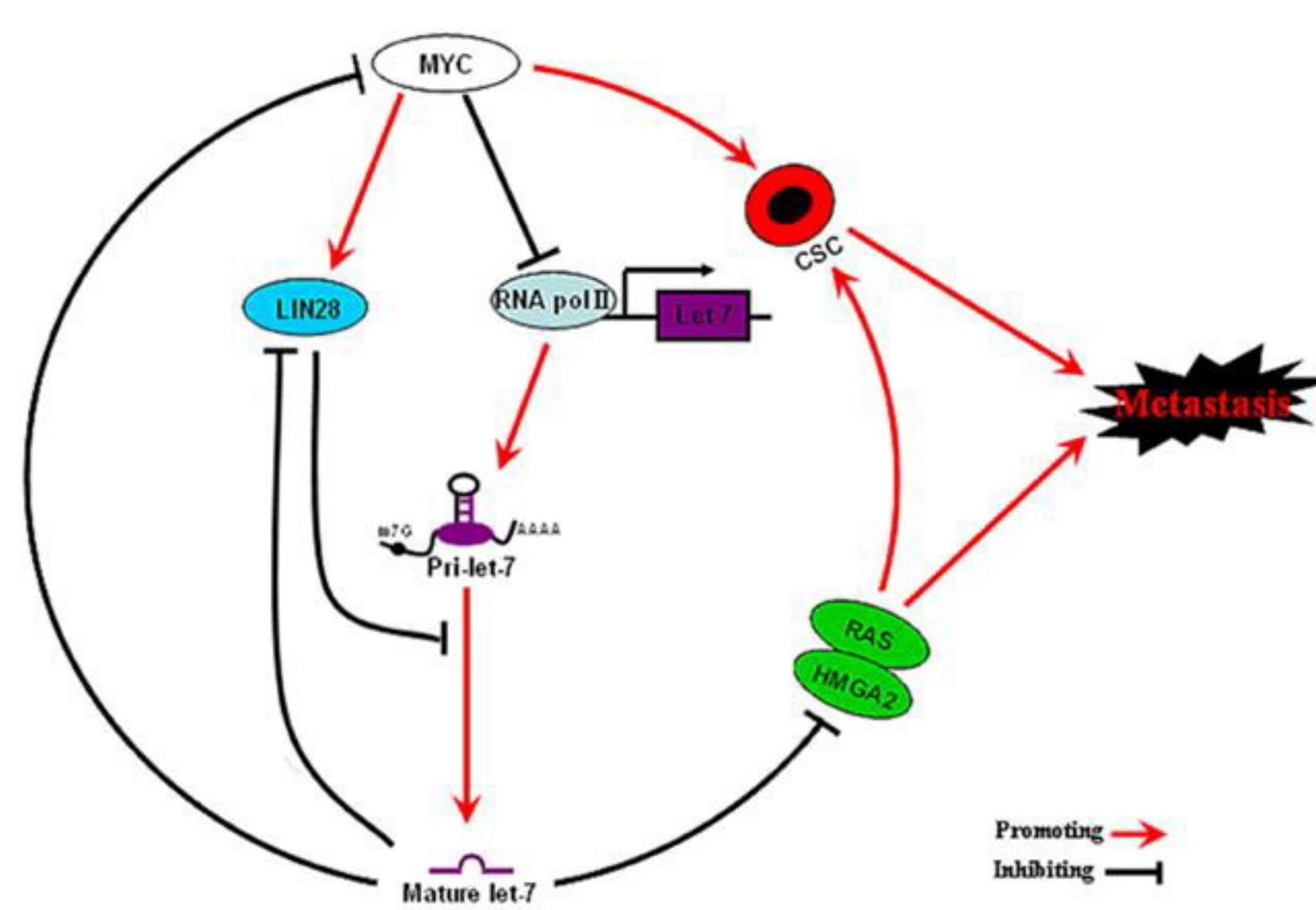


BRMS1/Twist/miR-10b/HOXD10/RHOC and HoxD10/miR-7/Pak1 pathways form a cascade effect for tumor metastasis.



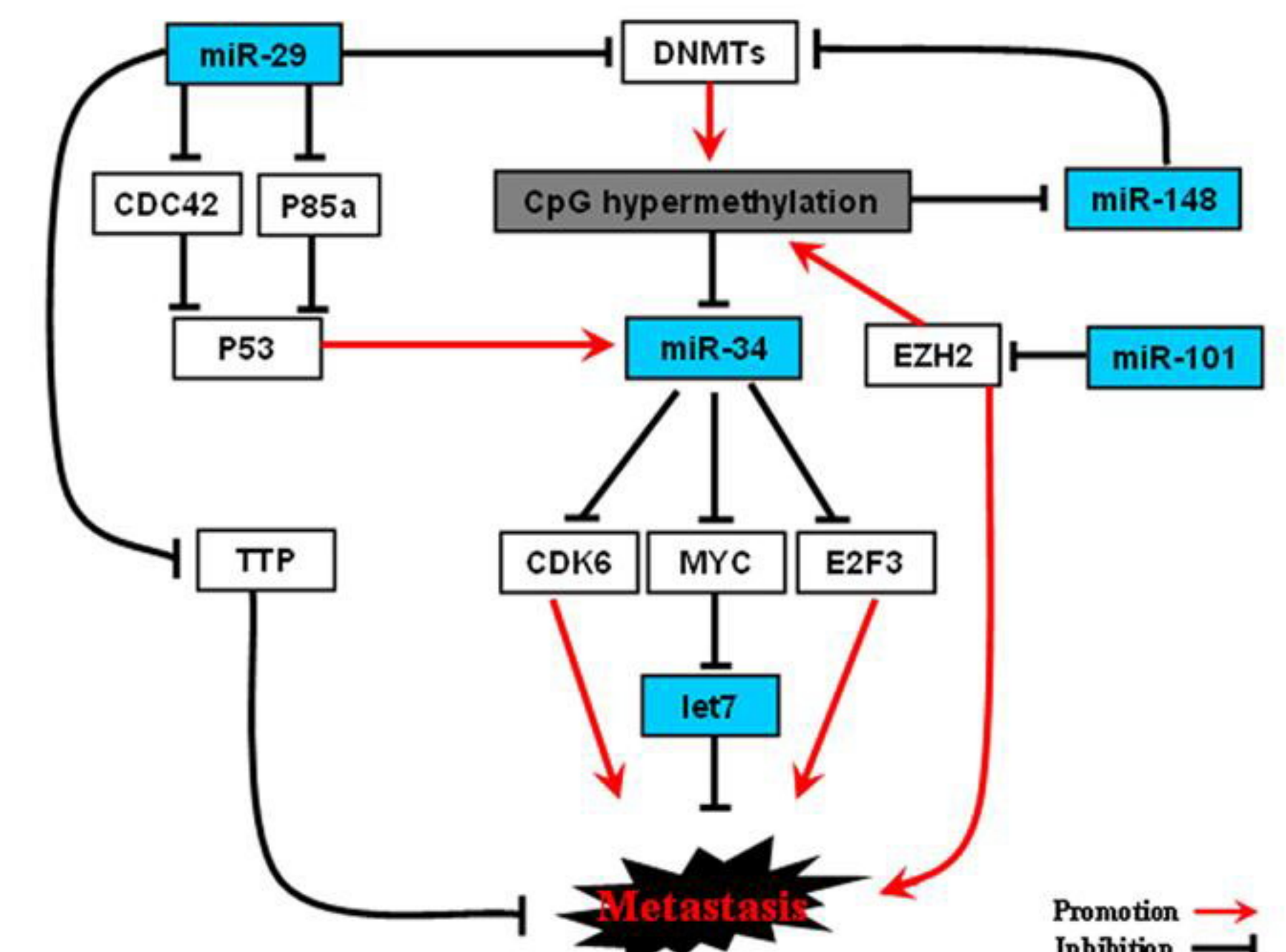
Multi-upstream-regulators and multi-targets of miR-21 constitute a delicate network to regulate tumor metastasis with miR-200 reciprocal negative feedback loop.

Anti-metastatic miRNAs



The let-7 miRNA inhibits tumor metastasis through silencing MYC, RAS and HMG2, however MYC can also inhibit let-7 in transcriptional and post-transcriptional level by regulating RNA Pol II and Lin28.

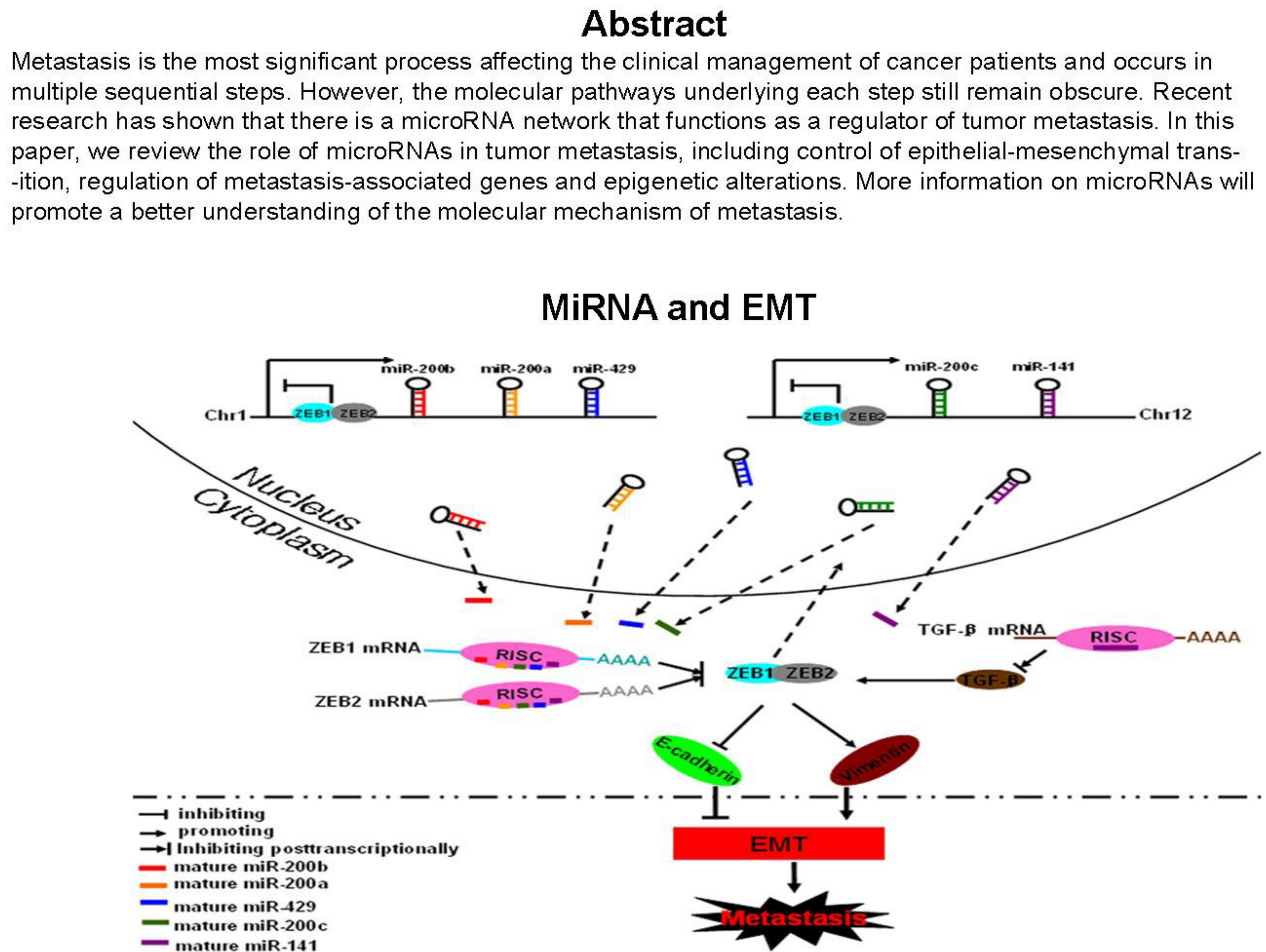
miRNA and epigenetic modification



The reciprocal regulation between miRNAs and abnormal methylation through DNA methyltransferases (DNMTs), EZH2 and P53 pathway may contribute to tumor invasion and metastasis.

Conclusion

A modest change of one miRNA will provoke a chain-reaction and feedback pathways involving multiple miRNAs and affecting multiple target genes of the same or different pathways. Accordingly, the de-regulation of one single miRNA is sufficient to trigger global alterations of genetic programs implicated in cell proliferation, differentiation, survival or invasiveness. The miRNAs will raise the curtain on the elucidation of the mechanism of tumor metastasis. Along with the identification of more miRNA signatures of tumor metastasis, they will weave a more complex and inter-related tumor metastasis network by interacting with protein-coding genes.



In the nucleus, the pre-miR-200 family (include pre-miR-200a, pre-miR-200b, pre-miR-200c, pre-miR-429, pre-miR-141) are transcribed and processed from miRNA genes in chromatin 1 and 12. Then these pre-miRNAs are exported to the cytoplasm where they are further processed into the mature miRNAs, which are incorporated into the multiple-protein nucleosome complex, the RNA-induced silencing complex (RISC). And these RISC inhibit the expression of ZEB1 and ZEB2 by directly binding 3'-UTRs of their mRNAs, moreover, miR-141 can also indirectly inhibit their expression by silencing TGF-β post transcriptionally. However, on one hand the ZEB1 and ZEB2 enter the nucleus to inhibit the pre-miR-200 family transcription; on the other hand, they can activate Vimentin and inactivate E-cadherin. Therefore, miR-200 family inhibits the ZEB1 and ZEB2 so as to prevent the EMT and metastasis by activating E-cadherin and inactivating Vimentin.