EDITORIAL

TUMOR SUPPRESSOR MIRNAS ARE DOWNREGULATED IN BCR-ABL AND TMPRSS2-ERG POSITIVE CANCER CELLS: TIME TO TRANSLATE CELL TYPE SPECIFIC STUDIES

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Research over the years has progressively shown substantial broadening in miRNA regulation of signaling landscape. Increasingly it is being realized that an individual miRNA may post-transcriptionally regulate over one hundred different mRNAs. It is noteworthy that overwhelmingly increasing data on miRNA biology has revolutionized current understanding of cancer cells and recently cancer-targeted miRNA drug -MRX34, has entered into Phase I clinical trials in patients with advanced hepatocellular carcinoma. Emergent themes have started to shed light on targeting of individual key targets by miRNAs thus promoting and suppressing carcinogenesis. Mechanistically, orchestrated modulation of target batteries, and reconstitution of signaling cascades in fusion positive cancer cells has recently gained tremendous appreciation. It is getting sequentially more understandable that leukemic cells carrying BCR-ABL are difficult to target because of rewiring of intracellular signaling cascades. Likewise, substantial fraction of information has been added into prostate cancer biology and it is now evident that prostate cancer cells harbor a fusion transcript TMPRSS2-ERG. In this editorial we will attempt to provide an overview obtained from cell type specific pieces of information regarding miRNA regulation of cell proliferation in BCR-ABL and TMPRSS2-ERG carrying cancer cells.

There are some direct pieces of evidence which substantiate tumor suppressing role of miRNAs in BCR-ABL positive cancer cells. Overexpression of miR-203 in T315I mutant BaF3-BCR/ABL cells inhibited cell growth and colony formation ability Li et al, 2013. Interestingly, there is a contemporary study that suggests epigenetic silencing of miR-203 and BCR-ABL positive cancer cells treated with imatinib demonstrated upregulation of miR-203 Shibuta et al, 2013. There are some other miRNAs which are downregulated in leukemic cells and enforced expression of miR-29b in K562 cells resulted in remarkable suppression of cellular growth Li et al, 2013. In accordance with similar approach, enforced expression of miR-30a in K562 cells resulted in growth inhibition Liu et al, 2013. Significantly reduced cell proliferation and substantially enhanced apoptosis was noted in CD34+ CML stem/progenitor cells upon enforced expression of miR-326.[5]

Prostate cancer biology was further complicated after identification of a fusion transcript TMPRSS2-ERG in prostate cancer cells formed by chromosomal translocations that juxtapose the androgen-sensitive TMPRSS2 gene promoter to the oncogenic ETS-family transcription factor ERG. Experimentally verified data is more detailed and convincing related to miRNA regulation in BCR-ABL carrying leukemic cells as compared to dysregulation of miRNA subsets in TMPRSS2-ERG positive prostate cancer cells. miR-200c was found to be downregulated in TMPRSS2-ERG positive prostate cancer cells and reconstruction assays revealed considerably reduced cell migration and invasive potential of cancer cells. It is relevant to mention that tumor suppressor miRNAs are lost in cancer cells and rapidly emerging studies are pointing towards underlying mechanisms which suppress expression of miRNAs in BCR-ABL and TMPRSS2-ERG carrying cancer cells. Better understanding of the mechanisms and comprehensive analysis of role of miRNAs in xenografted mice will be helpful in getting fuller information of miRNA biology.

Previous study has shown that Cb17. SCID/SCID mic inoculated with scrambled miRNA transfected Ba/F3 Ber-Abl cells succumbled with 1425 days. The ice inoculated with Ba/F3 Bcr.Abl Cells transfected with shRNA against Ber-Abl junction survived between 4 and 60 days. However there was notably enhanced survival of Cb17, SCID/SCID mic inoculated with single, double and triple miRNA minics transfected Ba/Bcr-Abl cells.

As there is considerable advancement in translational oncology and we are heading towards personalized medicine, information related to miRNA clusters in fusion positive cancer cells wil lbe helpful in designing and testing antisense nucleotides of inhibition of over-expressed oncogenic miRNAs. Moreover, sense nucleotides could be used to reconstitute cancer cells with tumor suppressive miRNAs..

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