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MiR-143 suppresses breast cancer proliferation through targeting KRAS and associates favorable tumor immune microenvironment with improved survival for ER positive breast cancer patients

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Background

MicroRNA-143(miR-143) is known to function as the tumor suppressor in various cancers, including breast cancer. Recently, tumor immune microenvironment has attracted attention because it has been proposed that predominance of pro-cancer over anti-cancer immune cells is associated with cancer progression. For instance the predominance of T helper cell type 2 (Th2) over Th1 is reported to associate with the breast cancer development and .progression. Among the subtypes, estrogen receptor (ER) positive is the most common subtype of breast cancer. Therefore, it is critical to investigate the mechanism of how the tumor immune microenvironment is shaped in the ER positive subtype. Regarding the association with the tumor immune microenvironment, miR-143 has been reported to suppress tumor evasion of colorectal cancer cells.

In this study, we hypothesized that the miR-143 has favorable effect to the tumor immune microenvironment which leads to better survival of ER positive breast cancer patients.

Material & Methods

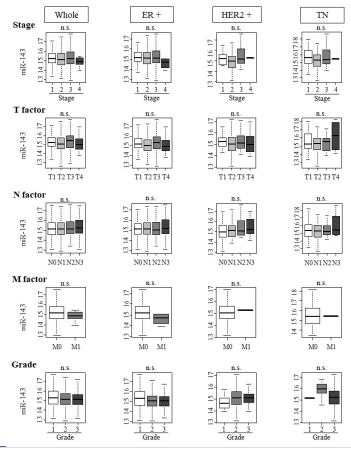
We obtained the clinicopathological data and survival information of 755 breast cancer patients from The Cancer Genome Atlas (TCGA) database. Survival analysis, Overall survival (OS) and Disease free survival (DFS), was conducted comparing the high and low expression groups. CYT score, CIBERSORT, and other immunological factors were used to estimate intratumoral immune cell composition in whole cohort of breast cancer patients. Also, gene set enrichment analysis (GSEA) was performed between miR-143 high and low expression groups within the whole cohort.

Results

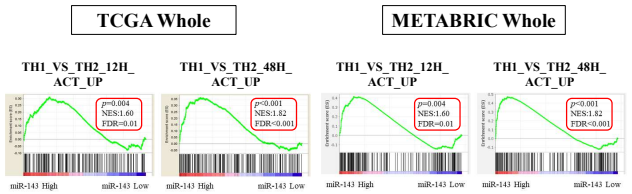
No significant difference in patient clinicopathological features between miR-143 high and low group

Clinicopathological demographics of the miR-143 High and miR-143 Low groups

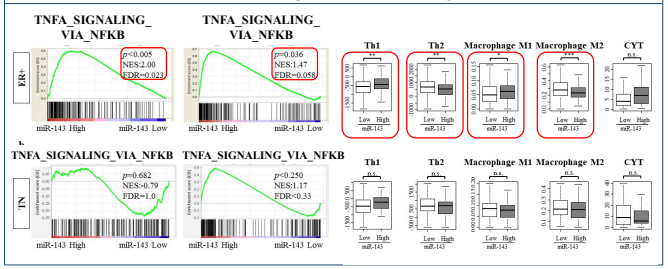
Clinicopathological	whole cohort (n=753) miR-143 High n = 189	miR-143 Low n = 564	*p* value
Age			
<65 y	142	386	0.098
≥65 y	47	177	
Unknown	0	1	
Race			
Asian	20	36	0.226
African American	39	117	
White	128	407	
Other	2	4	
Menopause status			
Pre	38	117	0.937
Post	121	361	
Other	30	86	
Stage			
I/II/III/IV	32/105/49/1	104/324/122/8	0.565
Unknown	2	6	
pT			
T1/T2/T3/T4	53/101/30/5	158/321/66/18	0.629
Tx	0	1	
pN			
N0/N1/N2/N3	88/61/21/17	269/195/56/35	0.683
Nx	2	9	
M			
M0/M1	150/1	443/8	0.761
Mx	38	113	
Grade			
G1/G2/G3	19/54/38	47/170/153	0.254
Gx	78	194	



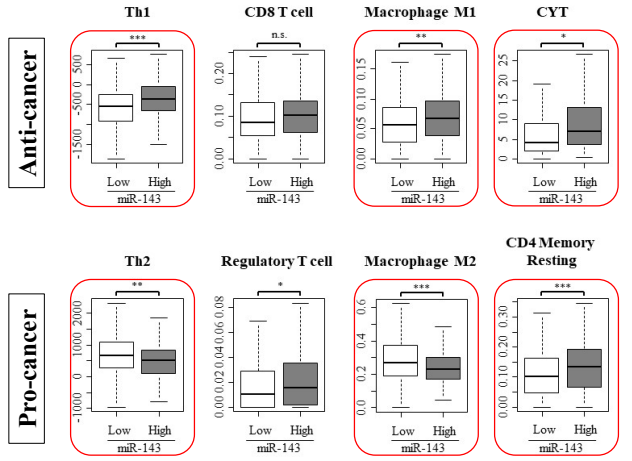
MiR-143 high expression tumors was associated with enrichment of Th1 related gene sets in whole cohort



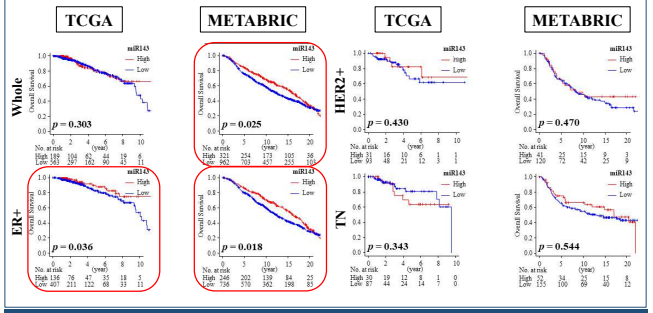
miR-143 functions differently to the tumor immune microenvironment depending on ER positivity.



High expression of miR-143 was associated with increase of anti-cancer tumor immune microenvironment



High expression of miR-143 was associated with better OS in ER positive patients



Conclusion

High expression of miR-143 was associated with improved OS in ER positive breast cancer patients. Also, miR-143 was found to associate with the high Th1 and low Th2 cells as well as enriching the genes relating to Th1 cells, which may explain the favorable role of miR-143 in ER positive breast cancer.

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