Serum Exosomal miRNAs as Predictive Biomarkers of Long-term Response Patterns to Dupilumab in Atopic Dermatitis

Learning objective : To explore molecular differences between durable and non-durable responders to dupilumab, focusing on exosomal miRNA-mediated regulatory networks. To identify potential pathogenic and prognostic biomarkers linked to treatment durability and recurrent flare-up patterns in atopic dermatitis.

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Conflict of Interest: The authors declare no conflicts of interest
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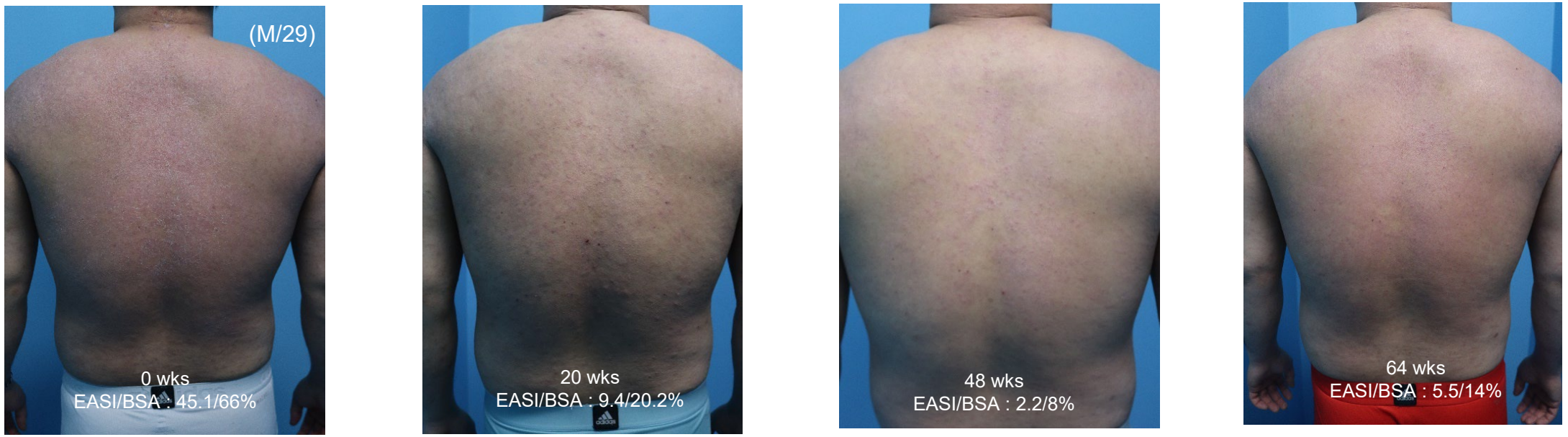
Introduction

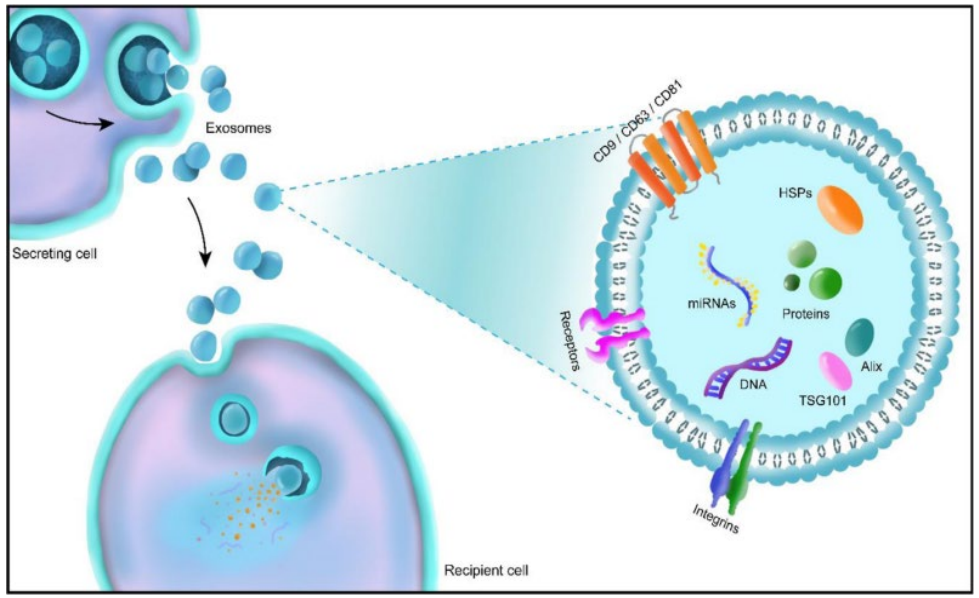
- Recent clinical data demonstrated that long-term treatment with dupilumab led to a clinically significant reduction in AD that was sustained over follow-up to 52 months
- However in real-world setting, long-term responses vary: some patients achieve durable remission, while others experience recurrent flares
- **Non-durable responder with more thant 2 times of intermittent relapse after treated with dupilumab**



- Although the definition is not yet well established, reports continue to describe non-durable responders, partial responders, and inadequate responders to dupilumab treatment.
- Non-durable responders who achieve therapeutic endpoint with subsequent partial loss of efficacy
  - acute AD flare, drug tolerance, or development of a secondary diagnosis

Introduction

- **Exosomes**
  - Membrane-bound EVs released from eukaryotic cells among with microvesicles, apoptotic bodies, etc. including DNA, microRNA, mRNA, and proteins
  - May play in cell-to-cell signaling (intercellular communication)



- **Exosomal miRNAs in Atopic Dermatitis**
  - Stability : protected from RNase degradation and more reliable than free serum miRNAs
  - Cellular specificity : reflect disease-related changes from keratinocytes and immune cells
  - Functional role : directly regulate inflammation, angiogenesis, and immune responses
  - Clinical significance : Potential biomarkers for disease activity and treatment response; promising therapeutic targets

Disease	Exo-miRNA	State in disease group/ specific cells	Origin of exosome	Target cell	Target gene	Significance	References
psoriasis	miR-381-3p	up	keratinocyte	CD4-positive T-cell	*UBR5* and *FOXO1*	induce Th1 and Th17 polarization and promote psoriasis development	(17)
	246 miRNAs	up/down	plasma	-	-	provide abundant circulating exosomal miRNAs, target genes and signaling pathways for further research	(18)
	let-7b-5p and miR-30e-5p	down	plasma	-	-	biomarkers for arthritis in psoriasis patients	(19)
	miR-151a-3p, miR-199a-5p, miR-370-3p, miR-589-5p, and miR-769-5p	up	plasma	-	-	participate in the common pathogenesis of psoriasis vulgaris, psoriatic arthritis, rheumatoid arthritis and gouty arthritis	(20)
atopic dermatitis	miR-147	down	plasma	HaCaT cell	*TLSP*	exert protective effects by inhibiting *TLSP* expression	(21)
	25 miRNAs	up/down	plasma	-	-	biomarkers for psychological stress	(22)

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Materials and methods

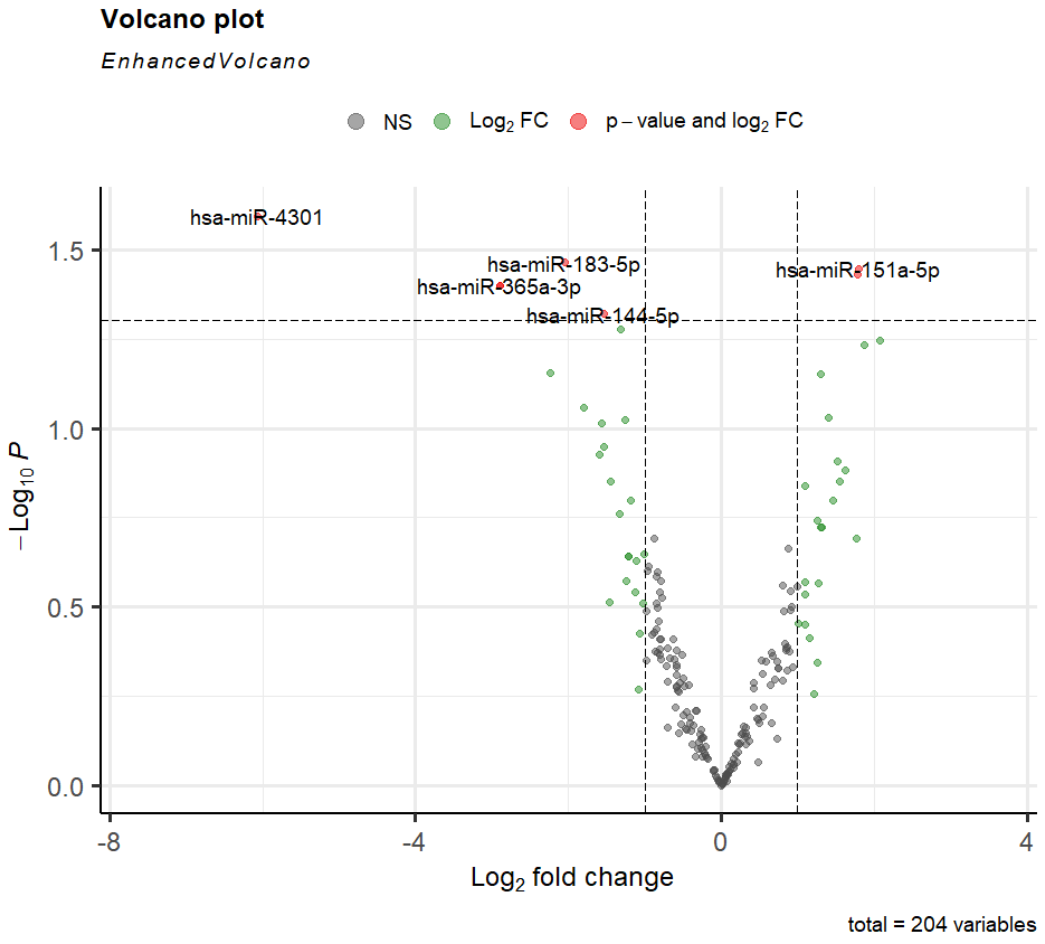
- **Purpose of the Study**
  - To investigate the differential expressions of exosomal miRNAs associated between durable responders and flare-prone patients in severe AD receiving dupilumab during long-term follow-up
  - To identify pathogenic mechanisms and prognostic biomarkers, including exosomal miRNA signatures, associated with treatment durability in dupilumab-treated AD patients (durable vs non-durable responders)
- **Patients information**
  - 6 adults with severe AD (baseline EASI ≥23)
  - Serum-derived exosomes collected at baseline and at 12–18 months after dupilumab.
  - Durable responders: EASI90 within 16 weeks, stable ≥1 year
  - Non-durable responders: EASI75 before week 16, but ≥2 systemic flares within 1 year
- **Analysis**
  - Exosomal miRNA extraction → differential expression profiling
  - 2 samples excluded due to quality issues

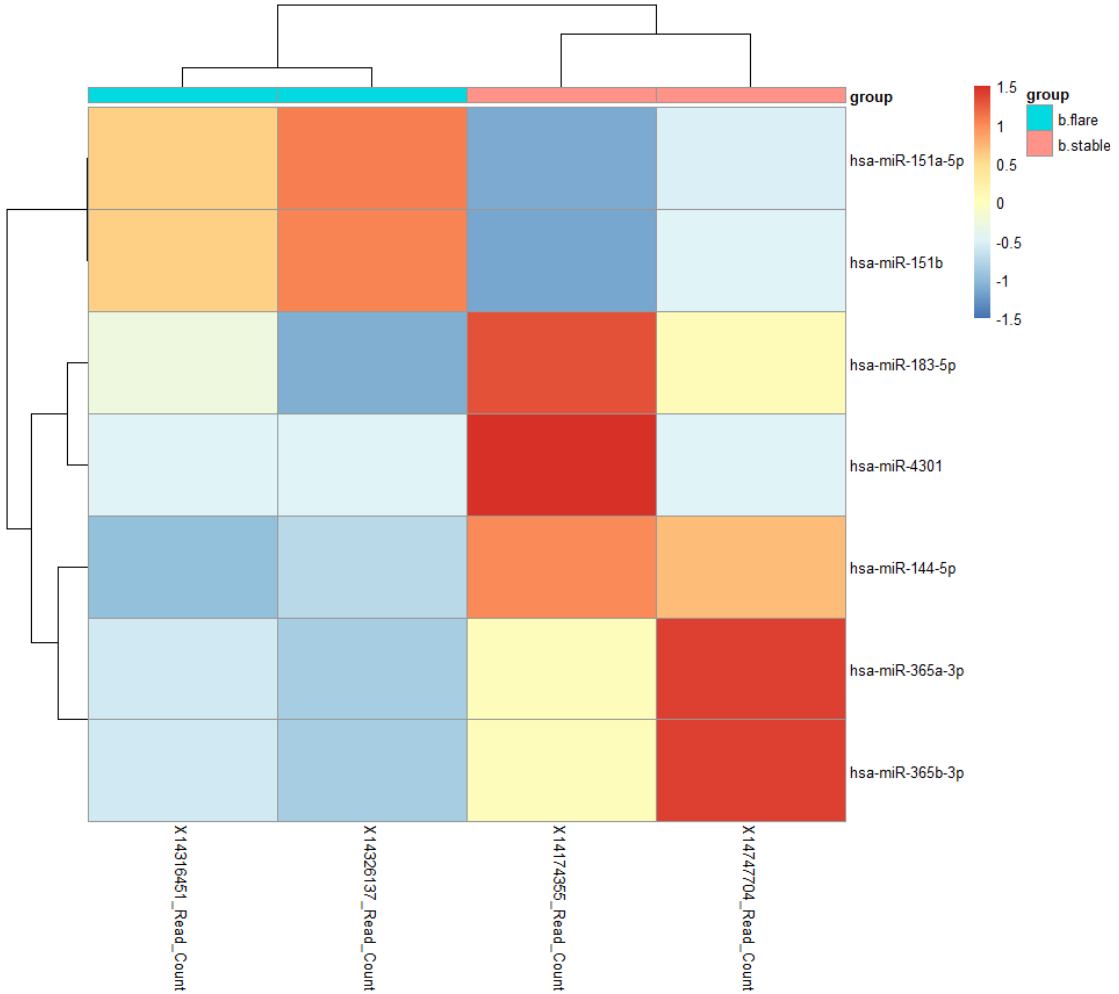
ID	State	Baseline/FU
14174355_Read	stable	Baseline
14747704_Read	stable	Baseline
14316451_Read	flare	Baseline
14326137_Read	flare	Baseline
14174355_After_Read	stable	FU
14477319_After_Read	stable	FU
14326137_After_Read	flare	FU
14729699_After_Read	flare	FU

Results

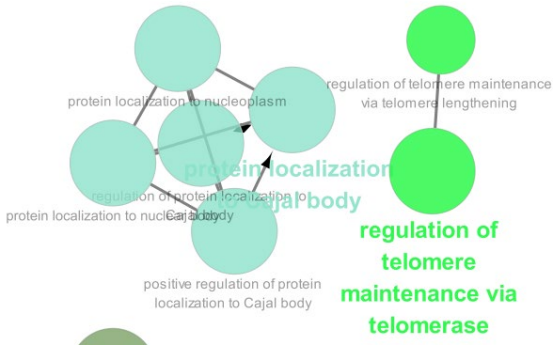
Non-durable responder vs Durable responder (Baseline)

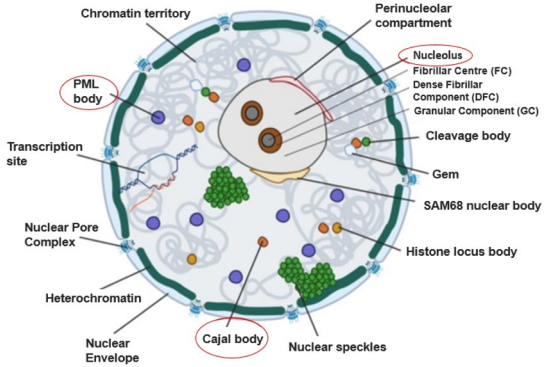
- Volcano plot and heatmap of differentially expressed exosomal miRNAs at baseline
- The expression of **miR-151a-5p and miR-151b** were significantly higher in non-durable responders than in durable responders.

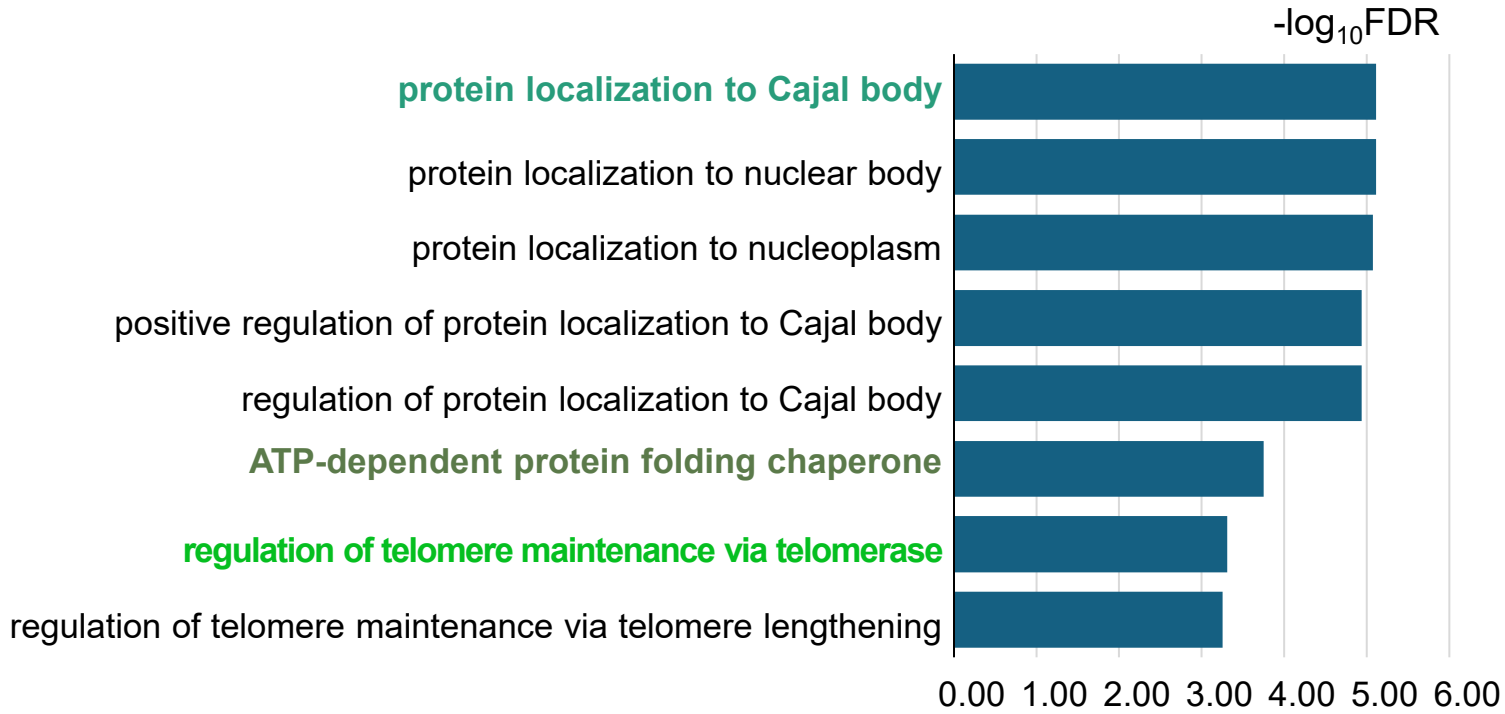




- **Gene ontology (biological process) enriched by 57 genes targeted by upregulated two miRNAs in non-durable responders group**



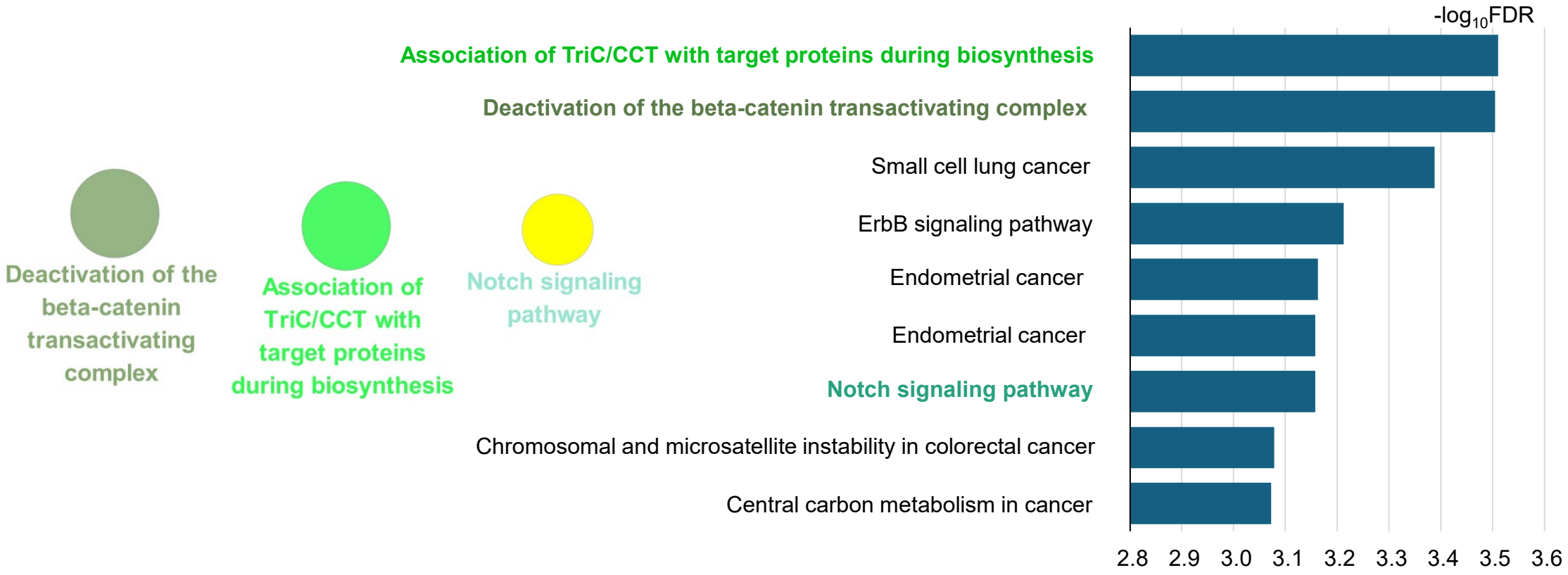




The Cajal body is a nuclear RNA-processing center that plays a key role in *snRNP assembly, spliceosome maturation, RNA modification, and stabilization of telomerase RNA.*

Upregulation of miRNAs targeting Cajal body, telomere maintenance, and ATP-dependent chaperones reflects a breakdown of **nuclear protein quality control**. This leads to **protein misfolding, impaired RNA and chromatin organization**, and premature cellular aging → chronic inflammation and recurrence

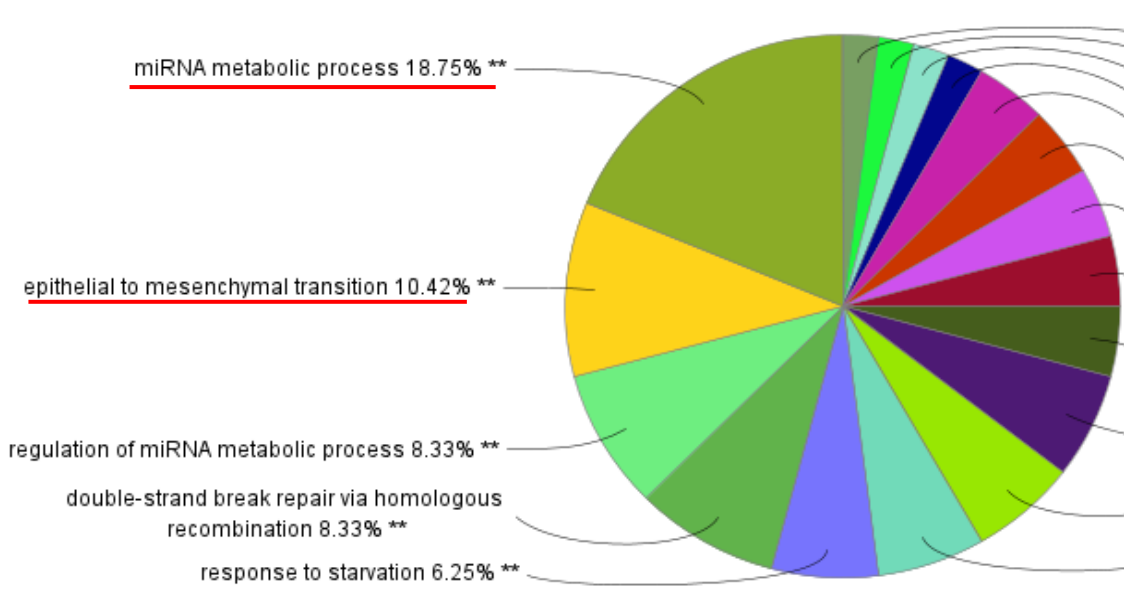
- **Pathways enriched by genes targeted by upregulated two miRNAs in non-durable responders group**

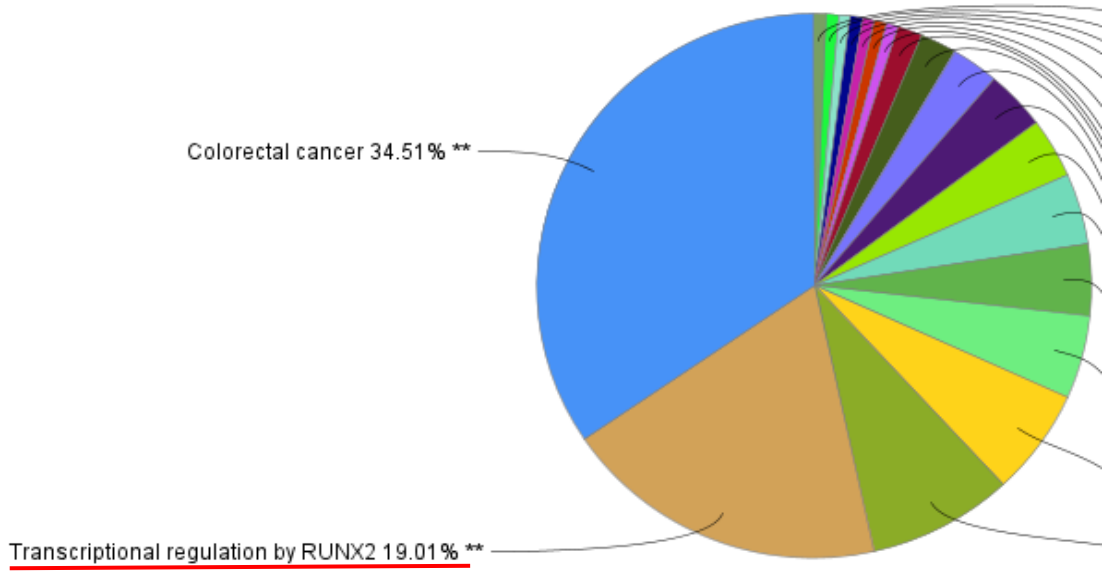


↓ *TriC/CCT complex* : **Protein/RNA homeostasis** and poor nuclear and protein quality control
↓ Notch signaling : impaired keratinocyte differentiation, epidermal barrier formation, and immune homeostasis, resulting in persistent Th2 inflammation.
↓ Deactivation of the β-catenin transactivating complex : enhanced β-catenin activity, leading to dysregulated keratinocyte proliferation and incomplete barrier remodeling in the flare group.

The expression levels of **miR-183-5p, miR4301, miR-1445p, miR365A3p, miR365b3p** were significantly lower in non-durable responders than in durable responders.

- **Gene ontology (biological process) and pathway enriched by genes targeted by downregulated 5 miRNAs in non-durable responders**

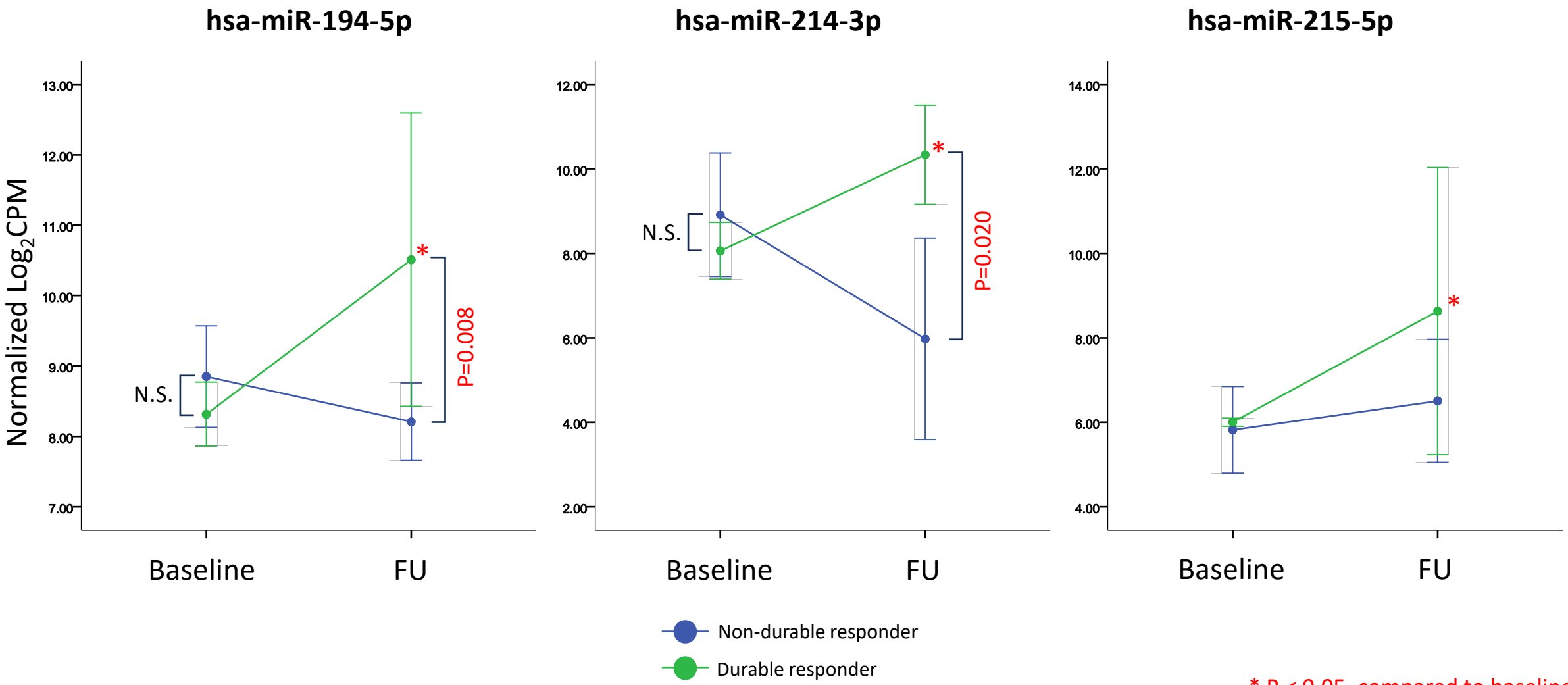




↑ **Epithelial–mesenchymal transition (EMT):**
: Impaired keratinocyte differentiation compromises epidermal stratification and barrier stability → chronic tissue remodeling
↑ **Transcriptional regulation by RUNX2:**
: aberrant keratinocyte differentiation and fibrosis-related transcription.
↑ **mRNA metabolic process:**
: sustain cellular stress responses and prolong inflammatory signaling.

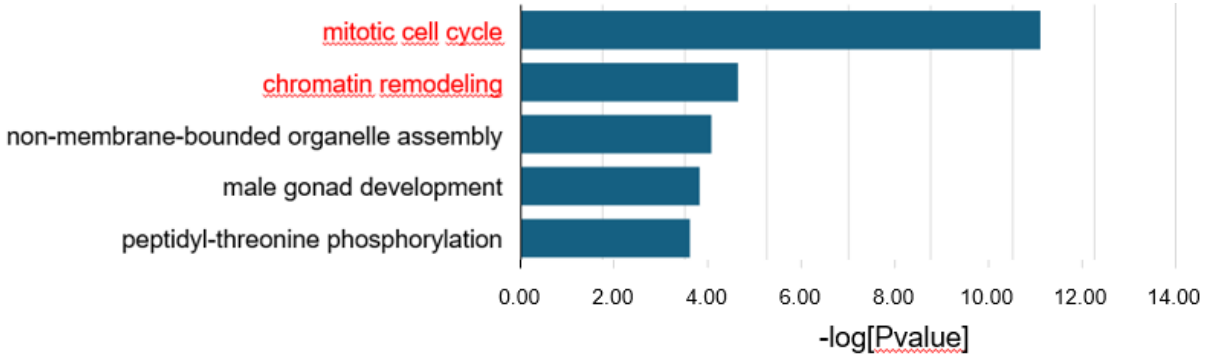
Durable responder vs. Non-durable responder (FU)

- **miRNAs increased at follow-up in durable responder group compared to non-durable responder group**

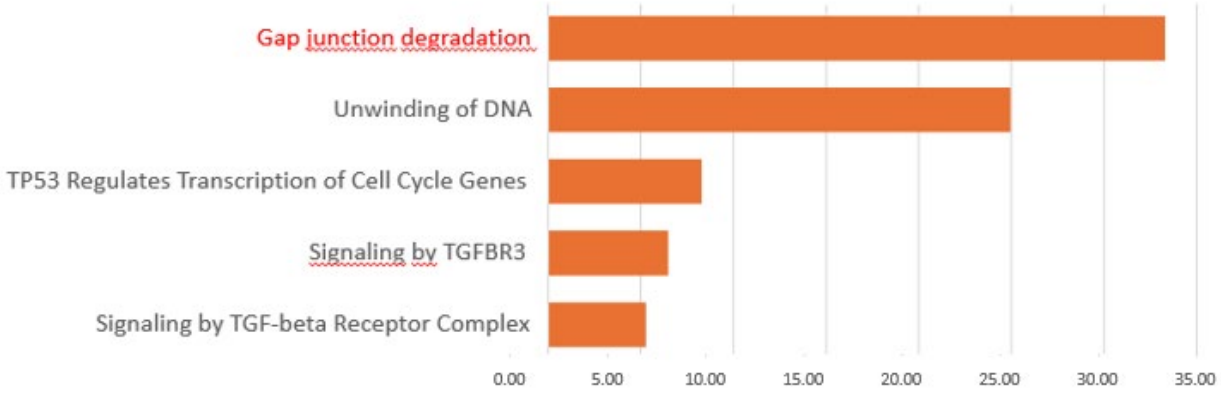


* P < 0.05, compared to baseline

- **Representative GO terms of each cluster of 272 target genes of 3 upregulated miRNA at follow-up in durable responder group compared to non-durable responder group**



- **Representative reactome pathway of each cluster of 146 target genes based on human protein atlas of 3 upregulated miRNA at follow-up in durable responder group compared to non-durable responder group**



↓ **Gap junction degradation**
: stabilize cell–cell communication and epithelial integrity, maintaining coordinated tissue repair

↓ **TP53 regulates transcription of cell cycle genes**
: prevents excessive keratinocyte proliferation and supports post-inflammatory recovery and homeostasis.

↓ **Signaling by TGFB3 / TGFB receptor complex**
: Downregulation of fibrotic and EMT-related TGF-β signaling alleviates fibrotic remodeling

↓ **Adherens junction**
: barrier cohesion and mechanical resilience, counteracting chronic flare and epithelial detachment.

Conclusion

Thank you for listening

Non-durable Responders

- Decreased cellular stability and impaired adherens junction integrity
- Loss of nuclear protein quality control → protein misfolding and stress accumulation
- Suppression of Notch and TriC/CCT pathways → defective differentiation
- Persistent TGF-β and β-catenin activity → chronic remodeling and recurrent inflammation

Durable Responders

- Reinforced cell–cell adhesion (adherens/gap junctions)
- Suppression of fibrotic and proliferative signaling (TGF-β, TP53, EMT)
- Restoration of epithelial stability and resolution of inflammation
- Maintenance of immune–barrier homeostasis and long-term remission

- *In durable responders, preserved protein homeostasis ensures nuclear and epithelial stability, whereas its disruption in non-durable responders leads to protein misfolding, stress accumulation, and recurrent inflammation*
- *Long-term AD control under dupilumab is associated with preserved cellular protein homeostasis and epithelial junctional integrity while non-durable response reflects nuclear stress and defective tissue recovery mechanisms.*