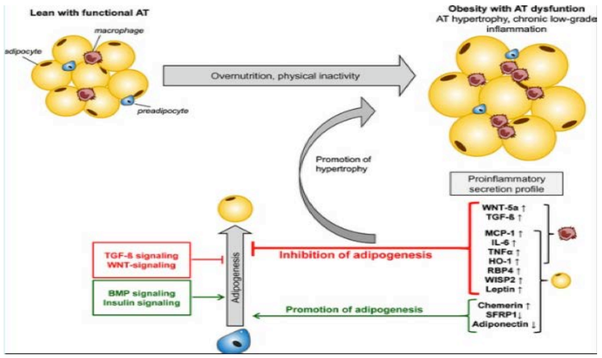
Rosacea and WNT: The Effect of Fatty Liver on Follicle Cell Fate in the Midface

Brooks Kimmis, Colleen Reisz

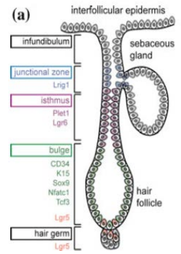
University of Missouri-Kansas City School of Medicine

INTRODUCTION

- WNT/B-catenin signaling regulates many aspects of development and disease. WNT expression is elevated in the early stages of follicle development and governs follicle fate throughout life. Both WNT/B-catenin and hedgehog pathways have an important impact on follicle differentiation and tissue homeostasis throughout life.
- Rosacea is a common skin disease of middle age characterized by a disturbance in tissue homeostasis of the follicle and related structures of the face. The typical presentation can include central facial erythema, papules and pustules, sebaceous gland overgrowth and blepharitis. Rosacea has been associated with underlying metabolic syndrome, as well as cardiovascular and neurologic diseases.
- Fatty liver (NAFLD or NASH) changes the transcription profile of embryologic patterning genes responsible for follicle fate.
- We hypothesized that rosacea is a biomarker for NAFLD and represents distortion of growth and differentiation control mechanisms between WNT and hedgehog. The consequences of NAFLD may be seen in sebaceous hypertrophy, ectopic hair growth, blepharitis, and the development of basal cell carcinoma.
- The treatment of rosacea should include primary prevention strategies for NAFLD.

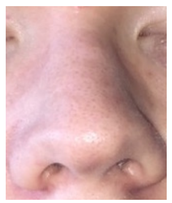


Reference 6

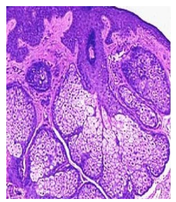


WNT and other patterning genes on follicular differentiation (Reference 5)

Normal histology of hair follicle and surrounding sebaceous gland (Reference 8)



Normal midfacial skin in young adult



Sebaceous hyperplasia surrounding a central hair follicle (Reference 7)

Central facial erythema

METHODS

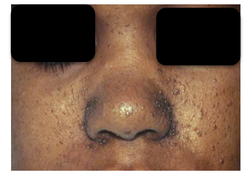
- Age, gender, Fitzpatrick phototyping, and drug data were collected from patients with rosacea identified by diagnosis codes from a general dermatology clinic.
- The patients were compared to an age matched control group without disease.
- Drug lists were included as proxies for comorbid states, as a measurement of access to health care, and because medications compete and engage the nuclear receptors that govern steroidogenesis and insulin sensitivity.
- Dermatologic medications, specifically medications for treatment of Rosacea, were excluded from the study.
- Fitzpatrick phototyping was used as a potential biomarker of genetic variation.

RESULTS

	Number of Cases	Percentage of Cases	Number of Controls	Percentage of Controls	P Value
Female	46	51.1%	52	66.7%	
Male	44	48.9%	26	33.3%	
Age <50	5	5.5%	14	17.9%	
Age 50-59	21	23.3%	16	20.5%	
Age 60-69	30	33.3%	22	28.2%	
Age ≥70	33	36.7%	26	33.3%	
BMI 18.5-24.9	27	30%	37	47.4%	
BMI 25.0-29.9	46	51.1%	25	32.1%	
BMI >30	16	17.8%	14	17.9%	
Statin	41	45.6%	28	35.9%	0.213
PPI	25	27.8%	13	16.7%	0.098
Hormone Replacement Therapy	14	15.6%	10	12.8%	0.344
SSRI	28	31.1%	9	11.5%	0.003
Antihypertensive Drugs	31	34.4%	22	28.2%	0.410
No Drug Intake	12	13.3%	22	28.2%	
Average Total Drug Burden		1.7 (Mean)		1.3 (Mean)	0.023
Fitzpatrick Scale 1	36	40%	34	44%	
Fitzpatrick Scale 2-4	54	60%	44	56%	

Sebaceous adenomas in Muir Torre. Mutations in MLH1 and MSH2 genes

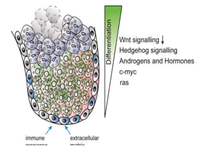
Favre-Racouchot Syndrome involving structures in the midface



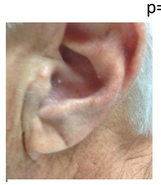
Birt Hogg Dube. Mutation in the FLCN gene

SUMMARY

- Mean Age: cases 66, controls 64
- Mean BMI: cases 27.2, controls 25.7
- No drug intake: 13% of cases vs 28.2% in the control group
- Total drug burden: cases 1.7 drugs, controls 1.3 drugs. p=0.023 (statistically significant with large standard deviation)
- Higher drug burden observed in cases than controls. 37% of cases took two drugs vs 16.7% of controls
- HRT: 28% of cases vs 19% of controls. p=0.344
- Statins: 45 % of cases vs 35% in the controls p=0.213
- PPI: 27% of cases vs 16% of controls p=0.098
- SSRI: 31% of cases vs 11% of controls p=0.003



Activation of hedgehog is required for the follicle to go from resting to growth phase. Hedgehog is also prominent in eye development. (Reference 5)



Follicular changes at tragus and conchal bowl

Elongation of mid-brow follicle growth

CONCLUSION

- Rosacea may be a biomarker for systemic proinflammatory changes that originate in the liver. The consequences of NAFLD may be appreciated by the clinician as changes in differentiation of the eye and in the follicular structures of the face. The treatment of rosacea should include primary prevention strategies for NAFLD. The control of embryologic signaling systems in the follicle may assist in controlling adnexal growth in tuberous sclerosis, Muir Torre, and Birt Hogge Dube
- There are several limitations to this study, including small sample size, suboptimal gender matching for cases and controls, and the possibility of false positive p-values created by multiple analyses

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