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Eosinophil activation in Aspirin Exacerbated Respiratory Disease (AERD)

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Today's topics are…

1. The clinical features of AERD
2. Eosinophil activation in upper and lower airway mucosa
3. Molecular genetic mechanism of eosinophil activation
4. Management of upper and lower airway inflammation

Clinical characteristics of the AERD patients in a Korean cohort

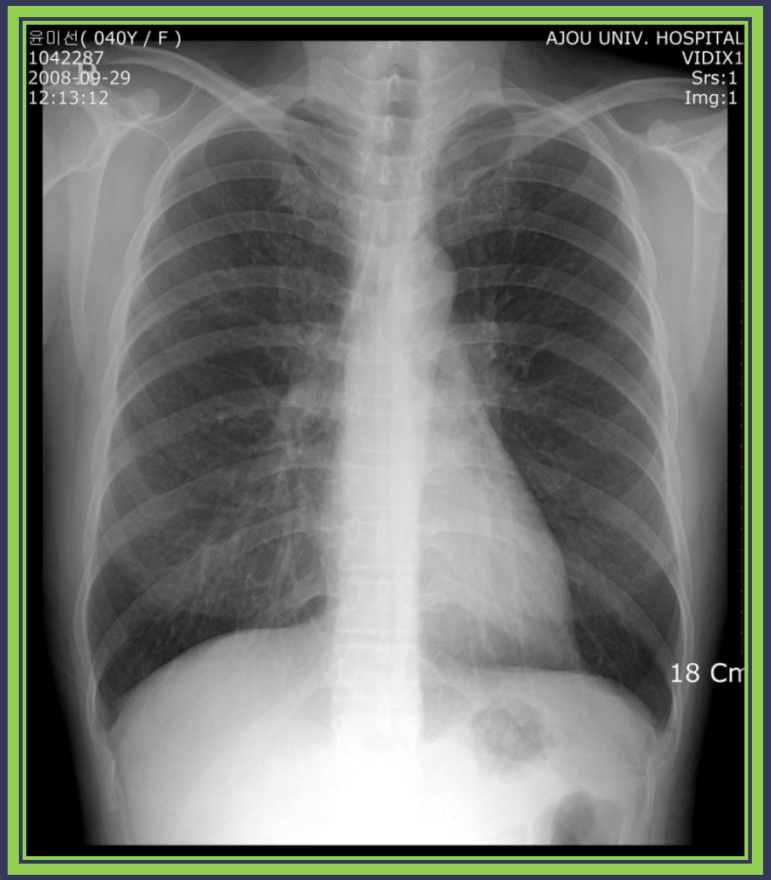
	AERD (n=267)	ATA (n=449)	*p* value
Atopy(positive)	114 (53.3%)	175 (60.8%)	0.101
Log_total IgE	2.23±0.55	2.22±0.64	0.773
FEV1(% Pred)	79.65±26.07	84.89±21.67	0.018
Metacholine_PC20	4.35±7.66	6.76±8.94	0.003
Rhinosinusitis (positive)	127 (75.6%)	198 (58.2%)	<0.001
Nasal polyp (positive)	78 (48.4%)	14 (6.5%)	<0.001
Asthma duration (year)	6.15±5.85	4.9±5.97	0.045

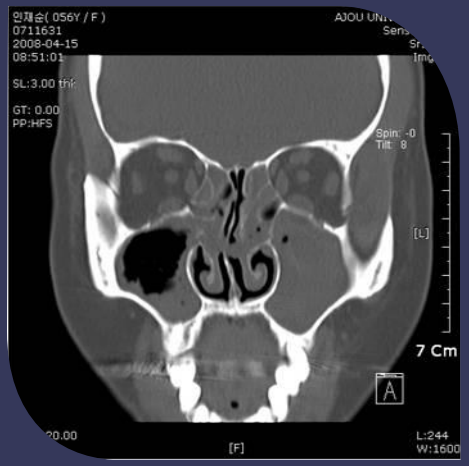
ATA; aspirin-tolerant asthma,

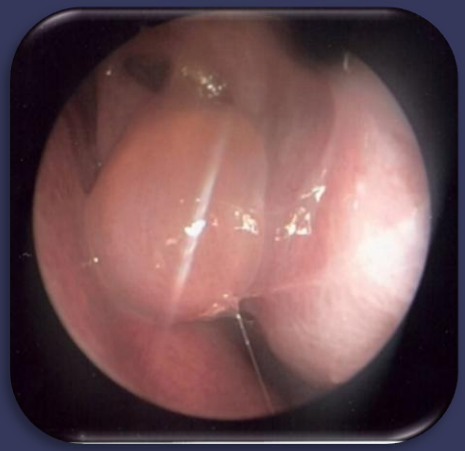
Male to Female ratio is 1:2, 24% of them had severe asthma
Present more severe symptoms and higher prevalence of RS/nasal polyps

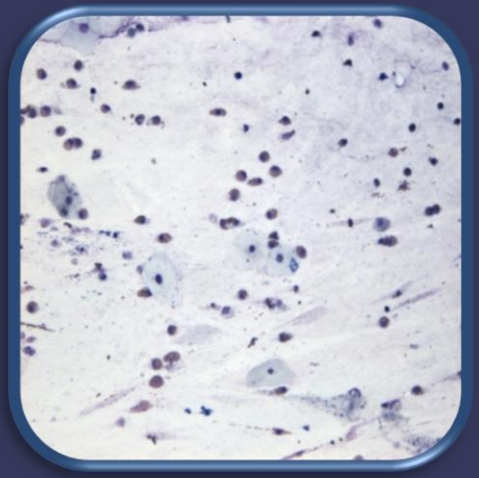
Palike N & Park HS. Yonsei Med J, 2009;50:744

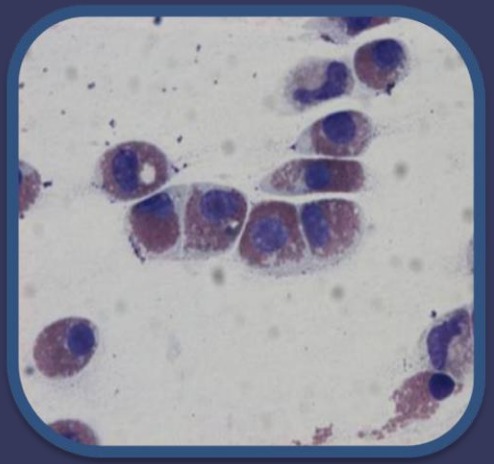
Eosinophils were found in airway mucosa and secretion











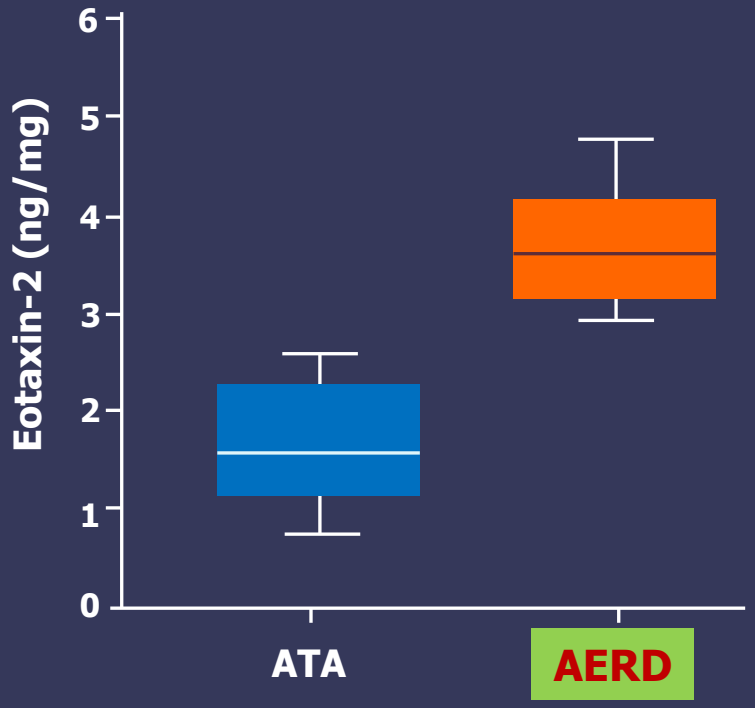
Eosinophils are more activated in nasal polyp tissue of the AERD patients

	AERD	ATA	*p* value
ECP (ng/mg)	**366.5 ± 89.1**	59.0 ± 14.0	**0.005**
MMP-9 (ng/mg)	**53.7 ± 21.1**	27.8 ± 6.3	0.70
MMP-2 (ng/mg)	**134.1 ± 30.5**	81.9 ± 14.1	0.29
TIMP-1 (ng/mg)	**42.7 ± 12.3**	11.1 ± 4.1	0.02

ECP in nasal polyp tissue homogenate was higher in AERD than in ATA, while other parameters were not significantly different.

Lee YM et al. J Kor Med Sci 2003;18:97

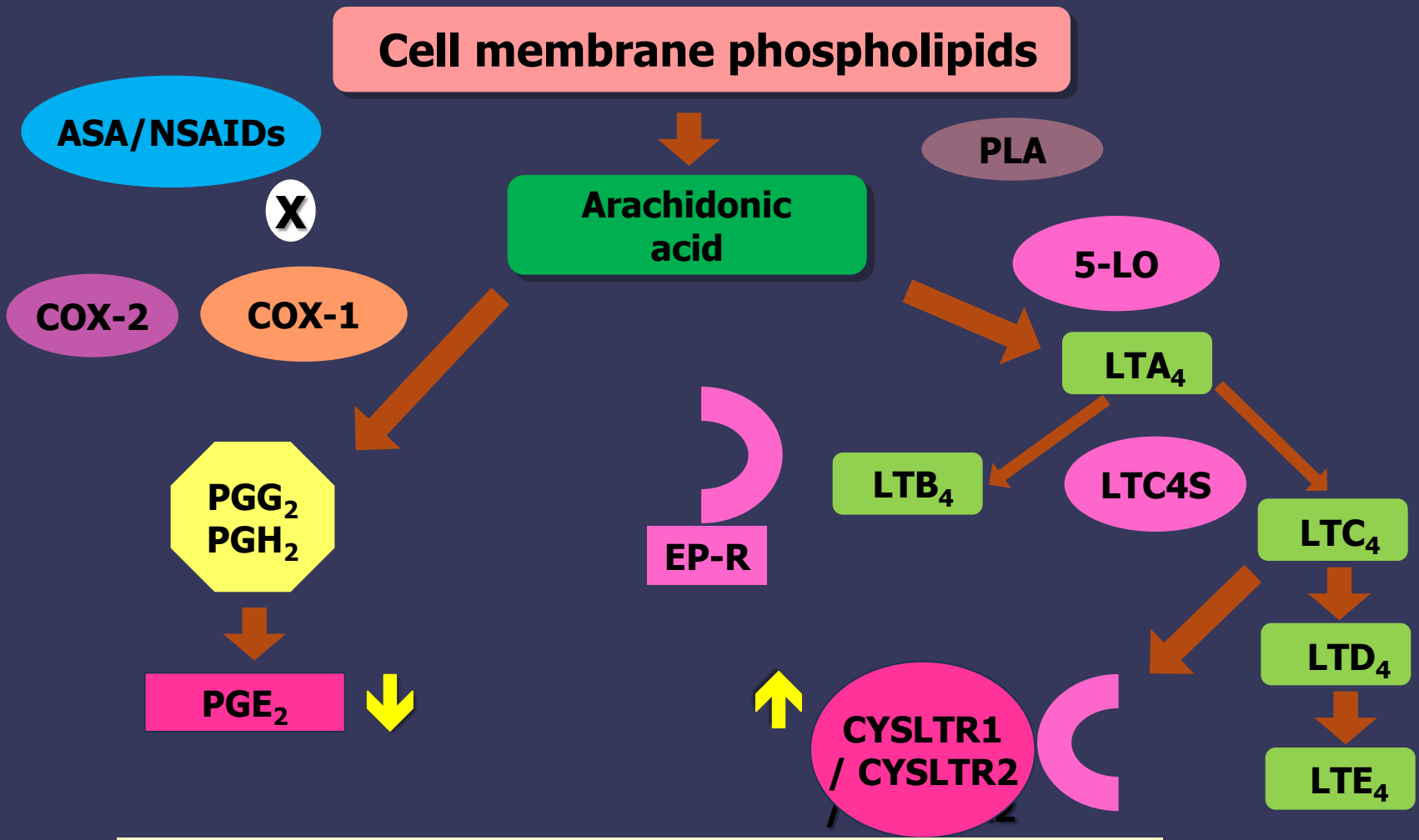
Eotaxin-2 level in the polyp tissues from ATA and AERD



Eotaxin 2 is a major chemokine involved in eosinophil activation of AERD patients.

Allergy 2003;58:1165

Pathogenic mechanism of AERD



Reduction of PGE2/overproduction of CysLT
increased expression of CysLTR1

Profile of eicosanoid generation in AERD and anaphylaxis

1. The levels of LTE4 and PGE2, PGD2 metabolites were measured before and after the ASA challenges in AERD patients compared to ATA.

2. Baseline level of LTE4 were significantly higher in AERD than in ATA, while PGE2 was significantly lower in AERD.

3. CysLTE4 and PGD2 metabolites increased significantly after the ASA challenges in AERD , while no significant changes were noted in ATA.

-> These finding indicates mast cell as well as eosinophil is a key cell to activate eosinophil in AERD

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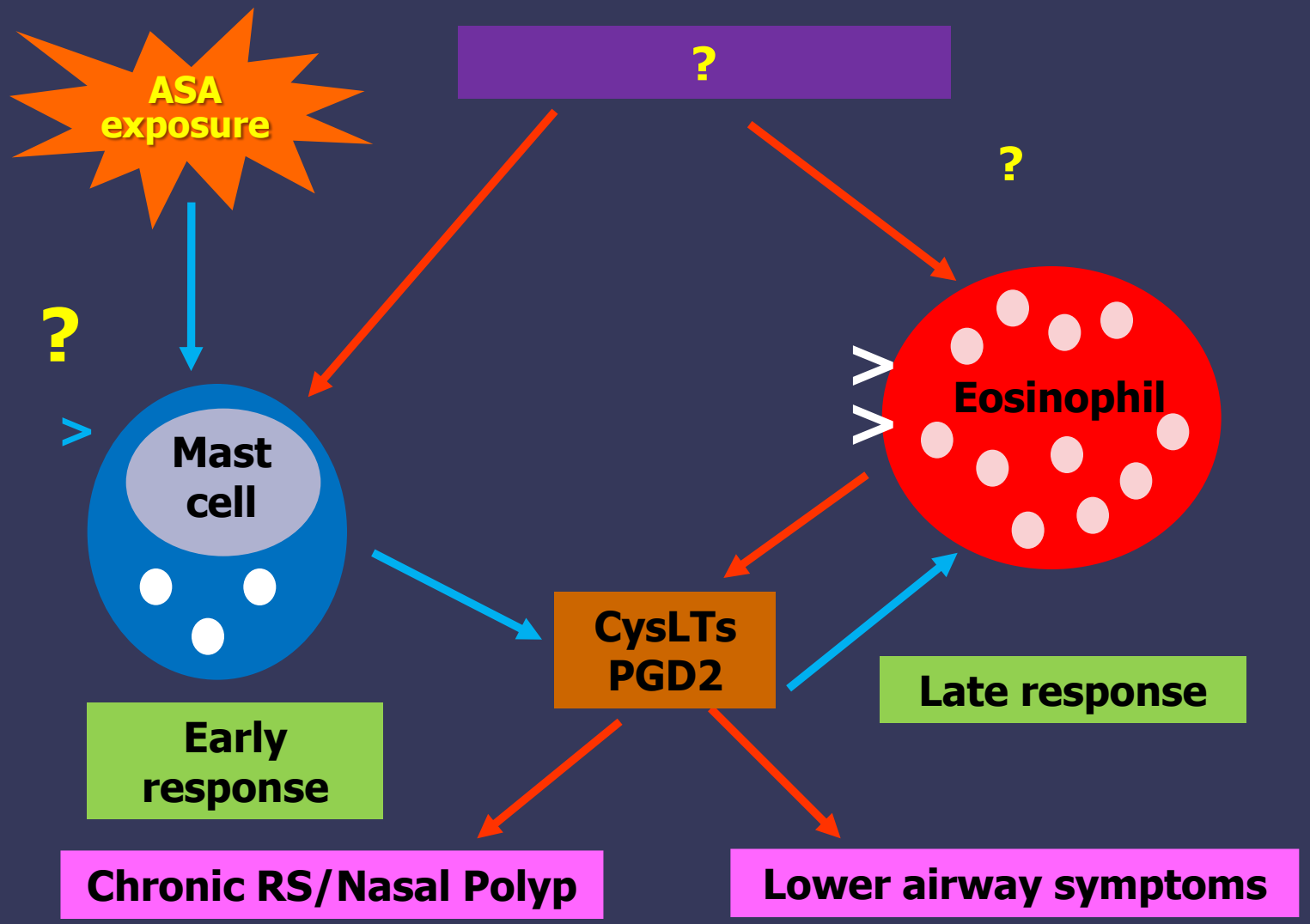
Higashi N et al, J Allergy Clin Immunol. 2010;125:1084-1091

How mast cell and eosinophil are activated after ASA exposure in AERD patients

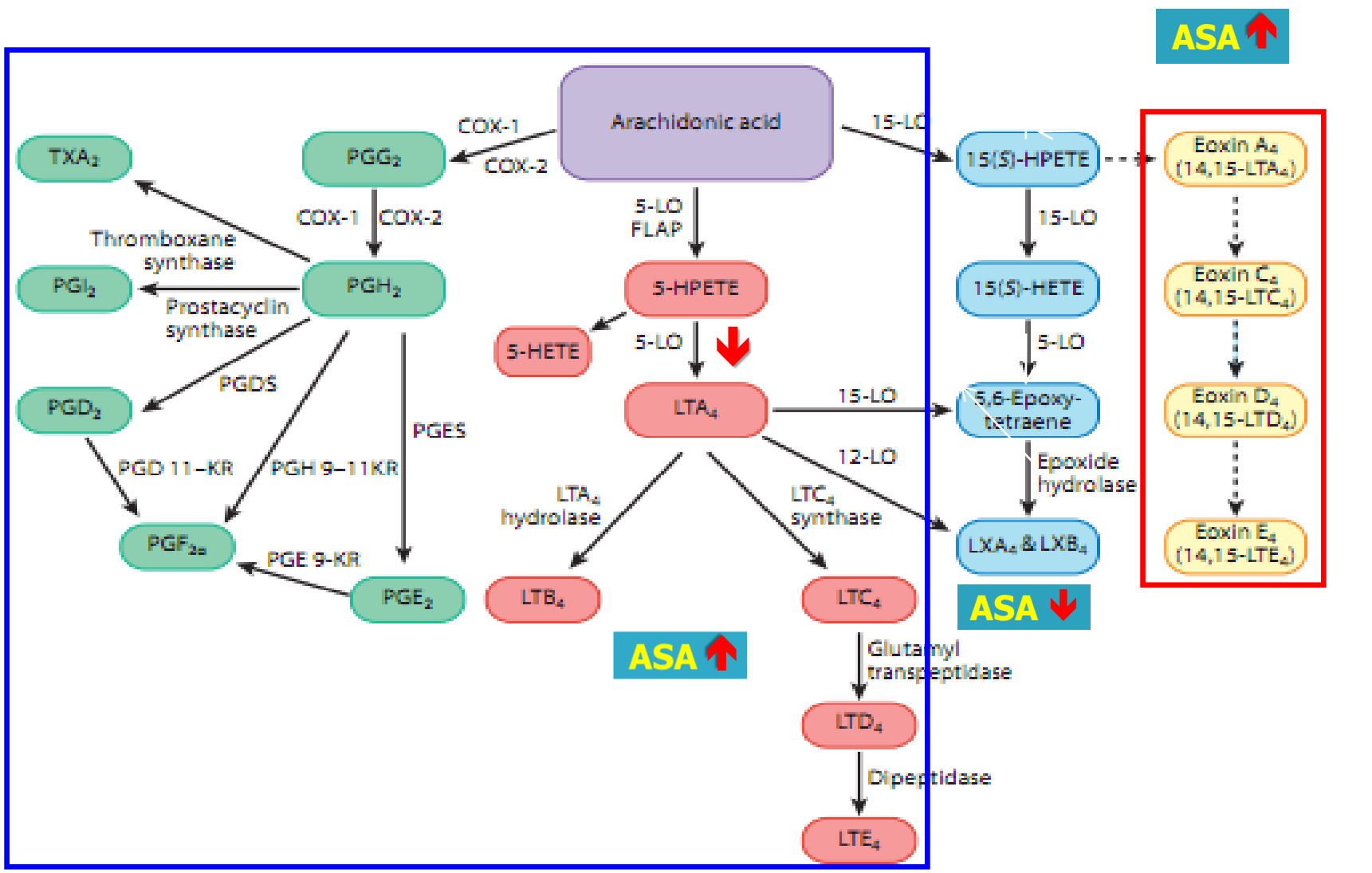


Targeted genes for AERD

1. HLA and LT related genes : HLA class II, 5-LO, LTC4S, CysLTR1, CysLTR2
2. COX-1/PG related genes: PGE2R, PGE4R, TXA2R
3. Mast cell activation genes: FceRIß, ADORA
4. Eosinophil activation genes: CCR3, CRTH2, IL13
5. Others: IL10, TGFß1

Palike N & Park HS. Yonsei Med J, 2009;50:744
Palike N & Park HS. J Allergy, 2011

The 12/15-LO pathway in AERD



→ 15-LO pathway and eosinophil activation

IgE response to Staphyloccal superantigens and eosinophil activation

1. The prevalence of serum specific IgE to Staphylococcal superantigen was higher in AERD patients

2. The AERD patients with specific IgE to superantigen had lower FEV1 and more severe AHR.

3. Several studies demonstrated sIgE response could involve in Th2 and eosinophil activation

-> These finding indicates sIgE response to superantigen may have a key role in eosinophil activaion in AERD

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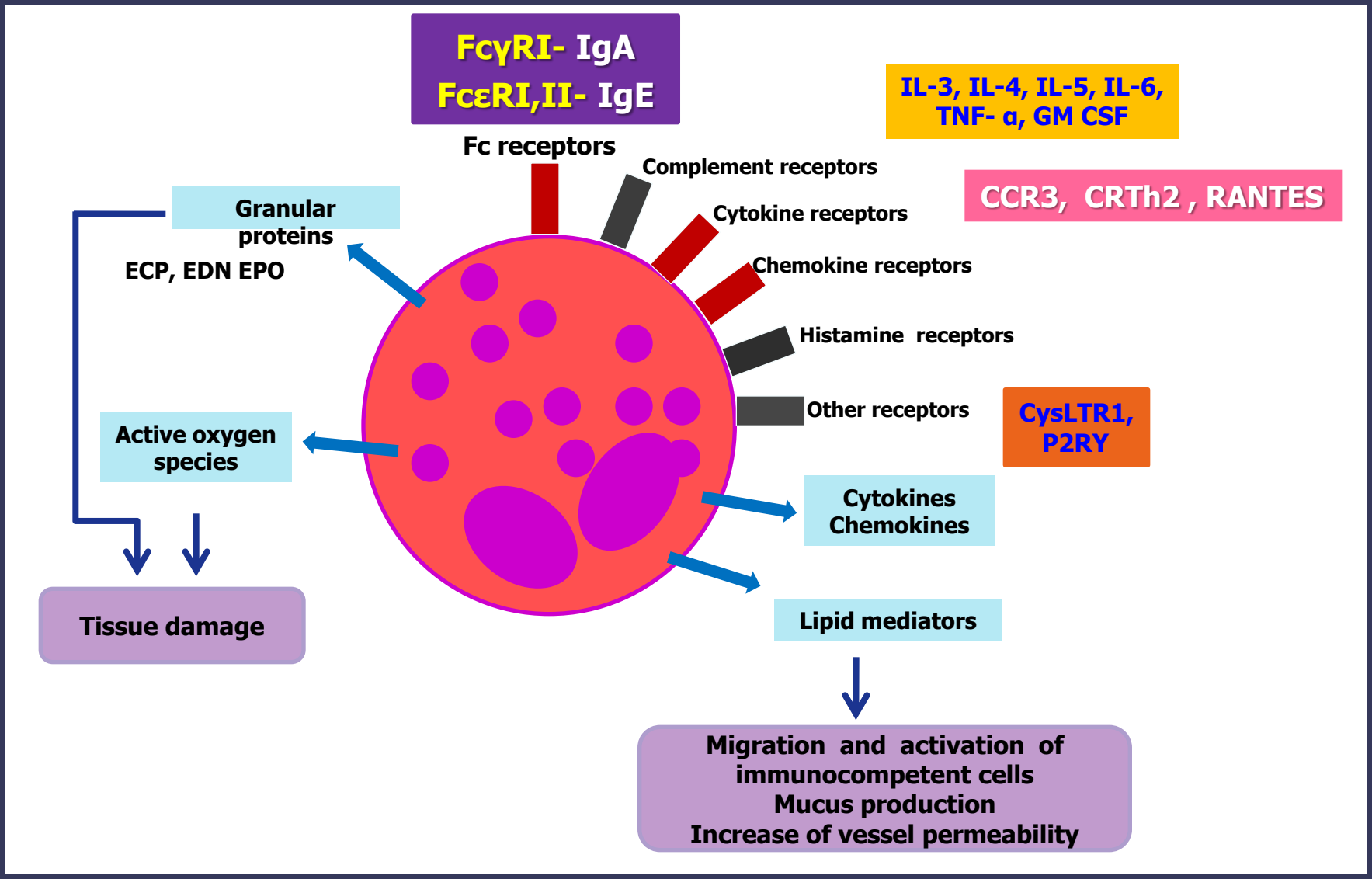
Eosinophil receptors



Management

1. Avoidance from ASA and cross reacting drugs of COX-1
2. Pharamcologic treatment
3. management of RS/nasal polyp

-> ICS and INS could suppress

upper and lower airway inflammation including eosinophils

Biologics: Anti-IgE antibody or anti-IL 5 antibody

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Thank You

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