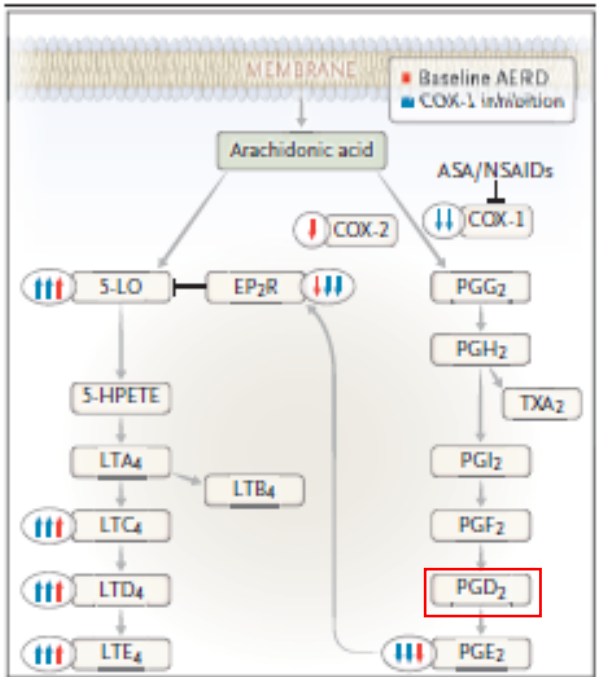

Figure 1. Mechanisms Underlying Respiratory Reactions to Cyclooxygenase 1 (COX-1) Inhibitors.

At baseline, inflammation of the respiratory tract is already ongoing in patients with aspirin-exacerbated respiratory disease (AERD). With COX-1 inhibition by any nonsteroidal antiinflammatory drug (NSAID), the loss of prostaglandin E_2 (PGE_2) inhibitory control leads to massive release of histamine and generation of cysteinyl leukotrienes by mast cells, an event that is unique to AERD. (Prostaglandin D_2 [PGD_2] is pharmacologically inhibited with COX-1 inhibition, but the level greatly increases during reactions through mast-cell and eosinophil activation.) COX-1 inhibition does not block this alternative pathway, which continues unchecked. Red arrows represent abnormal baseline conditions in patients with AERD, and blue arrows indicate changes after COX-1 inhibition. The number of arrows indicates the magnitude of change. ASA denotes acetylsalicylic acid, EP_2R prostaglandin E_2 receptor, 5-HPETE 5-hydroperoxyeicosatetraenoic acid, LT leukotriene (types A_4, C_4, D_4, and E_4), 5-LO 5-lipoxygenase, PG prostaglandin (types G_2, H_2, I_2, and F_2), and TXA_2 thromboxane A_2.

ロイコトリエン（LT）群は，1979 年に白血球中の急性炎症メディエーターとして発見されました。アラキドン酸から生合成されます。LT の代謝産物である LTC4, LTD4, LTE4 は，構造中にアミノ酸のシステインを含むことから，システイニルロイコトリエン（CysLT）と呼ばれています。

COX2阻害薬でPGE2は減少しますがAERDの場合に枯渇してしまい、左の経路のコントロールが出来なくなり、その結果ロイコトルエンの増加を呈し、炎症のカスケードではなく気管支痙攣となってしまいます。

AERDではそもそも気管支痙攣を起こすロイコトルエン系列が活性化しているようです。

次のグラフで示していますが、PGD2が中心のようです。つまりCOX2阻害薬で本来はこのPGD2は減少しますがAERDではマスト細胞の活性化を誘導してPGD2は増加傾向となりその結果好酸球細胞からロイコトルエン系が産生され、AERDの病態を形成するとの説明です。

（AKBと同じで名前が覚えきれません。次のグラフと併せて各自で確認ください。）

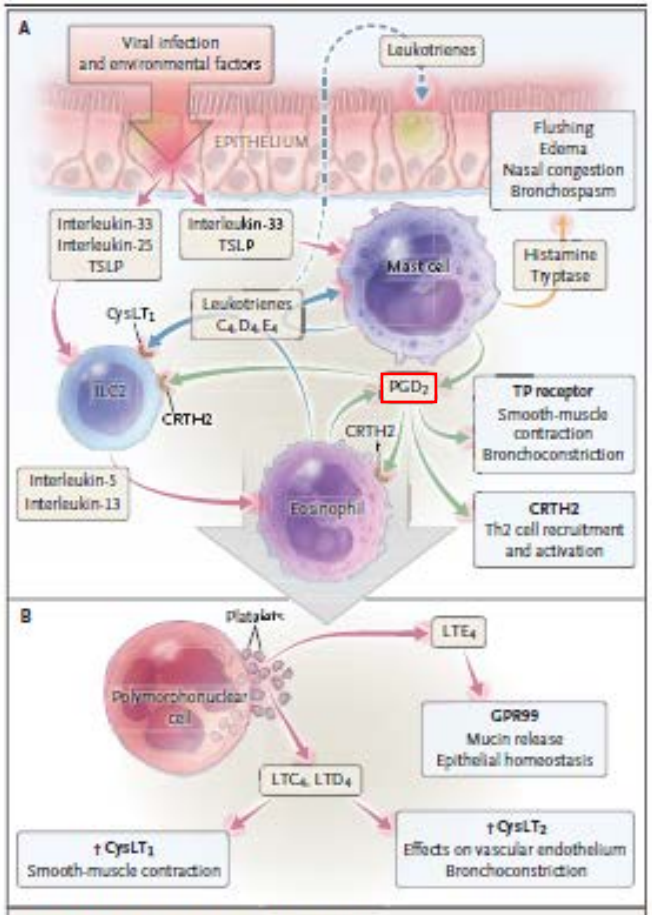

Figure 2. Inflammatory Pathways in AERD.

Type 2 inflammation has a circular path in patients with AERD (Panel A). Allergens, viral infection, and environmental factors are all capable of initiating epithelial injury and release of alarmins, interleukin-33, thymic stromal lymphopoietin (TSLP), and interleukin-25. These upstream cytokines have multiple effects focusing on type 2 inflammatory responses. Type 2 innate lymphoid cells (ILC2) and mast cells in AERD both amplify the responses, leading to eosinophilia and potential feed-forward mechanisms. Leukotrienes enhance these pathways and can control ILC2 responses. Platelet–adherent neutrophils (Panel B) further increase the leukotriene burden in AERD. Despite COX-1 inhibition of prostaglandins, a paradoxical oversynthesis of prostaglandin D_2 (PGD_2) occurs as a result of mast-cell and eosinophil activation through thromboxane (TP) receptors. PGD_2 receptors stimulate the recruitment of type 2 helper T (Th2) cells. Cysteinyl leukotrienes C_4 (LTC_4) and D_4 (LTD_4) act on both cysteinyl leukotriene receptor 1 ($CysLT_1$) and cysteinyl leukotriene receptor 2 ($CysLT_2$). Leukotriene E_4 (LTE_4) has minimal function at $CysLT_1$ and $CysLT_2$ but binds G protein–coupled receptor 99 (GPR99), leading to mucin release and submucosal swelling. CRTH2 denotes chemoattractant receptor-homologous molecule expressed on Th2 cells.

色々なメディエータが関与していますが本論文の説明ではPGD2が意外に関与していて好酸球にまで刺激し炎症のカスケイドから逸脱し、ロイコトルエン系を賦活してしまうようです。本来はアラキドン酸のpathwayの両方が機能すべき所を一方が優位になってしまったのがAERDでしょうか？