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Title: Lung B cell-derived CXCL13 is critical for lymphoid follicle formation in chronic obstructive pulmonary disease

Dr. Eleni 14464 Litsiou elitsiou@yahoo.gr [1], Dr. Maria 14465 Semitekolou msemi@bioacademy.gr [2], Dr. Ioannis 14466 Morianos jmor@bioacademy.gr [2], Dr. Aikaterini 14467 Tsoutsa aikaterinat@yahoo.com [1], Dr. Panagiota 14487 Kara tsoumak@yahoo.gr MD [3], Dr. Dimitra 14488 Rontogianni tsoumak@yahoo.gr MD [3], Dr. Ion 14489 Belenis tsoumak@yahooo.gr MD [4], Mrs. Maria 14495 Konstantinou tsoumak@yahoo.gr [5], Dr. Konstantinos 14496 Potaris tsoumak@yahoo.gr MD [5], Dr. Georgina 14503 Xanthou gxanthou@bioacademy.gr [2], Prof. Dr Spyros 14504 Zakynthinos szakynthinos@yahoo.com MD [1] and Dr. Maria 14506 Tsoumakidou tsoumak@yahoo.gr MD [1,2]. [1] Critical Care Medicine and Pulmonary Services, Evangelismos General Hospital, Athens, Greece ; [2] Cellular Immunology, Biomedical Research Foundation of the Academy of Athens, Greece ; [3] Pathology, Evangelismos General Hospital, Athens, Greece ; [4] Thoracic Surgery, Evangelismos General Hospital, Athens, Greece and [5] Thoracic Surgery, Sotiria Chest Hospital, Athens, Greece .

Body: Lymphoid follicles (LFs) that have a similar organization to lymph nodes are found in small airways and alveoli in Chronic Obstructive Pulmonary Disease (COPD), but the mechanism of their development is unclear. During lymph node ontogeny lymphotoxin (LT)-expressing lymphoid-tissue inducer cells induce lymphokine production (mainly CXCL13) to LT-receptor-expressing stromal cells. Lymphokines attract haemopoietic cells leading to lymphoid organ development. We examined peripheral lung tissue from COPD patients with LFs (COPD-LF^{+}), without LFs (COPD-LF^{-}) and never-smokers. Lung CXCL13 was significantly increased in COPD-LF^{+} compared to COPD-LF^{-} and never-smokers and positively correlated to surface area of LFs. Immunostaining showed CXCL13 expression in B cell areas of LFs. Flow cytometry indicated that among lung cells, B cells have the highest expression for LT receptors. Ex-vivo, lipopolysaccharide (LPS) and a LT-receptor agonist induced CXCL13 production to whole lung cell cultures from COPD-LF^{+}. The LPS induction of CXCL13 was decreased by neutralizing LT. Depletion of B cells from the cultures significantly decreased CXCL13 and LT. Isolated lung B cells showed high migration towards lung tissue homogenates from COPD-LF^{+} that was significantly decreased by CXCL13 neutralization. When isolated lung B cells were exposed to CXCL13, LT was significantly increased, indicating a positive feedback loop between LT and CXCL13. We propose that the initiating event to LF formation in CODP is B cell stimulation, leading to LT expression and CXCL13 production. CXCL13 positively feeds back LT, amplifying its levels and attracting more B cells that organize themselves into LFs.