

## **Cytokine mediated in vitro transcriptional activity of the CCR4 gene promoter**

The European Respiratory Society estimates the European prevalence of asthma to be 8.2% in adults and 9.4% in children, with an economic burden of €17.7 billion per year in Europe alone. Asthma is caused by inherited and environmental factors working together. Symptoms most commonly occur following an allergic reaction to external triggers such as house dust mites, pollen, and several types of animal fur and bird feathers. This causes inflammation and contraction of the airways, leading to symptoms such as breathlessness, cough, chest tightness and wheezing.

Amongst the most important contributors to airway inflammation, is a type of cell called  $T_{H2}$ . These cells produce a wide range of inflammatory chemicals, as well as a special protein on their surface called the “CCR4 receptor.” Patients with asthma have higher amounts of CCR4 receptors than normal. CCR4 is activated by other inflammatory proteins such as CCL17 and CCL22, causing the triggering of a mechanism which results in even more  $T_{H2}$  cells recruiting to the airways, and promoting further inflammation. Internationally, scientists have been working on new medicines which could block the effects of CCR4, as a potentially new way to manage asthma.

At the University of Malta, we have been studying why patients with asthma have an increased number of CCR4 receptors. We investigated whether other inflammatory chemicals which are released in asthmatic airways, have an influence on the genetic mechanisms which control the amount of CCR4 produced. To do this, we cultured airway cells in a laboratory, and treated them in such a way as to make them give off small amounts of light, when the DNA pathways necessary to produce CCR4 are active. We successively exposed the cells to various inflammatory chemicals called cytokines, which are normally found in the lungs of patients with asthma. We then used specialized equipment to study how much light was given off by these cells, under various experimental conditions.

Interestingly we found that particular cytokines are able to activate DNA mechanisms which lead to higher CCR4 production. This can explain why patients with asthma produce more CCR4 receptors than non-asthmatic individuals. This emphasizes their role in asthma, and strengthens the need to have new safe and effective anti-asthma medicines that work on CCR4 mechanisms. Indeed, we now aim to study how certain medicines influence these mechanisms, in order to be able to find ways to reduce their activity.

*Ms Alessia Carta, a medical laboratory scientist, carried out this research as part of her MSc (Melit.) degree in Molecular Pharmacology, under the supervision of Professor Anthony Fenech and Dr Vanessa Petroni Magri. She passed with Distinction and graduated on November 25, 2019. The degree was carried out following the award of an Endeavour Scholarship Scheme which is being financed out of national funds.*