
Journal Highlight: Eosinophil-Mediated Tumoricidal Activity

Reviewed by Neda Farahi

DIVISION OF RESPIRATORY MEDICINE, DEPARTMENT OF MEDICINE,
UNIVERSITY OF CAMBRIDGE, UK

The role of eosinophils in modulating tumour behaviour and tumour progression is an area of active research interest. In certain tumours (colon carcinoma, oesophageal squamous cell carcinoma and oral squamous cell carcinoma), a marked eosinophil infiltrate at the tumour site is a distinguishing clinical feature. Intriguingly, the accumulation of eosinophils at tumour areas, termed tumour-associated tissue eosinophilia (TATE) can, in certain cancers, also be accompanied with a better prognosis. This beneficial outcome is thought to be mediated by eosinophils exerting cytotoxicity towards tumour cells. However, the tumoricidal mechanisms of eosinophils are yet to be elucidated.

A recent paper by Gatault and colleagues¹ investigated the molecular pathways underlying the interaction between tumours and eosinophils. Their experimental protocol utilised human eosinophils (obtained from healthy, allergic and HES volunteers) and two human colon carcinoma cells lines (Colo-205 and Caco-2). Gatault et al. demonstrated that eosinophils induced tumour cytotoxicity in both a concentration- and time-dependent manner. A prerequisite to the anti-tumour effect was cell-cell contact, an effect dependent on ICAM-1 expression. Using a neutralizing antibody approach, eosinophil-derived IL-18 was found to have a pivotal role not only in mediating the cytotoxicity but also facilitating the cell-cell contact. Specifically, IL-18 upregulated membrane expression of the cell adhesion molecules CD11a and ICAM-1. The authors also demonstrate that eosinophils derived from allergic patients were more cytotoxic than those derived from healthy or HES donors.

In summary, this paper sheds light on the mechanism of eosinophil mediated tumour cell death, demonstrating how the tumour type, the cancer microenvironment and also eosinophil heterogeneity can influence tumour progression.

1. Gatault S, Delbeke M, Driss V, Sarazin A, Dendooven A, Kahn JE, Lefèvre G, Capron M. IL-18 Is Involved in Eosinophil-Mediated Tumoricidal Activity against a Colon Carcinoma Cell Line by Upregulating LFA-1 and ICAM-1. *J Immunol* 2015

Q & A with paper author Dr Solène Gatault

What sparked your interest in eosinophils?

Since 2010, I had the opportunity to prepare my PhD in Professor Monique Capron's laboratory, which focussed for a long time in the study of human eosinophil function in parasitic diseases and inflammatory disorders. Monique Capron gave me the passion for these surprising cells, notably by her original views, considering that eosinophils are not only "bad cells" but could also have beneficial role depending upon the cytokine environment.

Tell us how this specific project got started?

This project is entirely in keeping with the thematic of our lab. It was initiated by Dr Fanny Legrand with the discovery of a functional lymphoid receptor, the $\gamma\delta$ TCR/CD3 complex (Legrand F., Driss V. et al. *PLoS One*, 2009). This discovery, in addition to epidemiological data, brought new perspectives in the function of eosinophils in anti-

tumor immunity, leading to a publication in Journal of Immunology in 2010 (Legrand et al. J Immunol. 2010), and a review in 2012 (Gatault et al. Cancer Immunol Immunother. 2012). The molecular mechanisms remained misunderstood and I chose to focus on IL-18, given its involvement in immunity against cancer, especially against colon cancer.



Monique Capron's team. From right to left: Solène Gatault, Annie Standaert, Muriel Pottier, Marie Delbeke, Monique Capron and Arnaud Dendooven.

How would you describe this research to a non-specialist audience?

Growing evidence obtained in human patients suggested inverse relationships between a history of allergies and the risk of cancer. Increased numbers of blood eosinophils are often detected in allergic patients but also observed in large numbers close to the tumors. This infiltrate is generally linked with a good prognostic value, notably in context of colon cancer. Thus, our team was interested in the direct action of eosinophils against colon cancer cells. In this study, we have observed that human eosinophils are able to kill colon cancer cells after contact between them. Moreover, it is very interesting to note that eosinophils from allergic donors are more cytotoxic towards cancer cells than those from normal donors.

How do you plan to take this research forward?

Our results raise new issues. First, we plan to confirm the beneficial properties of eosinophils by in vivo models of colon cancer. We will also expand our research to other mediators and receptors in relation with IL-18 involvement (as IFN γ and Fas/FasL). Finally, the IL-18 involvement in the functional heterogeneity of eosinophils depending on the status of donors remains to be evaluated.

Can you elaborate on the therapeutic potential/avenues of your current findings?

Actually, therapeutics targeting eosinophils are to inhibit their activation or recruitment. However, this study supports growing evidence suggesting a beneficial role of these cells in certain contexts, notably in context of gastro-intestinal disorders. Recently, we have also shown that immunization with P28GST, a unique recombinant schistosome enzyme, ameliorates intestinal inflammation (a risk factor of colon cancer) through eosinophil-dependent modulation of type 1 responses (Driss V. et al. Mucosal Immunol, 2015). A future challenge may be to activate eosinophils locally by agonists or immuno-modulators.