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Commentary

IgE and macrophages for cancer rescue?

Pio Conti^{a,*}, Theoharis C. Theoharides^{b,c,d}^a Postgraduate School of Medicine, University of Chieti-Pescara, Italy^b Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Immunology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA, USA^c Sackler School of Graduate Biomedical Sciences, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA, USA^d Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, 136 Harrison Avenue, Boston, MA, USA

Pellizzari et al. report on the expression of the high affinity receptor for IgE (FcεRI) on the surface of a good portion of human macrophages obtained from peripheral blood of normal volunteers [1]. They further report on the ability of a monoclonal anti-tumour IgE antibody (SF-25-IgE) targeting a tumour-associated antigen (TAA) to retain pro-inflammatory mediator release from M1 macrophages, while stimulating both M0 and M2 macrophages to express the co-stimulatory molecule CD80 and secrete many pro-inflammatory cytokines including IL-1β and TNFα. Moreover, M2 macrophages are stimulated to secrete MCP-1, all actions leading to antibody-dependent, macrophage-mediated cytotoxicity (ADCC). Evidently, these actions occurred via FcεRI-associated downstream events activated by the anti-tumour IgE antibody either through endogenous IgE or exogenous IgE added to the cells [1].

Macrophages, often of the M2 type, frequently comprise 30–40% of the immune infiltrate in many tumours [2]. Hence, numerous efforts by many research groups have been aimed at repolarising M2 macrophages –such as in pancreatic cancer- towards M1 [3], associated with a pro-inflammatory cytokine environment similar to that promoted by IgE - which Pellizzari et al. report in their paper.

Pellizzari et al. report that repolarized M2 macrophages secrete MCP-1 [1], which may in the long run possibly have unexpected adverse outcomes on cancers and/or autoimmunity [4]. MCP-1 is a well-known chemoattractant for mast cells [5], which can then secrete many mediators in response to IgE or neuropeptides [6,7]. Pro-inflammatory molecules such as CXCL8 and TNF could have anti-tumour actions [8], while vasoactive and mitogenic molecules such as histamine and vascular endothelial growth factor (VEGF) can promote cancer growth [9].

The results presented in the study summarized above raise a number of questions:

- (a) Do *in vitro* results adequately reflect the *in vivo* cancer tissue microenvironment?
- (b) Do results obtained from mice represent that which happens in humans, especially since mice have been reported to not reflect inflammatory diseases in humans?

- (c) Could the anti-tumour IgE stimulate uncontrolled secretion of pro-inflammatory cytokines and lead to the development of inflammatory or autoimmune diseases?
- (d) Is the total IgE level different in cancer patients as compared to normal controls?
- (e) What is the effect of the anti-tumour IgE antibody on either normal or tumour-associated mast cells?
- (f) Are patients treated with the neutralizing anti-IgE antibody omalizumab more prone to develop more cancers? The results are still controversial.
- (g) Are patients with systemic mastocytosis [6], who are characterized by many more hyperactive mast cells and often high serum IgE levels, more or less likely to develop cancer? One report suggests that mastocytosis may be associated with a higher risk of developing cancers [10].

Regardless of the issues raised, the identification of functional FcεRI on human macrophages changes the playing field in immunity and inflammation.

Disclosure

The authors declared no conflicts of interest.

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* Corresponding author at: Immunology Division, Postgraduate Medical School, University of Chieti, Pescara 65100, Italy.

E-mail address: pioconti@unich.it (P. Conti).

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