

# Lung cancer and alveolar macrophage function with

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## What are alveolar macrophages and what is their role in the lung?

**Dodie Pouniotis, Christine McDonald & Vasso Apostolopoulos:** Alveolar macrophages (AMs) are mononuclear phagocytic cells that develop in a variety of tissues by maturation and differentiation from blood monocytes. They are localized in the air spaces of the lung and their major functions within the immune system are: (i) to regulate local inflammatory reactions

by the release of pro- and anti-inflammatory cytokines, (ii) to provide a primary defense mechanism via phagocytosis and respiratory burst and (iii) to mediate immune responses through antigen processing and presentation. In addition, AMs may exert direct cytotoxic effects on tumor cells or may produce anti-tumor effects through the release of a wide variety of cytokines.

## What are the effects on alveolar macrophage function in lung cancer patients?

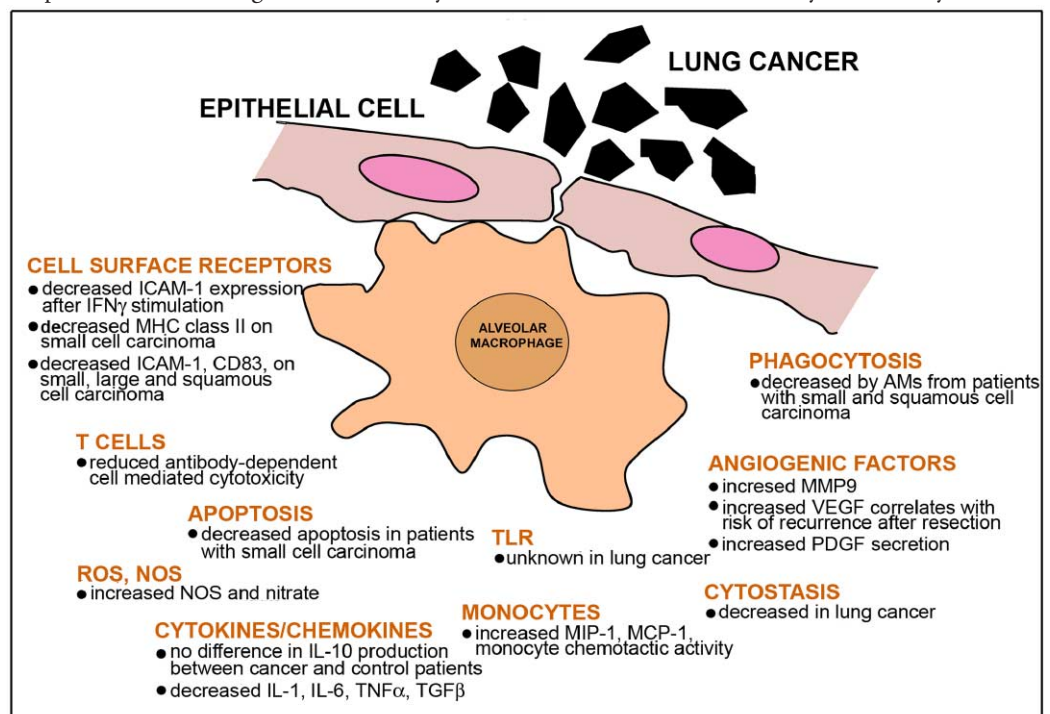
**Dodie Pouniotis, Christine McDonald & Vasso Apostolopoulos:** The functional role of AMs in lung cancer has been explored to a limited extent, and the findings are inconsistent. Various studies have looked at individual immunological parameters of AM function however none have studied these parameters in parallel. Most studies have combined all histological types of lung cancer together or, at most, have separated tumor types into small cell (SCLC) and non-small cell (NSCLC) carcinoma. There are a number of effector functions performed by AMs to enable activation of immune cells within the tumor environment. Macrophages are able to take up antigen by different mechanisms to process antigens and present peptides to T cells. We recently showed AMs from patients with lung cancer exhibit impaired uptake of different sized particles, decreased levels of TNF- $\alpha$ , IL-1, IL-6 and IL-10, decreased levels of MHC class II, ICAM-1 and

reduced mannose receptor and co-stimulatory marker surface expression compared to control patients. These effects are dependent on the histological subtype of lung tumor (1).

AMs have been suggested to have a dual role in lung cancer – although they kill neoplastic cells following activa-

tion by IL-2, IFN- $\gamma$  and IL-12, paradoxically, they may also to some extent favor tumor progression by contributing to tumor stroma formation and angiogenesis through their release of cytokines, chemokines, cytotoxic mediators including reactive oxygen species (ROS), proteases, matrix metalloproteinases, soluble mediators of killing and other angiogenic factors. There are various reports on the functional changes of AMs in lung cancer patients, demonstrating altered phenotype, increased/decreased secretion of various pro- and anti-inflammatory cytokines and altered function (1-3) (Figure). A marked increase in the numbers of AMs in the airways, lung parenchyma, bronchoalveolar lavage fluid and sputum has been found in lung cancer patients (4). This increase is thought to be due to increased recruitment of monocytes from the circulation in response to monocyte-selective chemokines

and/or due to extended survival in the lung tissue (2). AMs from patients with NSCLC reduced production of cytokines, IL-1, IL-6, TNF- $\alpha$ , TGF- $\beta$  as well as reduced antibody-dependent cell-mediated cytotoxicity and cytostatic activity (5,6). Also chemokine upregulation (MIP-1, MCP-1) has been shown on AMs in patients with lung cancer (5), however their functional significance in lung cancer remains to be determined. Recent evidence suggests that angiogenesis is related to poor prognosis in many solid tumors (5,7). MMP9-expressing AMs play a key role in preparing pre-metastatic sites for eventual malignant cell growth in a manner dependent upon vascular endothelial growth factor receptor-1 (VEGFR-1) (8). The balance between these factors plays a key role in the lung tumor microenvironment and may contribute to tipping the balance between pro and anti-tumor immunity mediated by AMs.



## How does the study of alveolar macrophage biology benefit the development of better immunotherapies?

**Dodie Pouniotis, Christine McDonald & Vasso Apostolopoulos:** It is becoming clear that a more immunological targeted approach for the treatment of lung cancer is needed. To develop biological therapies for lung cancer, we need to increase our understanding of the tumor microenvironment in lung cancer. In our own studies, we have shown differences in phagocytosis, cytokine secretion and cell surface receptor

expression between different tumor subtypes within the broader category of NSCLC as well as between SCLC and NSCLC histologies. These differences could significantly affect interactions between tumor and immune system cells and, therefore have a role in tumor progression and response to therapy. Further “stratified” analysis of AM function in different primary lung cancer types is needed, as is the additive effects of other fac-

tors that co-exist in lung cancer patients such as smoking status, COPD, age, as well as the different histological types and staging of lung tumors that may have differential effects on AM function. Results from these studies will contribute significantly to our understanding of how AM phenotype, activation state and function are altered in the presence of lung cancers and identifying these factors, we may be able to manipulate AM function in the development of immunotherapeutic regimes.

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