

Genetic diversity and tumor immunesurveillance

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Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related death; it mainly results from exposure to carcinogenic agents as well as genetic predisposition. It has been still estimated that around a million of people will die of lung cancer every year (Global Cancer statistics).

Usually NSCLC patients with a localized tumor are treated surgically, while patients with non-localized NSCLC are primarily treated with radio-chemotherapy (1). In about 40% of the cases, even with adjuvant postoperative chemotherapy and radiotherapy, patients develop recurrence of the disease locally or systemically hence there is a strong need for more efficient therapies. In this respect, immunotherapy is an interesting approach as it aims to develop memory cells that might attack the tumor at any time (2). As immunotherapy specifically relies on the capability of a patient's immune system to respond to a "stimuli", its overall efficacy has been very variable as variable probably is the human being capability to mount an immune response. Understanding genetic differences that influence the response to immunotherapy is of extreme importance to select the right patients for clinical trials and ultimately to move our knowledge towards a real personalized therapeutic approach. Along this line, impressive data were also shown by Kaufman and colleagues. They showed that if the cohort of patients is correctly selected a pox-virus based vaccine for advanced pancreatic cancer can significantly improve overall survival (3). Similarly Musolino and colleagues showed that polymorphisms of the IgG fragment of the C gamma receptors significantly influence the efficacy of Trastuzumab-based therapy in patients with HER-2/neu positive metastatic breast cancer (4). These and other similar observations emphasize the important role of the human genetic diversity and highlight that we have not taken this diversity enough in consideration in our clinical approach thus far.

In the work recently published in *Cancer Research* (5), Kreisel and colleagues have focused on the immunesurveillance of NSCLC elegantly demonstrating that genetic background deeply influences the development of such tumor. Simply but efficaciously, using bone marrow transplant, they determined that hematopoietic cells from lung cancer-resistant mice could significantly hinder the development of cancer in a susceptible strain and vice versa hematopoietic cells from lung cancer-susceptible mice could promote development of lung cancer in resistant-strain mice. More importantly they showed that this phenomenon was not due to differences in tumor-promoting inflammatory changes or variability in immunesurveillance by the adaptive immune system but it resulted from strain-specific differences in natural killer (NK) cell cytotoxicity. More specifically they demonstrated that polymorphisms in the natural killer gene complex (NKC) significantly influence the immunesurveillance of the tumor and consequently its susceptibility and development. The most striking experiment that they conducted was performed in a mouse strain (designed as 129/SvEv.B6-NKC Rag2^{-/-}) that bear the genome of a susceptible mouse strain but the NKC genomic region of a resistant strain (B6). This mouse model represents a unique mouse strain to study the impact of the NKC locus on tumor immunesurveillance. The results from this experiment were consistent with the hypothesis that NK-mediated immunesurveillance plays a major role in tumor immunoediting and tumor immunesurveillance. To deeper clarify what receptors in the B6 NKC are critical for eradication of lung cancer, they performed an *in vitro* chromium release experiment using a panel of blocking antibodies. The results showed that only the blockade of NKG2D led to near-complete inhibition of cytotoxicity suggesting that this protein specifically plays a critical role in lung cancer recognition and imply that polymorphisms in this activating receptor, or other inhibitory receptors that may prevent NKG2D signaling, may contribute to strain-specific differences in lung cancer cytotoxicity.

NK cells are cells of the innate immune system that were initially identified for their capability to "naturally" kill cancer cells *in vitro* (6), however these cells are also crucial for the innate host defense against pathogens especially viruses. Nowadays it is however very well recognized that NK cells play

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an important role in cancer immunosurveillance and cancer treatment (7,8). One of the peculiarities of NK cells is the ability to kill without being “sensitized”, they are always able to kill a target cell. For this reason as it is imaginable, they have to be tightly controlled to avoid that healthy cell are as well destroyed. The NK cell function and control is influenced by proteins encoded by the Natural Killer Gene Complex (NKC) (9,10). Detailed analyses have indicated that these molecules are involved in NK-cell recognition, activation, and inhibition. The importance of this genomic region is highlighted by studies indicating that NKC-associated genes significantly influence NK cell-mediated innate host defense against life-threatening pathogens and that the NKC is conserved among diverse species.

In our opinion, the most interesting part of finding illustrated by Dr. Kreisel and colleagues is that innate rather than adaptive mechanisms play such a drastic role in tumor immunosurveillance. In addition given that NKC genes are highly conserved across different species (11), it becomes of urgent importance to assess whether the finding illustrated in the present work are translatable to humans and if so in which way they can affect the present therapies and treatments.

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