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The immunoregulatory axis of tBregs in cancer escape and metastasis

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Recently we found a new subset of regulatory B cells, designated tumor-evoked Bregs (tBregs), which is generated in response to cancer-produced 5-lipoxygenase metabolites by targeting PPARα in resting B cells. The role of tBregs is to convert CD4+ T cells into FoxP3+ Treg cells and thereby protect metastasizing cancer cells through the inactivation of effector NK cells and CD8+ T cells. tBregs also activate immunoregulatory functions of MDSCs needed for suppression of antitumor effector cells and metastasis. In the absence of tBregs, metastasis cannot be established despite expansion of MDSCs. Thus, inactivation of tBregs or the blockage of any step of its immunoregulatory axis will provide anti-metastatic benefits. We show that the depletion of Tregs and tBregs by targeting their surface-expressed CD25 abrogates breast cancer lung metastasis in mice, although some strategies, such as the use of B-cell depleting anti-CD20 antibody, can instead be harmful and greatly enhance metastasis due to depletion of beneficial B cells and enrichment of CD20Low tBregs. The regulatory axis can also be blocked using modified chemokines to deliver siRNA or immunostimulatory CpG-ODN to tBregs and Tregs. For example, transient inactivation of FoxP3 or IL-10 in Tregs via siRNA delivered by CCL17 and, alternatively, inactivation of tBregs with CpG-ODN bound CXCL13 can efficiently abrogate metastasis. Overall, our data underscores the importance of tBregs as key initiators of immunoregulatory events needed for successful breast cancer metastasis.

Biography

Arya Biragyn received his PhD from the Institute of Molecular Biology at Engelgardt, Academy of Sciences of Russia, Moscow, in 1991. Since 2011, he is a tenured senior investigator and section chief at the National Institute on Aging. His research focus is to understand the "immunological paradox of aging"; that is, why cancer incidence is enhanced but cancers often grow more slowly in older people, and why autoimmunity is more prevalent in the elderly but older people have poor vaccine responses. He studies cancer-mediated immunoregulation to gain insight on the role of regulatory immune cells and to develop potent immunotherapeutics tailored for elderly. He has published more than 60 papers in peer-reviewed journals. He is an editorial board member or ad hoc reviewer of various journals and grant funding organizations.

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Leveraging bacterial and human genomic datasets at NCBI for immunological research

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In the last 15 years, we have gone from sequencing a single human genome to sequencing material, including exomes, transcriptomes and/or whole genomes from millions of individuals. This presentation will describe how NCBI displays this genomic information, sometimes in conjunction with phenotypic information and how some of its public databases can be queried for computational biology and clinical questions. We are in the process of indexing the exons of over 1 million samples from over 800,000 individuals housed in the dbGaP database at every position in the human genome, as well as having expanded access to the raw data in several ways, and made variant data in these and our medical genomics databases widely accessible. Examples of how investigators can leverage bacterial and human genomic datasets to further immunological research will be described.

Biography

Ben Busby is the Genomics Outreach Coordinator for NCBI, and the Chair of the Bioinformatics Department at the Foundation for the Advanced Education in the Sciences. He is very interested in the integration of large genomic datasets, specifically in the metadata harmonization and statistical normalization necessary to do so.

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