## ARTICLE IN PR

BBACAN-87943; No. of pages: 20; 4C: 3, 5, 6, 7, 8, 9, 10, 11, 16

Biochimica et Biophysica Acta xxx (2014) xxx-xxx

Contents lists available at ScienceDirect



Biochimica et Biophysica Acta



journal homepage: www.elsevier.com/locate/bbacan

#### Review 1

## Tumor-induced perturbations of cytokines and immune cell networks $\stackrel{ m transformed trans$ 2

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## ARTICLE INFO

Article history: 44 Received 2 November 2013 **\$**5 Received in revised form 3 January 2014 86 Accepted 4 January 2014 Available online xxxx

9 Keywords:

3

10 Cytokine

Cancer 11

Immunosurveillance 1213Immunosuppression

## ABSTRACT

Until recently, the intrinsically high level of cross-talk between immune cells, the complexity of immune cell development, and the pleiotropic nature of cytokine signaling have hampered progress in understanding the mechanisms of immunosuppression by which tumor cells circumvent native and adaptive immune responses. One technology that has helped to shed light on this complex signaling network is the cytokine antibody array, which facilitates simultaneous screening of dozens to hundreds of secreted signal proteins in complex biological samples. The combined applications of traditional methods of molecular and cell biology with the high-content, 19 high-throughput screening capabilities of cytokine antibody arrays and other multiplexed immunoassays have 20 revealed a complex mechanism that involves multiple cytokine signals contributed not just by tumor cells but 21 by stromal cells and a wide spectrum of immune cell types. This review will summarize the interactions 22 among cancerous and immune cell types, as well as the key cytokine signals that are required for tumors to sur- 23 vive immunoediting in a dormant state or to grow and spread by escaping it. Additionally, it will present exam- 24 ples of how probing secreted cell-cell signal networks in the tumor microenvironment (TME) with cytokine 25 screens have contributed to our current understanding of these processes and discuss the implications of this 26 understanding to antitumor therapies. 27

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Abbreviations: APC(s), antigen presentation cell(s); ARG1, arginase-1; BREG(s), regulatory B (cells); CAF(s), cancer-associated fibroblast(s); CD, cluster of differentiation protein; CD40L, cluster of differentiation protein 40 ligand; C/EBP, CAAT/enhancer binding protein; CCL, C-C motif (chemokine) ligand family member; CCR, C-C motif (chemokine) receptor family member; COX, cyclooxygenase; CTL(s), cytotoxic T lymphocyte(s); CTLA-4, cytotoxic T lymphocyte-associated protein-4; CXCL, C-X-C motif (chemokine) ligand family member; CXCR, C-X-C motif (chemokine) receptor family member; CSF, colony stimulating factor; DC(s), dendritic cell(s); ECM, extracellular matrix; EGF, epidermal growth factor; ELR+, contains aminoacid sequence "glutamate-leucine-arginine"; ENA-78, neutrophil activating peptide 78 (CXCL5); FasL, Fas ligand (TNFSF6); G-CSF, granulocyte colony stimulating factor (CSF3); GM-CSF, granulocyte-macrophage colony stimulating factor (CSF2); Gr-1, granulocytic myeloid marker protein; GRO, growth related oncogene  $\alpha$  (KC/CXCL1),  $\beta$  (MIP-2/CXCL2) and/or  $\gamma$  (CXCL3); HIF-1 $\alpha$ , hypoxia-induced factor-1 $\alpha$ ; HNSCC, head and neck squamous cell carcinoma; IDO, indolamine 2,3-deoxygenase; IFN, interferon; IgA, immunoglobulin A; IGF-1, insulin-like growth factor 1; IKB, inhibitor of kappa B; IL, Interleukin; IP-10, IFN-\gamma-induced protein 10 (CXCL10); IRF, interferon regulatory factor; LGALS, galectin (lecithin, galactoside-binding, soluble protein); KC, keratinocyte chemoattractant (mouse CXCL1); M1, type 1 macrophage; M2, type 2 macrophage; M-CSF, macrophage colony stimulating factor (CSF1); MCP-1, monocyte chemoattractant protein-1 (CCL2); MDSC(s), myeloid-derived suppressor cell(s); MHC, major histocompatibility complex; MIG, monokine induced by IFN-y protein (CXCL9); MMP, matrix metalloproteinase; MPO, myeloperoxidase; MyD88, myeloid differentiation primary response gene 88; N1, type 1 neutrophil; N2, type 2 neutrophil; NF+KB, nuclear factor kappa B; NK(s), natural killer (cells); NK-T(s), natural killer T (cells); NO, nitric oxide; NOS2, nitric oxide synthase 2; PD-1, programmed death receptor 1; PD-L1, programmed death receptor 1 receptor; PGE2, prostaglandin E2; RNOS, reactive nitrogen oxide species; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor 1 (CXCL12); SMAD, homolog of Drosophila "mothers against decapentaplegic" protein; TAAs, tumor-associated antigens; TCR, T-cell receptor; TGF, transforming growth factor; TGFBR2, type II TGF-β receptor protein; Th0, immature T helper cell precursor; Th1, type 1 T-helper cell; Th2, type 2 T-helper cell; Th17, type 17 T-helper cell; TIMP, tissue inhibitor of metalloproteinases; TME, tumor microenvironment; TNF, tumor necrosis factor; TNFRSF, TNF receptor superfamily member; TNFSF, TNF superfamily member (ligand); TREG(s), regulatory T (cells); TAM(s), tumor-associated macrophage(s); TAN(s), tumor-associated neutrophil(s); VEGF, vascular endothelial growth factor

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Please cite this article as: B. Burkholder, et al., Tumor-induced perturbations of cytokines and immune cell networks, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbcan.2014.01.004

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## 72 1. Introduction

Tumors are not homogenous population of cancerous cells; instead, 73 tumors are heterogeneous groups of cells from diverse origins, such as 7475 stem cells, stromal cells, endothelial cells and a wide range of immune cells [1]. These heterogeneous populations secrete multiple signals 76 that, individually and collectively, may promote or hinder any or all of 77 the hallmarks of cancer required for tumor growth, development, and 78 79progression, as well as the enabling characteristics of genomic instability and tumor-promoting inflammation [2]. The immune system is 80 constantly patrolling the body for foreign invaders and aberrant cells 81 to destroy, a process commonly referred to as immunosurveillance [3]. 82 83 Thus, to remain viable and to continue to grow and thrive, tumors must not just blunt the antitumor immune response in its microenvi-84 85 ronment, the growing tumor must maintain other hallmarks of cancer, such as avoiding apoptosis and maintaining self-sufficiency of growth 86 signals, inflammation, and angiogenesis [4]. 87

Tipping the balance of immunosurveillance from tumor elimination 88 89 to tumor promotion appears to be a complex process that spans multiple 90 signal pathways that can be influenced by cytokine expression from tumor cells [5], immune cells [6], and other non-cancerous cell types, 91 such as epithelial cells or cancer-associated fibroblasts (CAFs) [7], in 92the surrounding tissue. Thus, net cytokine signal inputs from multiple 93 cell types in the tumor microenvironment (TME) can tip the overall bal-94 ance in immunoediting from tumor-promoting to tumor-suppressing, or 95 vice versa. As we described in a previous review, cytokine biology is quite 96 complex [8]. How, then, does one go about decoding such a complex 97 network of multiple signals (some of which may be additive, antagonis-98 99 tic, or synergistic) that may originate from multiple potential sources and pleiotropic effects on the heterogeneous cell types in the TME? 100

A proteomic technique that has shown great promise in detecting key cytokines in cancers and in decoding tumor-related cytokine signal networks is the multiplexed immunoassay [9–13]. The two major types of multiplexed immunoassays are antibody arrays (wherein capture antibodies are printed on a planar solid support, such as membranes, 105 glass slides, or microtiter plates) and bead-based assays, in which 106 capture antibodies are attached to fluorescently-tagged beads. The capabilities, challenges, advantages, and disadvantages associated with 108 these various multiplexed immunoassay technologies—compared with 109 one another and with more traditional approaches to proteomics and 110 genomics—have been well documented in the literature [8,13–17] and 111 are beyond the scope of this review. 112

However, the salient aspects of these methods that make them 113 useful are the sensitivity and specificity of immunoassays and the ability 114 to detect multiple proteins as once. Low-density bead-based assays and 115 antibody arrays may detect a dozen or so targets simultaneously, but 116 high-density (high-content) antibody arrays can potentially screen for 117 hundreds of proteins in as little as 20 µl of sample. Thus, targeted screens 118 for known inflammatory, angiogenic, apoptotic, or growth factors can 119 help identify key biomarkers related to cancer hallmarks from among 120 many potential candidates. High-density screens that allow for detec- 121 tion of cytokines with diverse functions may reveal crucial but unex- 122 pected expression of key factors by one or more cell types. Moreover, 123 the heterogeneous nature of tumors lends itself naturally to analysis 124 of the collective secretion profiles within tumor lysates or to dissect 125 secretion profiles of single cell types (cancerous or non-cancerous) or 126 co-cultures in vitro to discover which cells are contributing these critical 127 signals and which cells are receiving them. After key factors are identi- 128 fied by these cytokine screens, more traditional methods of cell biology, 129 molecular biology, and genetics can be used to complement these 130 results, confirming and further dissecting and defining the complex net- 131 work of secreted cell-cell signals and intracellular signaling pathways 132 that contribute to the biological process being studied. Thus, antibody 133 arrays are extremely powerful tools for the identification of cancer- 134 specific biomarkers either secreted by cells in the local microenviron- 135 ment or by the cancer cells themselves. 136

The balance of this review will summarize much of what is known of 137 the cellular and secreted signaling networks that constitute the native 138

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