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Review article

The "Yin-Yang" of cytokines in cancer

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Cytokines exert both pro- and anti- cancer effects which determine the fate of a tumor [1,2]. Depending on the stage and microenvironment of a tumor, the same cytokine can exert both these effects [3]. Thus, there is a greater need to understand the complex intricacies of cytokine signaling pathways for harnessing their therapeutic potential. Keeping this important goal in mind, the 2nd Aegean Conference on Cytokine signaling in Cancer was organized at Heraklion, Crete, Greece was organized in June 2017. This special issue of CYTOKINE contains several critical reviews by leaders (who were also speakers at the 2nd Aegean Conference) on various aspect of cytokine signaling and their impact on tumor growth. Most of these review articles in this special issue are focused on cytokine induced post-transcriptional and post-translational processes and their aberration in tumor development. In addition, several original research articles related to cytokine actions in cancer are also published in this special edition. Although not comprehensive enough in terms of coverage of various cancers and cytokines, I believe that these articles will be helpful to the readers in appreciating the effects of certain important cytokines.

Transcriptional control of tumor-specific gene expression has been described more extensively in the literature than the post-transcriptional mechanisms. This area of cytokine actions is emerging as a major player in growth control in the recent years. The epithelial to mesenchymal transition (EMT) is a common mechanism used by many tumor cells for metastatic spread [4]. Transforming Growth Factor-β (TGF-β) exerts both pro- anti-tumor effects depending on the tumor stage [5,6]. Howley *et al* discuss a novel post-transcriptional mechanism employed by TGF-β for promoting tumor growth. These authors critically reviewed the role of a RNA binding protein hnRNP E1, which regulates splicing and translation of a cohort of EMT and stemness-associated transcripts. The global nature of such regulation in several tumor types has also been described in their article.

Mammalian RNAs undergo multiple different post-transcriptional modifications in a dynamic manner for controlling gene expression. RNA modifications are attractive targets for developing anti-cancer drugs [7]. Notable among these is the methylation of N6-methyladenosine (m6A). A set of proteins that positively (writers) and negatively (erasers) regulate this specific mark [8]. Other proteins, such as the readers, recognize the m6A and regulate mRNA function. Together, the writers, the readers, and the erasers impact the processing, export, stability, and translational initiation, and the biogenesis of long-non-coding RNAs (LncRNA), which epigenetically regulate gene expression for modulating cellular functions. m6A is critical for cancer development and self-renewal of cancer stem cells. Chang *et al* reviewed the role of m6A and LncRNA in regulating cell growth, immune response, and cytokine activities.

Chronic inflammation has been identified one of the emerging hallmarks of the advanced tumors [9], which allows their survival and proliferation [10]. In addition, tumor-secreted cytokines aid in the recruitment of other immune suppressive stromal cells for promoting metastases [11]. The Th17 cell-associated cytokines IL-17A, IL-23, IL-22, and the IL-1 family members IL-1β and IL-18 are among the list of cytokines that are known to advance tumor growth directly or indirectly (*via* microenvironmental changes). Nguyen *et al* reviewed the roles of IL-17 and IL-18 in driving gastric cancer growth.

The Janus kinase (JAK) -Signal transducer and activator of transcription (STAT) pathways are essential for promoting the survival and activation of immune cells [12]. The suppressor of cytokine signaling (SOCS) proteins play regulate the JAK-STAT pathways by serving as feedback inhibitors of the activated JAKs [13]. The Natural Killer (NK) cells are innate immune cells that participate in the elimination of transformed cells. IL-15 is a direct regulator of NK cell development, survival, and activity. The activity of this cytokine is controlled by two SOCS proteins, CIS and SOCS2. Keating et al. reviewed the importance of CIS and SOCS2 in regulating NK cell functions. Their review also identified SOCS proteins as potential targets for drug development, for blockade of these proteins likely enhances the immune response against tumors. Such drugs along with immune checkpoint blockers will pave way for a better clinical management of cancers [10].

The JAK-STAT signal transduction pathways are critical for exerting the effects of over fifty cytokines, growth factors and hormones in the mammals [12]. These kinases regulate such as hematopoiesis, regulation of the immune system, metabolism, and growth. Hammaren *et al* reviewed the central role of this pathway in human pathophysiologies. JAK mutations in diseases are reported in a wide range of human diseases such as immunodeficiency, obesity and many cancers [14,15]. Several inhibitors are currently in clinical use for treating JAK-mutation associated diseases such as immunodeficiency and cancer. In this review, they have discussed the intra- and inter-molecular regulation of the JAK-STAT pathway, and diseases arising from the disruption of these mechanisms. Apart from their classical role, as signaling partners

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for the cytokine receptors, certain JAKs have been reported to regulate epigenetic modulation of histones, which impact gene expression *via* non-STAT pathways. The authors suggested that the newer understanding of this area will lead to next-generation drug development.

Transcription factor STAT3 is important for cell proliferation, maturation, and survival driven by IL-6 [10]. While many studies suggest a central role for STAT3 in cancer development and progression, some recent studies suggest that STAT3 also acts as a tumor suppressor. Alternative splicing of STAT3 produces STAT3α and a shorter version STAT3β. Both these are transcriptionally active and display distinct physiological and pathological functions. Aigner *et al* reviewed the current understanding of STAT3 in tumorigenesis, including the unique and complex roles played by its alternatively spliced isoforms. A selective blockade of these isoforms may allow a better control over oncogenic processes.

The interferon family of cytokines are essential players in innate immune response against infectious pathogens and neoplastic cells [16]. They play a major role in cancer immune surveill.ance [17,18]. The immune checkpoint inhibitors have shown a glimmer of hope for several patients with advanced cancers [19]. However, they have not made a significant difference to patients with triple negative breast cancers. Brockwell et al. reviewed that tumor intrinsic IFNs and the expression of the IFN-regulated genes are essential for restraining tumor growth. Their studies in triple breast cancers suggest that tumor intrinsic type I IFNs upregulate the antitumor immune response by supporting T-cell activity. Such tumors can be targeted with checkpoint inhibitors [20]. They also suggest that IFN/immune checkpoint inhibitor combinations provide a more robust approach for blocking triple-negative breast cancers than either agent alone.

These articles represent a small fraction of what will come. Cytokine will continue to bring more studies related to the cancer field in the future. In this connection, it is important to remind the readers that the 3rd Aegean International conference on Cytokine Signaling in Cancer is planned and will be held at the Sheraton Conference Center in Ixia, Rhodes, Greece, from June 2–7, 2019. This will be a great opportunity to present data and meet leaders in this area.

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