Therapeutics targeting innate immune/inflammatory responses through the interleukin-6/JAK/STAT signal transduction pathway in patients with cancer

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Over the last 15 years, there has been an evolution in the thinking of how tumors grow and disseminate: from the earlier work where it was considered that the intrinsic characteristics of the tumor largely determined the process to more recent work where local and systemic inflammatory responses play a key role in disease progression and survival in patients with cancer. Although the immune/inflammatory responses to cancer are complex, it is clear that targeting the host immune/inflammatory responses (in particular, innate/humoral responses) has considerable potential to improve outcomes in patients with a variety of common solid tumors. There are a wide variety of agents from the nonselective glucocorticoids to the selective Janus Activated Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) inhibitors that has considerable therapeutic potential. They may be considered to act through a main signal transduction mechanism, the interleukin-6/JAK/STAT pathway. This work heralds a new era in which it will be important not only to treat the tumor but also to treat the host, so called oncoimmunology. (Translational Research 2016;167:61–66)

Abbreviations: JAK = Janus Activated Kinase; STAT = Signal Transducer and Activator of Transcription; EGF = epidermal growth factor; TGF-B = transforming growth factor beta; VEGF = vascular endothelial growth factor; TNF-a = tumour necrosis factor alpha; CRP = C-reactive protein; COX = cyclooxygenase; TNM = tumour node metastases; CD3 = Type I transmembrane protein found on T-lymphocytes; AOM-DSS = azoxymethane- dextran sodium sulphate

INTRODUCTION

Over the last 15 years, there has been an evolution in the thinking of how tumors grow and disseminate: from the earlier work where it was considered that the intrinsic characteristics of the tumor largely determined the process[1] to a realization that local[2] and systemic[3] inflammatory responses play a key role in disease progression and survival in patients with cancer. Cancer-associated alterations in patient immune and inflammatory responses are complex but are clearly linked. Broadly, these inflammatory responses have been considered as a result of perturbed innate, humoral, and adaptive immune responses to the tumor.[4]

To consider how these tumor and immune/inflammatory responses vary or are similar across all tumor types is outwith the scope of this review. Therefore, specific examples of these will be given from the colorectal cancer, a common solid epithelial tumor, literature.

In particular, components of the innate immune response composed of a cellular response (mainly neutrophils and monocytes/macrophages but also including dendritic cells and myeloid-derived suppressor cells)

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and a humoral response (mainly components of complement, collectins, ficolins and pentraxins) are known to have complex interactions potentially detrimental to the host.[5] For example, it is now recognized that pentraxins activate Fc gamma receptors on macrophages and neutrophils.[6,7] Indeed, in patients with cancer, innate immune responses such as increased tumor[8–10] and circulating[11,12] granulocytes are associated with poor outcome independent of tumour node metastases (TNM) stage. Similarly, humoral immune responses such as increased tumor[13] and circulating[12] pentraxin C-reactive protein are also independently associated with poor cancer outcome.

In contrast, adaptive immune responses such as the increase in tumor[9] and circulating T lymphocytes (Type I transmembrane protein found on T-lymphocytes [CD3], CD8) are independently associated with better cancer outcome (eg, in patients with colorectal cancer)[14–16] and are likely to reflect the normal functional immune response to an antigenic challenge posed by the cancer.[17] Therefore, the question arises whether it is better to upregulate the adaptive immune responses or to downregulate the innate and humoral responses. This is an area of intense investigation, and currently, both approaches are being explored and the subject of ongoing randomized controlled trials (Diakos et al[18] and Zavala and Kalergis[19]).

Therefore, it is of interest that the cytotoxic T-lymphocytic infiltrate can be downregulated and the immune competence of the host overridden by the presence of activated innate and humoral immune responses.[20–23] For example, in colorectal cancer, it is increasingly appreciated that as tumors grow, there are changes in the tumor microenvironment such that adaptive immune cells are displaced by innate immune cells.[24,25] Such displacement results in tissue repair which if repeated or excessive results in stromal changes supporting the growth of the tumor and protecting it from elimination by the adaptive immune responses.[26] Finally, there is accumulating evidence that innate immune cells such as neutrophils, monocytes/macrophages, and myeloid-derived suppressor cells promote the metastatic process.[27]

Much of the previously mentioned information describes associations (not a cause-and-effect relationship) and therefore may be considered speculative. However, through ongoing immunologic interventions, in patients, the true nature of such associations is being revealed. An interpretation of the present literature is that it would be rational to focus on moderating the innate/humoral immune responses. Indeed, much of current clinical management of cancer revolves around minimizing the resultant innate/humoral immune responses associated with injury from surgical, radiotherapy, and chemotherapy treatments or the concurrent use of anti-inflammatory agents to reduce the detrimental effects of such treatments. However, to date, such interventions (eg, corticosteroids) have been carried out empirically for symptom control and not against the background of specifically targeting elevated innate/humoral immune inflammatory responses. Therefore, previous reports of possible deleterious effects of, for example, corticosteroids on T-lymphocytic responses, may not be relevant in such selected patients.

TARGETING INNATE/HUMORAL IMMUNE/ INFLAMMATORY RESPONSES

With reference to colorectal cancer, the tumor inflammatory cell infiltrate of neutrophils and macrophages (50:50) account for approximately 40% of inflammatory cells[28] (Richards et al., 2012) and together (85:15) approximately 70% of the circulating immune cells.[29] Surgery is the primary treatment modality for many cancers including colorectal cancer and is likely to exacerbate such innate immune responses. For example, in such an acute injury, in humans, the systemic inflammatory response is characterized by the activation of the innate/humoral immune system. In particular, circulating interleukin-6 (IL-6), neutrophils and C-reactive protein show quantitatively the most significant increases,[30] and these are recognized to be important in tissue repair and remodeling and activated granulocytes can produce growth factors (epidermal growth factor [EGF], transforming growth factor beta [TGF-β], vascular endothelial growth factor [VEGF], IL-6, tumour necrosis factor alpha [TNF-α] and chemokines) that can act directly on cancer cells and confer mitogenic and angiogenic capabilities.[3,31] They also act on the surrounding stromal tissue to increase the amount of stromal tissue, thus reducing the effectiveness of the adaptive immune system. Indeed, an increase or maintenance of the numbers of neutrophils and of the concentrations of IL-6 and C-reactive protein in the circulation are recognized prognostic features of cancer-associated inflammation[9,32,33] and as such represent an objective marker and potential therapeutic target.

The pleiotropic cytokine IL-6 and related cytokines are central to the regulation of such innate immune/inflammatory responses.[34,35] IL-6 is known to stimulate the production of neutrophils and macrophages from myeloid tissue and C-reactive protein from hepatocytes.[32,34] Many of the cellular responses to circulating IL-6 are regulated by the Janus Activated Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signal transduction pathway[36,37] that has an important role in the initiation and resolution of inflammatory processes.[38] The JAK/STAT pathway also transduces signals from