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Implications of Corticotropin Releasing Factor in Targeted Anticancer Therapy

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Abstract

There is a need to develop novel anticancer therapies that eliminate adverse side effects produced by current treatments. Corticotropin releasing factor (CRF), an endogenous neuroendocrine factor, which typically regulates biological and psychological indicators of stress, has recently been found to be expressed by tumor malignancies. Here, we discuss the implications of CRF as a target for antitumor therapy through regulation of tumor immune escape mechanisms.

Keywords

cancer; corticotropin releasing factor; cytokine; chemokine; immune; drug therapy

Introduction

Surgery, chemotherapy, and radiotherapy remain common treatment strategies against malignant tumors. However, their success is challenged by the risk of recurrence, progression, and secondary health complications (eg, secondary infection, drug toxicity). Treatment may be improved by novel drug delivery strategies, which target the tumor microenvironment. Thus, a deeper understanding of the physiology of carcinogenesis and malignant tumor environments will encourage the development of a new generation of anticancer drugs that may result in increased treatment specificity with lower toxic potential. This article highlights the potential of corticotropin releasing factor (CRF) as an attractive agent for anticancer treatment through interaction with the tumor microenvironment.

Endocrine-Mediated Regulation of Carcinogenesis

The tumor environment is not an isolated or homogenous cellular composite, but a cellular milieu consisting of an array of various cell types, which coexist through direct cell-to-cell interaction and paracrine/autocrine release of soluble factors including cytokines, chemokines, growth factors, neurotransmitters, and hormonal factors.¹ Typically known to

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regulate biophysical and behavioral responses to external and perceived stresses, endocrine factors have been found within the tumor microenvironment and are considered targets for the regulation of carcinogenesis.² Among endocrine influences, the most notable endocrines relevant to carcinogenesis have been ascribed to estrogens, their active metabolites, and androgens associated with breast and prostate cancer.³ In fact, a close relationship between tumor vascular and neurotransmitter/endocrine is known to exist and provide important cues for tumor survival by impacting vascularization of the tumor mass and signaling tumor migration.⁴ Furthermore, paraneoplastic syndromes induced by inappropriate ectopic production of hormones, cytokines, and growth factors occur in approximately 10% of patients with malignant disease. This autocrine, paracrine, or endocrine interaction between a resident tumor cell type and normal tissue stroma has been regarded as a neuro-neoplastic synapse.⁵ In this context, CRF may serve as a neurogenic “barometer,” potentially dictating the fate of tumorigenesis.

Corticotropin Releasing Factor: A Neurogenic Mediator of Carcinogenesis?

CRF is a 41-amino-acid peptide primarily produced in the hypothalamus and brain regions,⁶ where it plays an important role in behavior and autonomic response to stress.⁷ The functional activity of CRF is regulated by 2 major receptors, CRFR1 and CRFR2, having diverse affinities for CRF and the CRF homologue, urocortin subtypes (UCN 1-3).⁸⁻¹⁰ Historically, CRF and its receptors have a functional role in brain and peripheral tissues including heart, lung, intestine, and skin.¹¹ Particularly, the urocortins as members of the CRF family of peptide hormones are known for their cardioprotective capacity.¹² Also, evidence suggests that CRF is involved in the inflammatory process of gastrointestinal tract disease in which pharmacologic antagonist exerts beneficial anti-inflammatory responses in colonic tissues.¹³ Similarly, pharmacologic benefits have been documented in the treatment of inflammatory arthritis.¹⁴ On the basis that inflammation in many ways is involved in initiation and tumor progression, insight into the relationships between the CRF and the tumor microenvironment is worth probing its potential exploitation in anticancer therapy.

The prospect of CRF as a potential target for antitumor therapy was initiated by various studies demonstrating altered physiological responses by tumors on the basis that CRF was secreted by various human tumors as well as their expression of CRF receptors.^{15,16} Experimentally, CRF/UCN binding to tumor cells expressing CRF receptors either potentiate antitumor responses or promote tumor malignancy.¹⁷ MCF7 cells were found to express CRFR1a, CRFR1b, CRFR2a, and CRFR2c receptors.¹⁸ Urocortin 2 was found to inhibit cell proliferation and vascularization of a murine experimental lung tumor through CRFR2 binding.¹⁹ Clinically, proliferation and invasiveness of malignant MC7 breast cancer cells is induced by CRF²⁰ through binding of either CRFR1 or CRFR2 receptors. Recently, the mechanism of action revealed in studies demonstrating CRF's inhibition of proliferation of the Ishikawa (IK) human endometrial carcinoma cell line was through the activation of CRH-R1 receptors. Moreover, identification of CRFR1 expression to control tumors was examined from tumor tissues from 19 patients with endometrial cancer. In this case study, CRF counteracted the increase in cell proliferation caused by estradiol; type 1 receptors mediating this effect belonging to the alpha subtype. In another study on human tumors, CRFR1 was expressed in 4 out of 19 (21%) surgical specimens obtained from untreated

patients with a diagnosis of primary endometrial cancer.²¹ In this population, 50% of the populations expressed CRFR1 and had extrauterine metastasis, whereas tumors absent in CRFR1 expression were nonmetastatic. Thus, the potential exploitation of CRFR receptor expression could prove beneficial in targeted anticancer therapy. To date, however, there is limited data of its clinical use in other cancer types or the mechanisms through which CRF modifies tumor physiology.

Consideration for CRF as a Biomarker of Tumor Immune Escape Mechanisms

Briefly mentioned above, inflammatory status is believed to play an integral role in the regulation of the tumor microenvironment. A large supplier of the inflammatory milieu is contributed by the immune cells within and surrounding the tumor mass, commonly referred to as tumor-infiltrating lymphocytes (TILs).²² In many ways, our host immune defense system serves as the first line of defense against tumorigenesis by recognizing aberrant cells for destruction. Unfortunately, anti-tumor immune defenses are in constant antagonism by tumor cells, which are equipped with tumor immune escape machinery including tumor-associated antigenic disguise, downregulation of cellular death receptor signals such as Fas ligand (FasL), and even the release of immune factors such as cytokines and chemokines, which in turn can dictate the functional character of TILs to the benefit of the tumor microenvironment. Thus, optimal antitumor surveillance by immune cells is often offset by the tumor cells' ability to actively promote survival, vascularization, and angiogenic properties.

The implication of CRF as a target for tumor therapy may be revealed through the potential relationship between immune mediators released by the tumor cell itself in response to CRF. As referenced in Table 1, immune mediators such as cytokines and chemokines released by tumor cells can play a significant role in controlling tumor microenvironments. Cytokines and chemokines represent soluble mediators that function in an autocrine/paracrine manner, facilitating cell-to-cell communication and cellular recruitment, respectively, that translate into specific effector function. In terms of tumor surveillance, cytokine and chemokine activation has been shown to facilitate resistance against tumor development as well as promote tumor escape^{23–29} through augmentation of tumor-infiltrating lymphocytes including natural killer,³⁰ macrophages, and T cell subpopulations³¹ by regulating tumorlysis.³² Suarez-Cuervo et al³³ demonstrated that tissue growth factor beta (TGF- β), tumor necrosis factor alpha (TNF- α), and interleukin-1 beta (IL-1 β) upregulated IL-6 and IL-11 cytokine responses in human breast cancer cells.³³ In addition, CXCL12 chemokine secretion by stromal fibroblasts was found to enhance mammary carcinomas.³⁴ We have also demonstrated IL-10 and TGF- β cytokine messenger RNA (mRNA) expression in 2 rodent lung metastatic tumor cell lines (unpublished data). Given the strong association of immune cells as mediators of tumor physiology, one might consider how CRF and CRF receptors' effect on tumor cells' ability to secrete its repertoire of cytokine and chemokines result in tumor immune escape responses. Presently, our investigations are the first to propose the CRF-mediated regulation of cytokine and chemokine responses by a tumor cell line. We demonstrate that CRF exposure can elicit IL-1 β and IL-6 inflammatory cytokine

responsiveness (data submitted for publication). In addition, prior to our studies, no reports have documented the effect of CRF on chemokine expression by tumor cells. We report CRF to induce CCL3, CCL17, and CCL22 chemokines, while causing a downregulation of CCL4, CXCL1, and in particular CXCL10 expression by the J774 tumor cell line (submitted for publication). On the basis of current clinical findings of CRF and CRFR receptor expression by various tumors, one might consider whether preferences in CRF receptor expression by a given tumor mass also leads to preferential tumor-associated cytokine and or chemokine expression, thereby facilitating a pro-inflammatory or anti-inflammatory tumor environment that would predict tumor malignancy.

Concluding Remarks

The potential of CRF as a potential target for antitumor therapy is supported by previous findings that selectivity of CRF receptor activation can impact tumor cell physiology. Thus far, the expression of CRF receptor 1 type has been implicated as a plausible target in the diagnosis of endometrial cancers. Thus, the use of selective CRF receptor 1 agonists may be of prognostic value. In addition, as highlighted by our own studies, the effect of CRF on tumor-derived cytokine and chemokine expression may also provide insight toward novel combinational therapies. It is known that CRF and its homologue, urocortin, has various affinities for each receptor and their subtypes. As known modifiers of inflammatory conditions, an understanding of CRF's influence on the inflammatory tumor microenvironment promises to raise potential for targeted regulation of tumor immune escape pathways. Future investigations, which identify the consequence of cytokine and chemokine expression through targeted activation of either CRF receptors, are needed to clarify the underlying mechanisms of CRF and carcinogenesis as illustrated in our hypothetical model (Figure 1).

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Figure 1.

Hypothetical model of corticotropin releasing factor (CRF) and CRF receptor-mediated regulation of carcinogenesis. Representative diagram of tumor-associated cytokine and chemokine response mediated by CRF and CRF receptor expression. CRF release within the tumor microenvironment by peripheral or tumor cells can orchestrate preferences in cytokine and/or chemokine activation by tumor cells, dictating immune escape mechanisms (eg, immunosuppression and angiogenesis). The selectivity of tumor-associated CRF receptor 1 and receptor 2 expressions may serve as putative therapeutic targets by modifying cytokine/chemokine activation. Abbreviations: IL-1β, interleukin-1 beta; NK, natural killer; TGF-β, tissue growth factor beta.

Table 1

Tumor-Associated Cytokine Expression

Cytokines/Chemokines/Toll-Like Receptors	References
Pro-inflammatory cytokines	
IL-1 β (interleukin-1 beta)	35
TNF- α (tumor necrosis factor alpha)	36
IL-6 (interleukin-6)	37
Anti-inflammatory cytokines	
IL-10 (interleukin-10)	38
TGF- β (tissue growth factor beta)	39
IL-4 (interleukin-4)	40