Expression of Urocortin I in Normal Tissues and Malignant Tumors

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Corticotropin-releasing factor (CRF) is a key player in the hypothalamus-pituitary-adrenal axis, and exerts its actions through two types of receptors: CRF type 1 and type 2 (CRF1 and CRF2) receptors. After the discovery of CRF and these receptors, a CRF-related peptide, urocortin I (UCN I), was identified. UCN I is a more potent agonist than CRF on CRF receptors, especially CRF2, which is involved in stress response. UCN I has various beneficial actions and is distributed in central and peripheral normal tissues, including the brain, heart, vascular cells, and endometrium. Recently, UCN I expression was also discovered in malignant cells, such as human glioblastoma cells, pituitary adenoma cells, hepatic carcinoma cells, gastric cancer cells, adrenocortical adenoma cells, and renal clear-cell carcinoma cells. Recent developments into the pathophysiological roles of UCN I and its related peptides will potentially lead to new anticancer therapies. Here, we review the expression of UCN I in normal and malignant cells and discuss the future of UCNs in anticancer therapy.

Keywords: urocortin I; CRF; CRF receptors; malignant cancer


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tissues, such as retinal cells, cardiovascular cells, pancreatic cells, gastric cells, and so on, and metabolic and energy homeostasis [9-16].

The CRF receptor is classified into two different types of receptors, and each receptor is further classified into isoforms. Isoforms of CRFR1 are CRFR1α to CRFR1i [17], whereas those of CRFR2 are CRFR2α, CRFR2β [3], and CRFR2γ [18]. CRFR1 isoforms impact various intracellular signaling pathways due to alternative splicing. In contrast, there are differences in the extracellular structure of CRFR2 isoforms but the transmembrane and intracellular structure of CRFR2s are not varied, indicating similar functions of CRFR2 isoforms but potential differences in the affinities of CRFR2 isoforms [18].

The tissue distribution of CRFR1 and CRFR2 in normal tissues has been reported. CRFR1 expression has been identified in the brain (including the anterior lobe of the pituitary [19]), skin [7], aortic endothelial cells [20], gastrointestinal tract [21], hepatocytes [22], pancreatic β cells [23], mast cells [24], and myometrium [25]. CRFR2 expression has been identified in the brain [3, 18], aortic smooth muscle cells [26], vascular endothelial cells [20, 27, 28], heart (including cardiac myocytes [3, 29-31], skeletal muscle [3], gastrointestinal tract [21, 32], hepatocytes [22], pancreatic β-cells [33], and myometrium [25].

UCN I reportedly exerts protective actions via CRFR1 and CRFR2 in normal tissues. For example, UCN I triggers anti-oxidative responses via CRFR1 in hippocampal neurons [34] and human umbilical vein endothelial cells, and UCN I exerts protective actions against ischemic/reperfusion injury via CRFR2 in cardiomyocytes [35-37]. In addition, UCN I exerts anti-apoptotic action through CRFR2 in human gastric cells [13]. UCN I also stimulates the release of cytokines, including interleukin (IL)-4, IL-6, and IL-10 [38-40], indicating that UCN I may modulate immune response [41].

UCN I is a ligand of CRFR2 and, like CRF, acts via CRFR1. However, unlike CRF, which is mainly distributed in the central nervous system and skin [7, 42], UCN I is distributed in the central nervous system [3, 43], including the pituitary gland [44], and also ubiquitously in normal peripheral tissues, such as the skin [42], thyroid gland [45, 46], heart (including cardiac myocytes and non-myocytes) [3, 29-31, 47, 48], aortic and umbilical endothelial cells [20, 49], stomach [32], liver [22], gastrointestinal tract [41], colon [50], kidney [51], adrenal gland [52], lymph organs [53], uterus [54], placenta, and myometrium [55]. The plasma concentration or expression of UCN I is reportedly elevated in patients with various diseases, such as heart failure [36, 57], diastolic and hypertrophic cardiomyopathy [29, 48], acute myocardial infarction [58], liver cirrhosis [22], ulcerative colitis [50], benign prostate hypertrophy [59], endometriosis [60], preterm labor [61], and both maternal and fetal plasma concentration during normal pregnancy [55, 61]. The plasma concentration or intracellular expression of UCN I may correlate with the severity of disease [50, 56, 57].

In addition to normal and diseased tissues, numerous recent studies have revealed UCN I is expressed in various cancer cells and cell lines, including human glioblastoma cells (KSN42, T98G, RT2, 9L, A172, and U-138 MG cells) [62], pituitary adenoma cells [44, 63], malignant melanoma cells [42], both thyroid carcinoma and pHChromeocytoma (multiple endocrine neoplasia type II) cells [64], breast cancer cells [65], gastric adenocarcinoma cells and the STKM-1 cell line [66, 67], primary and metastatic liver carcinoma cells [22], pancreatic ductal adenocarcinoma cells and neoplasms [68], the MIN6 insulinoma cell line [33], clear cell renal cell carcinoma cells [51], NCI-H295R human adrenal carcinoma cells [69], human endometrial carcinoma cells [70], and human prostate adenocarcinoma cells [59]. Interestingly, UCN I and its working receptors (CRFR1 and CRFR2) do not always co-localize; for example, they do not colocalize in RT2 and 9L human glioblastoma cells [62]. In addition, UCN I immunoreactivity has been detected in the nuclei of carcinomas, like clear cell renal carcinoma [51], indicating the abnormal transport of UCN I in malignant cells.

Although the available data on the regulation, mechanism, and effects of UCN I in malignant carcinoma cells are limited, a few studies have reported on UCN I and its related peptides in cancer physiology. Our studies have indicated that the regulation of UCN I is not significantly altered by cellular stresses induced by anti-cancer drugs and ionizing radiation [62, 66], however, our previous report has shown the regulation of UCN I and UCN II by oxidative stress and inflammatory stress, respectively, in the HL-1 mouse atrial cardiomyocyte cell line [31].

The stimulation of CRFR2 by UCN II results in cell proliferation, while the stimulation of CRFR1 may lead to an increase in prostate cancer cell apoptosis [71]. In contrast, CRFR2 signaling in the MCF-7 human breast cancer cell line and small cell lung carcinoma cells may cause apoptosis [65, 72]. In addition, CRFR2 signaling may be involved in vascularization after birth and affect tumor progression [73]. Because the action of UCN I is exerted through CRFR1 and CRFR2, UCN I may suppress tumor growth [73] and UCN I was shown to reduce tumor microvessel density in nude mice transplanted with hepatocellular carcinoma [74] and vascular endothelial growth factor secretion from small lung cell carcinomas [72]. In addition, it was that UCN II, another UCN I-related peptide and a specific ligand for CRFR2, reduced tumor vascularization and exerted anti-proliferative effects in Lewis lung carcinoma cell tumors [75] in spite of cell-proliferative actions of UCN II in prostate cancer cells [71], which indicates that CRFR2 signaling has different effects.
in various cell types. Furthermore, Zhu et al. recently reported that UCN I has dual roles on the migration of the hepatocellular carcinoma via regulation of phospholipase A2 enzymes [76]. Therefore, the usage of UCN related agents in the patient with malignant cancer should be attentive to potential adverse actions because of the differential signaling properties of CRF receptor signaling in various cancer cell types.

In conclusion, although UCNs, especially UCN I, are expressed not only in normal tissues, but also in various cancer cells, the actions and physiological properties of UCNs in cancer cells is still remain to clarified. And the usage of UCN related agents in the patient with malignant cancer should be attentive to potential adverse actions because of the differential signaling properties of CRF receptor signaling in various cancer cell types (for example, the effects of CRFR2 signaling pathway in lung cancer tissue and prostate cancer cells). But, based on continuing knowledge on the pathophysiology of UCN I and its related peptides in cancer, future studies may contribute to new cancer therapies.

Conflicting interests

The authors have declared that no competing interests exist.

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