Somatostatin/cortistatin system

The somatostatin/cortistatin system refers to the network of molecules and receptors related to two closely related neuropeptides: somatostatin (SST) and cortistatin (CORT). These peptides play important roles in the regulation of endocrine, immune, and nervous systems. Here’s a breakdown:

 1. Somatostatin (SST) A peptide hormone originally discovered as an inhibitor of growth hormone (GH) from the hypothalamus.

Exists in two main forms: SST-14 and SST-28.

Has inhibitory effects on many endocrine and exocrine secretions (e.g., insulin, glucagon, gastrin).

Widely distributed in the central nervous system (CNS), gastrointestinal tract, and pancreas.

 2. Cortistatin (CORT) A neuropeptide highly homologous to somatostatin.

Also binds somatostatin receptors (SSTRs) but has unique effects, particularly in the immune system and sleep modulation.

Unlike SST, CORT can bind additional receptors, such as ghrelin receptors and Mas-related G protein–coupled receptors (MRGPRs).

Plays a role in modulating sleep, neuronal excitability, and inflammation.

 3. Receptors (SSTRs) Both SST and CORT bind to five G-protein coupled somatostatin receptors:

SSTR1 – SSTR5

These receptors are differentially expressed in tissues and mediate the various biological effects.

⚙ 4. Functions of the SST/CORT System Neuroendocrine Regulation: Inhibition of GH, TSH, and many gut hormones.

Neurotransmission: Modulates neurotransmitter release.

Immunomodulation: Particularly cortistatin has anti-inflammatory effects.

Sleep and Cognition: Cortistatin promotes slow-wave sleep and has roles in memory processing.

Antiproliferative Effects: SST analogs are used in neuroendocrine tumors due to their growth-inhibitory properties.

 Clinical Relevance SST analogs like octreotide or lanreotide are used for:

Acromegaly

Neuroendocrine tumors

Variceal bleeding (via inhibition of splanchnic blood flow)

Cortistatin, though not yet used clinically, is being studied for:

Autoimmune diseases

Inflammatory bowel disease

Epilepsy

Neurodegenerative disorders

G-García et al. comprehensively characterized (clinically and molecularly) the expression of the somatostatin/cortistatin-system components [ligands and receptors (SSTRs)] using five cohorts of patients and tested the in-vitro therapeutic response of different SSTR-agonists and somatostatin analogs (SSAs) in primary patient-derived glioblastoma cells. A clear downregulation of the whole somatostatin/cortistatin-system (except for SSTR5) in glioblastoma vs. non-tumour brain samples was demonstrated, with high discriminatory capacity. Moreover, poor overall-survival and critical aggressiveness-parameters (i.e., recurrence, IDH1-wildtype and G-CIMP status, classical and mesenchymal GBM-subtypes, EGFR-amplification) were robustly associated with SSTR1/SSTR2 downregulation. Notably, octreotide, pasireotide, and SSTR1/2/5-agonists treatments significantly reduced cell-proliferation in primary patient-derived GBM-cells. Molecularly, antitumour effects of octreotide/pasireotide were exerted through key signalling-factors related to glioblastoma-aggressiveness (i.e., CDKN1A-B/JAK-STAT/NF-κB/TGF-β-pathways). Altogether, this study demonstrated that somatostatin/cortistatin-system is drastically altered in GBM representing a useful prognostic tool, and that SSTR-modulators might represent a potential therapeutic strategy to treat specific subsets of patients with GBM [1)].

This study by G-García et al. makes a significant contribution to the understanding of the somatostatin/cortistatin system in glioblastoma. It opens promising avenues for the development of diagnostic and prognostic biomarkers, and lays the groundwork for SSA-based therapeutic strategies, particularly in SSTR1/2-low GBMs with poor prognosis.

However, to realize clinical application, the following are essential:

In-vivo validation

Exploration of delivery strategies (e.g., intratumoral, BBB-penetrant analogs)

Development of predictive biomarker tools for SSA responsiveness.

1)
G-García ME, De la Rosa-Herencia AS, Flores-Martínez Á, Ortega-Bellido M, Sánchez-Sánchez R, Blanco-Acevedo C, Gahete MD, Solivera J, Luque RM, Fuentes-Fayos AC. Assessing the diagnostic, prognostic, and therapeutic potential of the somatostatin/cortistatin system in glioblastoma. Cell Mol Life Sci. 2025 Apr 23;82(1):173. doi: 10.1007/s00018-025-05687-9. PMID: 40268793.