

Somatostatin receptor subtypes in human immune cells

E G R Lichtenauer-Kaligis¹, P M van Hagen^{1,2}, S W J Lamberts¹ and L J Hofland¹

¹Departments of Internal Medicine and ²Immunology, Erasmus University, Rotterdam, The Netherlands

(Correspondence should be addressed to L J Hofland, Department of Internal Medicine, Room Bd277, University Hospital Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands; Email: hofland@inw3.azr.nl)

Introduction

Somatostatin is a neuropeptide hormone that is widely distributed throughout the body. It was first discovered as a factor inhibiting the release of growth hormone. Later it was shown to have many functions in the endocrine system including the inhibition of secretion of other pituitary hormones, in addition to that of gastrointestinal hormones. Moreover, somatostatin acts as a neurotransmitter in the nervous system where it also has generally inhibitory effects. Moreover, somatostatin receptors (sst) are detected in the immune system, although the exact role of somatostatin in the immune system remains elusive. A first step towards a better understanding of the role of somatostatin in the human immune system is to determine which cells express somatostatin and its receptors.

Somatostatin exerts its effects through binding to a family of five specific receptors, named sst₁ to sst₅. The human genes for these receptors were cloned in 1992 and 1993 (1–4). The genes do not have introns. However, for sst₂ a spliced mRNA variant has been identified (5, 6) and is named sst_{2B}, whereas the unspliced variant is designated sst_{2A}. After ligand binding the ssts transduce their actions into the cell via coupling to G-proteins (7).

Somatostatin is secreted in two biologically active forms: a 14 amino acid peptide (somatostatin-14) and a 28 amino acid peptide (somatostatin-28). Both forms bind with high affinity to all five receptor subtypes. The widely used synthetic analogue, octreotide, binds with high affinity only to sst subtypes 2 and 5 and with lower affinity to receptor subtype 3; binding to receptor subtypes 1 and 4 is undetectable (8, 9). sst have been demonstrated in both rodent and human immune cells (10, 11). In this paper, some of the recent novel insights in the expression and functional significance of ssts in human immune cells are discussed.

Somatostatin binding sites on human immune cells

Almost 20 years ago Bhathena *et al.* (12) demonstrated the presence of somatostatin binding sites on human peripheral blood mononuclear cells (PBMC). Using radioisotope-labelled somatostatin and Scatchard analysis, they showed that both lymphocyte-enriched cell populations and monocyte-enriched populations contained several hundred

binding sites per cell. Since then, somatostatin binding sites have been demonstrated on several immune and haematopoietic cells and tissues, by means of various techniques. Radioligand binding studies demonstrated ssts to be present on human lymphoid and myeloma cell lines (13, 14). Using radioligand binding as well as fluorescence-labelled somatostatin and FACS analysis, somatostatin binding sites were detected on mitogen-activated human peripheral lymphocytes (15). More than 95% of the cells in all subpopulations studied (both B-lymphocytes and T-lymphocyte subsets) were labelled by the fluorescent somatostatin derivative. In contrast, our own studies using fluorescein-labelled somatostatin failed to detect somatostatin binding sites on both resting and mitogen-activated lymphocytes (unpublished observations). On resting PBMC, red blood cells and granulocytes no binding sites were detectable by the radioligand assay (15). In the same study, human leukaemic cells were shown to contain somatostatin binding sites.

It is therefore a long established fact that human immune cells can express ssts.

Localization of somatostatin binding sites in human lymphoid tissues

sst expression can be detected *in vivo* by sst scintigraphy. After injection of radioisotope-labelled octreotide, the ligand will bind to its receptors and, subsequently, tissues with high densities of ssts (sst₂, sst₅ and possibly also sst₃) can be visualized with a gamma-camera. This technique has been used extensively to visualize neuroendocrine tumours (16). In addition, several disorders of the immune system have been shown to express such a high density of ssts that they can also be visualized with this technique. These disorders include malignant lymphomas (Hodgkin's disease and non-Hodgkin lymphomas), granulomatous diseases (tuberculosis, sarcoidosis, Wegener's granulomatosis) and other autoimmune diseases such as rheumatoid arthritis (17–20). However, among normal lymphoid tissues, only the spleen shows a high uptake of labelled octreotide; the thymus or lymph nodes are not visualized (21).

By means of somatostatin autoradiography (binding of radioisotope-labelled somatostatin or octreotide to tissue sections), the presence of ssts in the different areas of lymphoid tissues can be visualized.

Work by Reubi *et al.* (21, 22) demonstrated the presence of ssts in normal human lymphoid tissues, including gut-associated lymphoid tissue, thymus, spleen and lymph nodes. Moreover, in addition to ssts, several other peptide receptors, were localized in distinct compartments of the immune tissues (22, 23). SSTs were localized mainly in the germinal centres of lymphoid follicles, and more diffusely in the red pulp of the spleen and in the medulla of the thymus.

Thus not only do immune cells in the peripheral blood express ssts, but ssts are also present in normal lymphoid tissues. Moreover, the sites of the lesions in several haematological malignancies or immune-mediated diseases also show sst expression.

Which sst subtypes are expressed in the human immune system?

The fact that there are (at least) five different subtypes of ssts and the possibility that these subtypes might serve different (but probably overlapping) functions raise the question as to which sst subtypes are expressed in cells of the immune system. As somatostatin binds to all five subtypes with high affinity and octreotide and related synthetic analogues bind to three subtypes with high or moderate affinity, binding studies using these ligands are not informative as to which sst subtype is expressed. RT-PCR is exceptionally well suited to the examination of this problem, being a very specific and very sensitive method for the detection of RNA transcripts.

Unfortunately, different RT-PCR studies of sst subtype expression in human immune cells have not provided uniform results. sst subtype 2 was shown to be the most prominently expressed subtype among leukaemia cells and several lymphoid and myeloma cell lines (24). However, the cell lines also expressed sst₃ (all cell lines except one) and several of the cell lines expressed sst₄ or sst₅, or both, also. In the T-lymphoid cell line Jurkat, for instance, mRNA of sst₂, sst₃, sst₄ and sst₅ was detected. In the same study, human PBMC showed barely detectable sst₂ mRNAs, whereas this mRNA was increased in Epstein Barr Virus (EBV)-transformed lymphocytes and after phytohaemagglutinin (PHA) stimulation of PBMC. Our own studies of several T- and B-lymphoid cell lines showed only expression of sst₂ in four of 18 cell lines (25). This discrepancy can probably be explained by differences in assay sensitivity. Our recent studies applying a more sensitive RT-PCR assay than before clearly detected sst₂ and sst₃ in the Jurkat T-cell line and in EBV-transformed B-lymphocyte cell lines (Table 1). In contrast with the findings discussed above, is the report that the Jurkat T-cell line expresses only sst subtype 3 (26). Finally, it was recently found that human T-lymphocytes purified from PBMC expressed only sst₃, but that after mitogenic activation with PHA they additionally expressed sst₅ (27).

Table 1 RT-PCR analysis of mRNA expression of somatostatin (som) and somatostatin receptor subtypes in lymphoid cell lines.

	sst ₁	sst _{2A}	sst ₃	sst ₄	sst ₅	som
T-cell lines						
Peer	-	+	+	-	-	-
HPB-ALL	-	+	+	-	-	-
Jurkat	-	+	+	-	-	-
B-cell lines						
BLCL-APD	-	+	+	-	-	-
BLCL-BSM	-	+	+	-	-	-
BLCL-E091	-	+	+	-	-	-
BLCL-EDN	-	+	+	-	-	-

-, Absence and +, presence of mRNA as determined by RT-PCR.

From this collection of data the strong impression arises that immortalized cell lines are not representative of human immune cells *in vivo*, especially since different clones from the same cell line (Jurkat) appear to express different subtypes of the sst family. Moreover, when comparing animal studies concerning sst subtype expression in the immune system, care should be taken when extrapolating to the human situation, as there appear to be species-related differences. Rat PBMC, spleen, thymus and lymph nodes were shown to express sst₃ and sst₄ (28) whereas we found that mouse PBMC, spleen and thymus express sst₂ and sst₄ mRNA. These findings are summarized in Table 2. More intriguing are the divergent findings with *ex vivo* human immune cells, which cannot be fully explained from these data.

It also becomes apparent that it would be very desirable to have some sort of quantitative measurement of the amount of mRNA transcripts per cell (and its relation with receptor numbers per cell) in order to judge the biological relevance of the expressed receptor subtypes. It should be kept in mind that, when one is isolating RNA from 10⁶ cells and performing a sensitive RT-PCR that is able to detect 100 copies (or fewer) of template in the assay, a positive signal could mean that 1 cell in 10⁶ expresses 100 mRNA transcripts, or that 100 in 10⁶ cells express just one single mRNA transcript. Neither of these two extreme possibilities is relevant for the cell population as a whole.

This last statement touches upon one of the major drawbacks of the RT-PCR technique: it is not possible to determine which cell types among a heterogenous cell population express the SST subtypes detected. In order to address this question, and considering the sensitivity of the RT-PCR method, it is necessary to purify the cell populations to a very high degree, for example using magnetic beads coated with antibody specific for the cell type to be studied. An alternative approach, today feasible for sst₁, sst_{2A} and sst₃, is to perform immunohistochemistry using specific antibodies directed against the different sst subtypes.

Which cell types express ssts?

Although the final answer to this question has not yet been established, much has been learned from the different approaches described above. Immune cells can be classified according to the lineage along which they have developed during haematopoiesis. The major populations of immune cells found in the peripheral blood can roughly be characterized as T-lymphocytes, B-lymphocytes, monocytes and granulocytes. Each of these cell-types differentiates into more specific subsets. In addition, in the lymphoid organs many accessory cell-types are found, such as epithelial cells, dendritic cells, fibroblasts, nerve cells, endothelial cells and muscle cells of blood vessels, making the question of which cell type expresses ssts even more complex.

In the binding studies reviewed above, it was shown that both lymphocyte- and monocyte-enriched cell fractions from the peripheral blood possess ssts (12), whereas granulocytes do not (15). Purified T-lymphocytes have been shown to express *sst*₃ (27). In agreement with these observations we recently found a selective expression of *sst*₃ receptors on enriched populations of peripheral blood T- and B-cells, in addition to the expression of *sst*_{2A} receptors on activated cells of the monocyte-macrophage lineage (unpublished observations). Therefore we can deduce that T- and B-lymphocytes and monocytes do express ssts.

In the autoradiographic studies described above, it was found that germinal centres of lymphoid follicles express ssts. Moreover, the *sst*-positive tissue compartments did not co-localize with CD3-positive T-lymphocyte-rich compartments (23). In agreement with these observations, CD3-positive cells in tissue biopsy specimens from patients with rheumatoid arthritis or granulomatous disease did not express *sst*_{2A} receptors, as determined by immunohistochemistry (see below). Peripheral T-lymphocytes do express *sst*₃ receptors, but it remains to be established whether this receptor subtype is expressed in T-lymphocytes present in normal lymph nodes or in immune disease.

Effects of somatostatin on human immune cells

Functional studies performed with *sst*-expressing human immune cells provide further evidence for the important role somatostatin may have in the human immune system. Payan and coworkers showed in 1984 that somatostatin inhibits the incorporation of ³H-thymidine into PHA-activated human T-lymphocytes (29). However, other studies failed to detect any effect of somatostatin on proliferation of either unstimulated or PHA-activated human thymocytes (30).

Several studies investigated the effects of somatostatin on cytokine production by human immune cells. Interferon- γ secretion by PHA-stimulated PBMC was inhibited, although in one study only when non-physiological

Table 2 RT-PCR analysis of mRNA expression of somatostatin (*som*) and somatostatin receptor subtypes in normal rat and mouse immune cells.

	<i>sst</i> ₁	<i>sst</i> _{2A}	<i>sst</i> ₃	<i>sst</i> ₄	<i>sst</i> ₅	<i>som</i>
Rat						
PBMC	-	-	+	+	-	nd
Spleen	+	-	+	+	-	nd
Thymus	-	-	+	+	-	nd
Lymph nodes	-	-	+	+	-	nd
Mouse						
PBMC	-	+	-	+	-	-
Spleen	+	-	-	+	-	-
Thymus	-	+	-	+	-	-
Bone marrow	-	+	-	+	-	-

Data on rat SST subtypes are derived from ref. 34.

-, Absence and +, presence of mRNA as determined by RT-PCR; nd = not determined.

concentrations somatostatin (10^{-6} mol/l) were used (31), whereas in another study the maximal effect was observed between 10^{-9} and 10^{-8} mol/l (32). Natural killer cell activity was inhibited by somatostatin, but inhibition was only significant with high doses (33). Finally, in a human T-cell line (Jurkat) somatostatin increased interleukin-2 (IL-2) secretion and cell proliferation (26).

Immunoglobulin E (IgE) production by B-lymphocytes from atopic patients was inhibited by somatostatin, but only when B-lymphocytes were cultured together with T-lymphocytes and monocytes (34). This latter observation suggests an indirect mode of action of somatostatin on B-lymphocytes. In contrast, the synthetic somatostatin analogue, octreotide, inhibited pokeweed-mitogen-induced B-cell differentiation to plasma cells in PBMC from normal human donors (35). It is therefore not clear whether somatostatin exerts a direct effect on human B-lymphocytes.

In human monocytes, opposing effects of somatostatin have been described. Komorowski *et al.* (36) reported that somatostatin stimulated the release of IL-6 from lipopolysaccharide-activated, adherence-selected, monocytes, whereas Peluso *et al.* (37) demonstrated inhibition of IL-6 (and of TNF α and IL-1 β) by somatostatin. Monocyte activation, as measured by HLA-DR expression and chemotaxis of neutrophils to IL-8 produced by monocytes, was also reduced.

From these studies, it becomes clear that the actions of somatostatin in the immune system can be very diverse and are probably delicately regulated, as many contradictory effects have been observed.

Detection of *sst*_{2A} in human immune diseases by immunohistochemistry

After reviewing the current knowledge on *sst* expression in normal human immune cells, we consider the question of whether expression is altered in human

immune disease. Evidence that this is the case has been provided by *sst* scintigraphy. In patients with active rheumatoid arthritis, the affected joints could be visualized, whereas after treatment the radioligand uptake in the joints was significantly reduced. The amount of radioligand uptake correlated with the swelling and painfulness of the affected joints (19). Subsequent studies using an anti-*sst*_{2A} antibody in immunohistochemistry revealed that *sst*_{2A} receptors were expressed in biopsy specimens of synovia of affected joints from patients with rheumatoid arthritis (38). Receptors were present on endothelium of blood vessels and on dispersed cells throughout the inflamed tissue. Double staining with anti-*sst*_{2A} and cell-type-specific antibodies showed that *sst* subtype 2A receptors were expressed on CD31-positive endothelial cells, and on CD14- or CD68-positive monocytes and macrophages. *sst*_{2A} receptors were not expressed on CD3 positive T-lymphocytes.

In a similar way, it was shown that granulomas from nine of 12 patients with sarcoidosis were positive when stained with anti-*sst*_{2A} (39). The three negative tissue sections were highly fibrotic, with only a limited mononuclear infiltrate. Again, the *sst*_{2A} receptors were demonstrated on macrophages and not on T-lymphocytes.

It is therefore very likely that *sst*_{2A} expressed on monocyte-derived cells has an important role in inflammation. Besides the earlier mentioned correlation between inflammation and uptake of radiolabelled octreotide in scintigraphy (19), it was also demonstrated that somatostatin inhibits both proliferation of synovial cells from patients with rheumatoid arthritis and production of the pro-inflammatory cytokines IL-6 and IL-8 (40). Notably, these authors also report the presence of *sst*₁ and *sst*₂ on fibroblast-like synovial cells and the absence of receptors on T-lymphocytes. *sst*₂ receptors were up-regulated when the synovial fibroblast-like cells were stimulated with TNF α . Moreover, the fibroblast-like cells produced somatostatin, whereas the synovium-infiltrating lymphocytes did not.

Pro-inflammatory cytokine production is necessary to keep granulomas in sarcoidosis active. This cytokine production possibly can be influenced by somatostatin. In one of the aforementioned studies, it was shown that pro-inflammatory cytokine production by monocytes is inhibited by somatostatin, that monocyte activation is reduced, and that chemotaxis of neutrophils towards the activated monocytes is reduced (37). Whether somatostatin is produced locally in human sarcoid granulomas is not known. However, we speculate that *sst*_{2A} receptors on monocyte-derived cells in inflammatory diseases such as rheumatoid arthritis and sarcoidosis are important targets for somatostatin to modulate cytokine secretion and therewith inflammation.

Conclusion

To summarize our current knowledge concerning *sst* expression in human immune cells, we can conclude

that these receptors are expressed on normal human immune cells in peripheral blood and in normal human lymphoid tissue. Functional studies have demonstrated that somatostatin may influence cell proliferation, cytokine and immunoglobulin production and natural killer activity, in addition to HLA-DR expression and chemotactic activity of activated monocytes. *sst* subtypes appear to be differentially expressed on specific cell subsets of the human immune system. In immune-mediated diseases, *sst* expression can be altered. Understanding the clinical significance of these findings requires further studies.

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