# The Meaning of Mas

Michael Bader[1,2,3,4,5], Natalia Alenina[1,3], Dallan Young[6], Robson A.S. Santos[7], Rhian M. Touyz[8]

[1]Max-Delbrück-Center for Molecular Medicine, Berlin, Germany

[2]Charite – University Medicine, Berlin, Germany.

[3]German Center for Cardiovascular Research (DZHK), Berlin Partner Site, Berlin, Germany.

[4]Berlin Institute of Health (BIH), Berlin, Germany.

[5]Institute for Biology, University of Lübeck, Lübeck, Germany.

[6]Biochemistry & Molecular Biology, University of Calgary, Canada

[7]Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

[8]Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK

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**Corresponding author:**

Rhian M Touyz, MD, PhD

Institute of Cardiovascular and Medical Sciences

University of Glasgow

126 University Place

Glasgow G12 8TA

Telephone number: 0141 330-7775/7774

Email: rhian.touyz@glasgow.ac.uk

In the early 1980s, in their search for systems that import proteins into mitochondria, Yaffe and Schatz identified a mutant in the yeast *Saccharomyces cerevisiae*, mas1 (for mitochondrial assembly 1), that accumulates mitochondrial precursor proteins (Table 1).[1] In 1988 they cloned and sequenced the wild type yeast *MAS1* gene (systematic name: *YLR163C*), which encodes the catalytic subunit of the mitochondrial processing protease, a component of the mitochondrial import pathway and essential for cell viability.[2] Later, homologs of this gene were found in other eukaryotes including humans, in which the gene was called *PMPCB* (Peptidase, mitochondrial processing beta subunit).[3] Around the same time, in 1986, a new gene was isolated from DNA of a human epidermoid carcinoma cell line, identified as a proto-oncogene, and named *MAS*.[4] Initially the function of the MAS protein was unknown and it was only in the early 2000s that it was identified as the G protein-coupled receptor (GPCR) through which angiotensin (Ang)-(1-7) signals. Unfortunately, the *MAS* gene was later renamed by the HUGO Human Gene Nomenclature Committee to *MAS1* (Full name: MAS1 proto-oncogene, G protein-coupled receptor) and also in mouse, rat and all other tetrapods it got the new name *Mas1*. Fortunately, MAS is still an accepted alias of the MAS1 proto-oncogene protein and we will use this name in the following to distinguish it from the yeast Mas1 protein. We would also like to suggest that the name MAS should be used in future publications. There is no homolog of *MAS* in any clade outside tetrapods.[5] However, several homologous genes were discovered in each tetrapod species and the name MAS was given to this new family of receptors, the Mas-related GPCRs (Mrgprs).[5,6]

The duplication in nomenclature (Table 1) has unfortunately resulted in some misunderstandings and confusion in the Ang field, because there are some papers that attribute Ang-(1-7) effects to yeast mitochondrial assembly protein 1, Mas1.[7-10] This may be especially important in the context of interpretation of results and consideration of tools used to interrogate mammalian MAS, because it is likely that in some studies antibodies to the yeast Mas1 protein rather than to the GPCR MAS may have been used erroneously. To further add to the complexity, the

molecular size of the yeast Mas1 protein (~50 kDa) is not that dissimilar to that of human MAS (~40 kDa) and antibodies against MAS, which we tested, were nonspecific.[11] The confusion was additionally increased in 2016, when a putative thermostable lipase from a marine Streptomyces species was also named Mas1 (Table 1)[12]. However, at least until now this protein has not been confused with MAS.

The aim of this brief review is to highlight the importance of discriminating between the different 'Mas1' proteins and to ensure that the GPCR MAS is indeed the protein of interest when examining Ang-(1-7) (patho)physiological actions. Here we provide a historical overview of MAS and describe the origin of the name and how its functions have been unravelled.

**Discovery of *MAS* as a Proto-oncogene**

The *MAS* gene was first identified in 1986 using an assay for human oncogenes based on their ability to induce tumorigenicity of NIH 3T3 cells in nude mice.[13,14] Briefly, NIH 3T3 cells were cotransfected with DNA purified from a human tumor along with a G418 selectable marker. After selection and growth in culture, the G418 resistant cells were injected into nude mice. Several weeks later, DNA from tumors that formed in the mice was purified. The human DNA isolated from one of these tumors contained the *MAS* gene. The name *MAS* is an abbreviation of the last name (Massey) of the person who donated the human tumor from which the *MAS* gene was derived. This gene was cloned and shown to possess the ability to induce NIH 3T3 cells to form foci of transformed cells in culture and to form tumors in nude mice.[4] Therefore *MAS* was called a proto-oncogene. However, *MAS* likely did not contribute to the formation of the human tumor since the gene did not appear to be rearranged or mutated in the original human tumor DNA; rather, the transforming potential of *MAS* in NIH 3T3 cells appeared to be activated by DNA rearrangement and/or amplification during transfection into NIH 3T3 cells.[4,15] Moreover recent findings have suggested that MAS-activation by Ang-(1-7) could actually be a therapeutic target against tumors and has been suggested as a putative anti-cancer treatment .[16]

**MAS as Angiotensin II Receptor?**

Already at the time of its discovery, the DNA sequence of the *MAS* gene was determined and shown to encode a protein with a seven-transmembrane domain structure similar to that of GPCR.[4] Despite the fact that only one protein is encoded by the gene, we recently demonstrated that the mouse *Mas* gene with 4 promoters and 12 exons generates at least 12 different mRNAs by alternative splicing at the 5' untranslated region and is thereby the most complex gene of all GPCRs[17]. In order to define its ligand, Jackson et al.[18] expressed *MAS* in *Xenopus* oocytes and in a mammalian cell line. Oocytes exhibited a dose-dependent induction of an inward current in response to angiotensin (Ang) I, II, and III, and in transfected cells Ang II and III led to intracellular $Ca^{2+}$ release and to the initiation of DNA synthesis. Based on these results MAS was suggested to be a functional Ang II receptor. However, whereas several follow-up studies supported this assumption[19-22], Ambroz et al.[23] showed that the $Ca^{2+}$ release after Ang II treatment was only observed in *MAS*-transfected cells additionally expressing endogenous Ang II receptors. Cloning of the real Ang II receptor, $AT_1$, in 1991[24,25] and the discovery of a direct interaction between MAS and $AT_1$ in 2005,[26,27] partly explained the original observations of Jackson et al.[18] in *Xenopus* oocytes and revealed that MAS is not an Ang II receptor *per se*, but modulates $AT_1$ signaling.

***Mas* as Imprinted Gene?**

In 1994, *Mas* was reported to be maternally imprinted in mice[28] and in human breast tissue,[29] i.e., one of the two parental *Mas* alleles was epigenetically silenced. The *Mas* gene is located in close proximity to the imprinted *Igf2r* gene in the human and mouse genomes.[30,31] Imprinting of this chromosomal area is regulated by an intronic control element starting the transcription of the long noncoding RNA, *Airn* (Antisense *Igf2r* RNA Noncoding). The transcribed antisense RNA overlaps (and silences) the *Igf2r* promoter and partially the *Mas* gene.[32,33] Using *Mas*-deficient mice[34] we could show that *Mas* is biallelically expressed.[34] Since Villar and Pedersen[28] and

Miller et al.,[29] used RT-PCR assays which lack strand selectivity to discover imprinting of *Mas* it is very likely that they detected *Airn* as maternally imprinted RNA and not the *Mas* transcript. Thus, *Airn* but not *Mas* is monoallelically expressed in mouse and man.

**MAS as Angiotensin-(1-7) Receptor**

The first evidence for a receptor for Ang-(1-7) distinct from the Ang II receptors came from the observation that Ang-(1-7) was equipotent to Ang II for vasopressin release from hypothalamus-neurohypophyseal explants,[36] but in contrast to Ang II had no effect on drinking behavior.[37] Moreover, Ang-(1-7) was reported to exert vasodilatory effects by releasing NO resulting in a blood pressure decrease.[38] This and other actions of Ang-(1-7), which all opposed the effects of Ang II, further supported that Ang-(1-7) mediates its effects through a novel non-$AT_1$/$AT_2$ receptor subtype. The final proof for the existence of a specific receptor for the peptide was the discovery of a selective antagonist for Ang-(1-7) in 1994.[39,40]

Yet, it was only in 2003 that more definitive evidence for a specific binding site for Ang-(1-7) was demonstrated with the finding that MAS is a receptor for the heptapeptide.[41] In that study, specific binding of $^{125}$I-Ang-(1-7) to *Mas*-transfected cells was reported. Moreover, the specific binding of $^{125}$I-Ang-(1-7) but not of $^{125}$I-Ang II or $^{125}$I-Ang IV to kidney sections, was abolished by genetic deletion of *Mas*. In addition, *Mas*-deficient mice completely lack the antidiuretic action of Ang-(1-7) after an acute water load and *Mas*-deficient aortas lost their Ang-(1-7)-induced relaxation response. These findings provided the first clear molecular basis for the physiological actions of this biologically active peptide. At this point an orphan receptor met an orphan peptide filling an important gap in our understanding of the renin-angiotensin system. Further support for these findings was obtained in different laboratories. In 2005, Tallant et al.[42] showed that transfection of cultured myocytes with an antisense oligonucleotide to *Mas* blocked the Ang-(1-7)-mediated inhibition of serum-stimulated MAPK activation, whereas a sense oligonucleotide was ineffective. Ang-(1-7) was found to stimulate NO release and eNOS

activation in endothelial cells and these effects were blocked by the specific MAS-antagonist, A-779[43,44]. In addition, *Mas*-deficiency abolishes all the known cardiovascular effects of Ang-(1-7).[45] Indeed, in most instances genetic deletion of *Mas* causes alterations opposed to those produced by treatment with Ang-(1-7).

Nevertheless, there are recent reports that Ang-(1-7) has no effect on *MAS*-transfected cells but exerts biased agonism or even antagonism at the $AT_1$ receptor.[46-48] Moreover, using other MAS agonists (NPFF and AR234960) and inverse agonists (AR244555) biased signaling of MAS itself was described.[49] Heteromeric interactions of MAS with $AT_1$, $AT_2$, bradykinin B2 and endothelin B receptors further complicate this issue.[26,27,50-52] Therefore future studies need to clarify the relationship between MAS and Ang-(1-7) which may depend on the specific cell types and their expression of other GPCRs.[53]

## Conclusions

In conclusion, this brief review highlights some important points related to some misconceptions and confusions regarding the nomenclature of MAS and its functions (Table), especially in the context of cardiovascular pathophysiology. We suggest that the original name of "Mas" be used for the GPCR.

## Important take home messages

1. The *MAS1* gene in yeast codes for Mas1p (mitochondrial assembly protein 1) a protease essential for protein import into mitochondria and homologous to the human PMPCB gene.

2. MAS1 or MAS in tetrapods is a G protein-coupled receptor for Ang-(1-7), but not for Ang II.

3. Yeast Mas1 protein has a molecular size of 50-52 kDa, while mammalian MAS has a molecular size of 37-40 kDa.

4. When probing for MAS1 or MAS in the context of Ang-(1-7) biology, ensure the correct primers and antibodies are used to assess expression of mRNA and protein respectively. It should be noted though that currently the authors are unaware of commercially available antibodies that specifically detect MAS at physiological expression levels. However, we demonstrated that the following primer pair is suitable to quantify human *MAS* mRNA by qPCR and may also be used in mice: 5'-GCTACAACACGGGCCTCTATCTG-3'; 5'-TACTCCATGGTGGTCACCAAGC-3', fragment length 160 bp.
5. The mouse *Mas* gene is not imprinted.
6. The *MAS* gene is a proto-oncogene, but has not yet been shown to cause a human tumor.
7. Ang-(1-7)/MAS mediates effects that oppose actions of Ang II/$AT_1$.
8. MAS interacts with other G protein-coupled receptors.

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**Conflicts:**

RMT - No conflicts to declare

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