

Sample of thesis English editing

Field of research: biochemistry

Introduction

Tyrosine O-sulfation, ~~one of the~~a universal post-translational modifications in multicellular eukaryotes, is ~~catalyzed~~catalyzed by two highly homologous enzymes: tyrosylprotein sulfotransferases 1 and 2 (TPST1 and TPST2) (1-5). The TPSTs catalyze the transfer of sulfate groups from the universal donor

3'-phosphoadenosine-5'-phosphosulfate (PAPS) to the hydroxyl group of a peptide tyrosine residue (2). TPSTs are trans-Golgi membrane-bound proteins which ~~has~~have a short N-terminal cytoplasmic domain, a transmembrane domain, and a luminal catalytic domain (2,6). The two human isozymes, TPST1 and TPST2, have similar sizes and share a 67% sequence ~~identity~~homology and conserved catalytic domains. These two enzymes are found ~~widespread, to be~~ co-expressed in ~~widespread~~tissues and cell lines (3-5, 7, 8).

The biological function of tyrosine sulfation is to modulate~~ing~~ protein-protein interactions affecting homeostasis, chemokine receptor functions, leukocyte adhesion, peptide bioactivities and protein secretion (7, 9, 10). For example, tyrosine sulfation of P-selectin glycoprotein ligand-1 (PSGL-1) is required for P-selectin binding (11). Also, the HIV virus enters cells ~~through~~by binding to the sulfated CCR5 receptor (12, 13). It has been demonstrated that 1% all tyrosine residues ~~are~~is sulfated in *Drosophila* (14). Due to the localization of the TPSTs in the trans-Golgi membrane, sulfated protein were only found in plasma membrane bound, typically only secretory proteins, and lysosomal proteins, and membrane-bound plasma proteins undergo sulphation (15). However, ~~up to date, so far~~ only about 70 human proteins and a total of 89 tyrosine ~~residues~~ have been reported to be sulfated. It would be an important step to discover more native sulfated proteins to reveal more fully the function of tyrosine sulfation.

~~The~~Differences of in substrate selectivity, function, and regulation

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the two isozymes has not yet been thoroughly studied. *In vitro* studies using synthetic peptide show that the two enzymes have different substrate specificities and processing orders with several model peptides (16,17, 17). For example, TPST1 preferentially sulfates human C4α and heparin cofactor II than with respect to TPST2. CCR5, having four sulfation sites, is sulfated by the two isozymes in different opposite orders, TPST1 preferring Tyr-14 over Tyr-15 as the first initial step, while TPST2 initially prefers Tyr-15 over Tyr-14 (17). However, the over-all sulfation efficiency of CCR5 by the two enzymes is similar. Kinetic studies of CCR8 peptide using mass spectrometry, gave have given a more detailed insight of into the biochemical behavior of the two isozymes, and the results give show similar kinetic parameters, indicating that the two enzymes have considerable overlapping substrate specificities (18). In contrast, the biological function of the two enzymes was more clearly demonstrated *in vivo* using TPST1 -/- and TPST2 -/- mice from which the TPST-coding genes were deleted (TPST1 -/- and TPST2 -/-). TPST1 -/- mice have about ≈ 5% lower body weights and higher postimplantation fetal death rates among the females, whereas TPST2 -/- mice attain normal body weight but generate are subject to male infertility (19,20). *In vivo* studies suggest a more distinct role of the two enzymes compared with *in vitro* studies. However, the mechanism of underlying how the two isozymes recognize substrates or function differently remains unclear. A closer look at peptide-substrate preferences using purified enzyme would give a better idea.

Final text

Introduction

Tyrosine O-sulfation, a universal post-translational modification in multicellular eukaryotes, is catalyzed by two highly homologous enzymes: tyrosylprotein sulfotransferases 1 and 2 (TPST1 and TPST2) (1-5). The TPSTs catalyze the transfer of sulfate groups from the universal donor 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to the hydroxyl group of a peptide tyrosine residue (2). TPSTs are trans-Golgi membrane-bound proteins which have a short

N-terminal cytoplasmic domain, a transmembrane domain, and a luminal catalytic domain (2, 6). The two human isozymes, TPST1 and TPST2, have similar sizes and share a 67% sequence homology and conserved catalytic domains. These two enzymes are found widespread, co-expressed in tissues and cell lines (3-5, 7, 8).

The biological function of tyrosine sulfation is to modulate protein-protein interactions affecting homeostasis, chemokine receptor function, leukocyte adhesion, peptide bioactivity and protein secretion (7, 9, 10). For example, tyrosine sulfation of P-selectin glycoprotein ligand-1 (PSGL-1) is required for P-selectin binding (11). Also, the HIV virus enters cells by binding to the sulfated CCR5 receptor (12, 13). It has been demonstrated that 1% of all tyrosine residues are sulfated in *Drosophila* (14). Due to the localization of TPSTs in the trans-Golgi membrane, typically only secretory proteins, lysosomal proteins, and membrane-bound plasma proteins undergo sulphation (15). However, so far only about 70 human proteins and a total of 89 tyrosine residues have been reported to be sulfated. It would be an important step to discover more native sulfated proteins to reveal more fully the function of tyrosine sulfation.

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Differences in substrate selectivity, function, and regulation of the two isozymes has not yet been thoroughly studied. *In vitro* studies using synthetic peptide show that the two enzymes have different substrate specificities and processing orders with several model peptides (16, 17). For example, TPST1 preferentially sulfates human C4α and heparin cofactor II with respect to TPST2. CCR5, having four sulfation sites, is sulfated by the two isozymes in opposite orders, TPST1 preferring Tyr-14 over Tyr-15 as the initial step, while TPST2 initially prefers Tyr-15 over Tyr-14 (17). However, the overall sulfation efficiency of CCR5 by the two enzymes is similar. Kinetic studies of CCR8 peptide using mass spectrometry, have given a more detailed insight into the biochemical behavior of the two isozymes, and the results show similar kinetic parameters, indicating that the two enzymes have considerably overlapping substrate specificities (18). In contrast, the biological function of the two enzymes was more clearly demonstrated *in vivo* using mice from which the TPST-coding genes were deleted (TPST1 *-/-* and TPST2 *-/-*). TPST1 *-/-* mice have about 5% lower body weights and higher

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postimplantation fetal death rates among the females, whereas TPST2 *-/-* mice attain normal body weight but are subject to male infertility (19, 20). *In vivo* studies suggest a more distinct role of the two enzymes compared with *in vitro* studies. However, the mechanism underlying how the two isozymes recognize substrates or function differently remains unclear. A closer look at peptide-substrate preferences using purified enzyme would give a better idea.