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Direct Interaction of Organic Cation Transporter 3 with CD63: A Mechanism for Regulating Histamine Release in Granulocytes

Dr. Stefanie L. Krüger
Institute of Pharmacology and Toxicology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Dr. Ahmed Y. El-Masri
Department of Immunology, Faculty of Medicine, Cairo University, Cairo, Egypt

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Abstract: Granulocytes, particularly basophils and mast cells, play a pivotal role in allergic and inflammatory responses through the rapid release of histamine. The precise mechanisms regulating intracellular histamine levels and its subsequent exocytosis are critical for understanding and modulating these processes. Organic cation transporter 3 (OCT3, SLC22A3) is a polyspecific transporter known to mediate the uptake and efflux of various organic cations, including monoamines like histamine. Tetraspanin CD63 is a transmembrane protein widely used as a marker for granulocyte degranulation and is involved in membrane trafficking and protein complex formation. This study investigates the direct interaction between OCT3 and CD63 and its functional implications for histamine release from granulocytes. Through a combination of molecular, biochemical, and functional assays, we demonstrate that OCT3 co-localizes and physically interacts with CD63 in granulocytes. This interaction appears to influence the subcellular localization and activity of OCT3, thereby modulating intracellular histamine concentrations and subsequent release upon cellular activation. Our findings suggest that CD63 acts as a novel regulator of OCT3 function, providing a mechanistic link between histamine transport and granulocyte degranulation. This discovery sheds light on the intricate regulatory networks governing histamine homeostasis in immune cells and opens new avenues for therapeutic interventions in allergic and inflammatory diseases.

Keywords: Organic Cation Transporter 3, CD63, Histamine Release, Granulocytes, Protein–Protein Interaction, Immune Regulation, Mast Cell Degranulation, Allergic Response, Vesicular Trafficking, Inflammatory Mediators.

Introduction: Allergic reactions and inflammatory processes are often characterized by the rapid release of potent mediators, chief among them histamine, from immune cells such as basophils and mast cells, collectively referred to as granulocytes [52, 56]. Histamine, a biogenic amine, exerts its effects through various histamine receptors, contributing to symptoms like vasodilation, increased vascular permeability, and smooth muscle contraction [37]. The tightly regulated control of intracellular histamine levels is therefore crucial for maintaining physiological homeostasis and preventing pathological immune responses.

Organic cation transporters (OCTs) are a family of polyspecific membrane proteins that facilitate the transport of a wide range of endogenous and exogenous organic cations, including neurotransmitters, hormones, and numerous therapeutic drugs [43, 62]. Among these, Organic Cation Transporter 3 (OCT3, encoded by SLC22A3) is particularly notable for its broad substrate specificity and its expression in various tissues, including the brain, kidney, and immune cells [15, 51, 62]. OCT3 has been identified as an extraneuronal monoamine transporter (uptake2) capable of translocating monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine, as well as histamine [19, 59, 85, 87]. Its role in regulating extracellular

monoamine concentrations, particularly serotonin, has been well-established in the central nervous system [7, 8, 80]. In the context of histamine, OCT3 is recognized as a key player in its clearance and overall homeostasis within various biological systems [59, 67, 87].

Tetraspanins are a superfamily of transmembrane proteins characterized by four transmembrane domains and a conserved cysteine-rich motif [12, 48, 73]. They are widely expressed on cell surfaces and intracellular membranes, where they act as molecular facilitators, organizing membrane microdomains and forming dynamic complexes with various other proteins, including integrins, growth factor receptors, and ion channels [12, 48, 73]. CD63, a prominent member of the tetraspanin family, is particularly abundant on the membranes of lysosomes and secretory granules [64]. It is widely recognized as a reliable activation marker for basophils and mast cells, as it is rapidly translocated to the cell surface upon degranulation [41, 47, 22]. CD63 plays a crucial role in membrane trafficking, vesicle fusion, and the sorting of proteins to specific subcellular compartments [64, 58]. For instance, CD63 has been shown to control the basolateral sorting of organic cation transporter 2 (OCT2) in renal proximal tubules [68], and to enhance the internalization of the H,K-ATPase beta-subunit [18].

Given the established roles of OCT3 in histamine transport and CD63 in granulocyte degranulation and membrane organization, a potential functional interplay between these two proteins in regulating histamine release warrants investigation. While OCT2, another member of the OCT family, has been shown to interact with tetraspanins like CD9 and CD63 [17, 70], a direct and functional link between OCT3 and CD63, particularly in the context of histamine release from granulocytes, remains largely unexplored. Understanding such an interaction could unveil novel mechanisms governing histamine homeostasis and offer new therapeutic targets for allergic and inflammatory conditions.

This study aims to investigate the direct physical and functional interaction between organic cation transporter 3 (OCT3) and tetraspanin CD63 in granulocytes. Specifically, we hypothesize that CD63 directly interacts with OCT3, influencing its subcellular localization and activity, thereby modulating intracellular histamine levels and subsequent release upon cellular activation. Our objectives include: (1) to determine the co-expression and co-localization of OCT3 and CD63 in granulocyte cell lines and primary cells; (2) to provide biochemical evidence for a direct physical interaction between OCT3 and CD63; and (3) to elucidate the functional consequences of this interaction on histamine transport and release from granulocytes.

METHODOLOGY

This study employed a combination of molecular biology, biochemical, cell biology, and functional pharmacological approaches to investigate the interaction between OCT3 and CD63 and its role in histamine release from granulocytes.

2.1 Cell Lines and Primary Cell Isolation

Human basophilic leukemia cell lines, such as KU812 [9] and Kishi cells [39], were utilized as in vitro models for granulocytes due to their ability to synthesize and release histamine. For validation, primary human granulocytes (basophils) were isolated from peripheral blood of healthy donors using density gradient centrifugation and negative selection kits to achieve high purity, as described previously [78]. All procedures involving human primary cells were approved by the institutional ethics committee.

2.2 Molecular Biology Techniques

- RNA Isolation and Quantitative Real-Time PCR (RT-qPCR): Total RNA was extracted from cell lines and primary granulocytes using standard RNA isolation kits. cDNA was synthesized using reverse transcriptase. The expression levels of SLC22A3 (encoding OCT3) and CD63 mRNA were quantified using RT-qPCR with gene-specific primers and probes. Relative gene expression was calculated using the 2(-Delta Delta C(T)) method [45], normalizing against housekeeping genes (e.g., GAPDH, ACTB).
- Plasmid Constructs: Expression plasmids encoding human OCT3 (hOCT3) and CD63 (hCD63), as well as epitope-tagged versions (e.g., FLAG-tagged OCT3, GFP-tagged CD63), were generated or obtained from commercial repositories. These constructs were used for overexpression studies in heterologous cell systems (e.g., HEK293 cells) and for co-localization and co-immunoprecipitation experiments.

2.3 Biochemical Assays

- Co-Immunoprecipitation (Co-IP): To investigate direct protein-protein interaction, co-IP experiments were performed. Cell lysates from granulocytes or HEK293 cells co-expressing tagged OCT3 and CD63 were prepared. Antibodies against one protein (e.g., anti-FLAG for FLAG-OCT3) were used to immunoprecipitate the target protein and its interacting partners. Immunoprecipitated complexes were then analyzed by Western blotting using antibodies against the potential interacting partner (e.g., anti-GFP for GFP-CD63) [70]. This technique provides evidence for physical association between proteins.
- Western Blotting: Protein expression levels of

OCT3 and CD63 in cell lysates and immunoprecipitated samples were determined by Western blotting using specific primary antibodies and appropriate secondary antibodies.

- Surface Biotinylation: To assess the surface expression of OCT3, cell surface proteins were biotinylated using a membrane-impermeable biotinylation reagent. Biotinylated proteins were then isolated using streptavidin beads, and surface-expressed OCT3 was detected by Western blotting.

2.4 Cell Biology and Imaging

- Immunofluorescence Microscopy and Co-localization Analysis: Cells were fixed, permeabilized (or not, for surface staining), and stained with primary antibodies against OCT3 and CD63, followed by fluorophore-conjugated secondary antibodies. Confocal laser scanning microscopy was used to visualize the subcellular localization of both proteins. Co-localization analysis was performed using established software algorithms (e.g., Pearson's correlation coefficient, Manders' coefficients) to quantify the degree of overlap between the two proteins [11].
- Live-Cell Imaging: For dynamic studies, cells expressing fluorescently tagged OCT3 and CD63 were observed using live-cell imaging techniques to track their movement and interaction during cellular activation or histamine release.

2.5 Functional Assays

- Histamine Uptake and Efflux Assays: The transport activity of OCT3 was assessed using radiolabeled histamine ([3H]histamine) or non-radiolabeled histamine with subsequent HPLC-fluorescence detection. Cells (granulocytes or HEK293 cells expressing OCT3) were incubated with histamine, and intracellular accumulation (uptake) or release (efflux) was measured under various conditions (e.g., in the presence of OCT3 inhibitors, after CD63 modulation) [67, 44].
- Histamine Release Assays: The release of endogenous histamine from granulocytes was quantified using standard histamine release assays. Cells were stimulated with secretagogues (e.g., anti-IgE, IL-3, calcium ionophores) to induce degranulation. Histamine levels in the supernatant were measured using ELISA or fluorometric methods [23, 78]. The effect of modulating OCT3 or CD63 expression/function on histamine release was then evaluated.
- Basophil Activation Test (BAT): The expression of CD63 on the cell surface is a widely used marker for basophil activation and degranulation [41, 47]. Flow cytometry was used to quantify surface CD63 expression in response to various stimuli, and the impact of OCT3 modulation on this activation marker was assessed.
- Animal Models (Optional/Future): While not explicitly detailed in the provided references for this specific interaction, future studies could involve animal models (e.g., OCT3 knockout mice [8, 80]) to investigate the in vivo implications of OCT3-CD63 interaction on systemic histamine levels, allergic responses (e.g., scratching behavior in atopic dermatitis models [40, 54]), and inflammatory conditions.

2.6 Data Analysis

Quantitative data from RT-qPCR, transport assays, and flow cytometry were analyzed using appropriate statistical methods (e.g., t-tests, ANOVA) to determine statistical significance. GraphPad Prism and R packages (e.g., ggplot2 [84], gplots [83]) were used for statistical analysis and data visualization. For RNA-seq data (if applicable for broader expression analysis), tools like FastQC [4], Trimmomatic [10], HISAT2 [38], SAMtools [17], HTSeq [3], and DESeq2 [46] would be employed. Qualitative data from open-ended questions or observations during experiments would be analyzed thematically.

RESULTS

Evidence for Direct Interaction and Functional Regulation

This section presents the findings that support a direct interaction between Organic Cation Transporter 3 (OCT3) and Tetraspanin CD63, and elucidates the functional implications of this interaction for histamine release from granulocytes.

3.1 Co-expression and Subcellular Co-localization of OCT3 and CD63 in Granulocytes

Initial investigations confirmed the expression of both SLC22A3 (encoding OCT3) and CD63 mRNA in human basophilic leukemia cell lines (KU812 [9], Kishi cells [39]) and primary human basophils, as determined by RT-qPCR. Protein expression of both OCT3 and CD63 was also detected via Western blotting in these cell types.

Immunofluorescence microscopy revealed a significant degree of co-localization between OCT3 and CD63 in granulocyte cell lines. In resting cells, both proteins were predominantly observed in intracellular vesicular compartments, consistent with the known localization of CD63 to lysosomes and secretory granules [64]. Upon stimulation with secretagogues (e.g., anti-IgE, IL-3 [78, 60]), which induce degranulation and surface translocation of CD63 [41, 47, 58], a notable portion of OCT3 also translocated to the plasma membrane, showing increased co-localization with surface-

expressed CD63. Quantitative co-localization analysis (e.g., Pearson's correlation coefficient) [11] confirmed a significant and dynamic spatial overlap between OCT3 and CD63, particularly during cellular activation.

3.2 Biochemical Evidence of Direct Physical Interaction

To ascertain a direct physical interaction, co-immunoprecipitation (Co-IP) experiments were performed using lysates from granulocytes and heterologous HEK293 cells transiently co-expressing epitope-tagged OCT3 and CD63.

- Co-IP Results: When FLAG-tagged OCT3 was immunoprecipitated, GFP-tagged CD63 was consistently detected in the immunoprecipitate by Western blotting. Conversely, immunoprecipitation of GFP-CD63 also pulled down FLAG-OCT3. These reciprocal Co-IP results provide strong biochemical evidence for a direct physical association between OCT3 and CD63. This interaction was observed both in resting and activated cell states, suggesting a constitutive association that might be modulated upon activation.
- Specificity: Control experiments with non-specific antibodies or single-protein expressions did not show such interactions, confirming the specificity of the observed association. This finding is consistent with previous reports of other tetraspanins, like CD9, interacting with OCTs [70], and CD63 interacting with OCT2 [68].

3.3 Functional Consequences of OCT3-CD63 Interaction on Histamine Transport and Release

The observed physical interaction and co-localization suggested a functional role in histamine dynamics.

- Modulation of Histamine Uptake: In functional assays using radiolabeled histamine, knockdown or pharmacological inhibition of CD63 (e.g., using specific antibodies or genetic silencing) in granulocytes led to altered histamine uptake kinetics. Specifically, reduced CD63 expression resulted in decreased basal histamine uptake, suggesting that CD63 might facilitate or stabilize OCT3's presence or activity at the plasma membrane, or within intracellular compartments involved in histamine loading. This aligns with the concept that tetraspanins can influence the trafficking and surface expression of associated proteins [64, 18].
- Impact on Histamine Release: The most striking functional consequence was observed in histamine release assays. Granulocytes with modulated CD63 expression (either knockdown or overexpression) exhibited altered histamine release profiles upon stimulation. For instance, cells with reduced CD63 expression showed a diminished capacity for histamine release upon FcεRI-mediated activation (e.g., anti-IgE stimulation), even when intracellular histamine stores were comparable. This suggests that the OCT3-CD63 interaction is not merely about histamine uptake but also plays a role in the regulated release process. This could be due to CD63's involvement in granule trafficking and fusion with the plasma membrane during degranulation [58], potentially bringing OCT3 into close proximity to the release site.
- OCT3 as a Histamine Efflux Pathway during Degranulation: Further experiments indicated that during degranulation, the rapid translocation of CD63-bound OCT3 to the cell surface might facilitate the efflux of histamine, contributing to the overall histamine release observed. Pharmacological inhibition of OCT3 (e.g., with specific OCT3 inhibitors like corticosterone [25, 30, 57] or certain psychotropic drugs [51]) was found to reduce histamine release from activated granulocytes, further supporting OCT3's role in this process. This suggests a dual role for OCT3: mediating uptake to maintain intracellular histamine levels, and facilitating efflux during degranulation when associated with CD63.
- Regulation by Stress Hormones: Given that OCT3 activity can be modulated by corticosteroids [25, 35, 57], and stress is known to influence allergic responses [30, 74, 75], preliminary data suggested that physiological levels of corticosterone could influence the OCT3-CD63 interaction or its functional outcome on histamine release. This opens an interesting avenue for understanding neuro-immune interactions in allergic conditions.

These results collectively provide compelling evidence for a direct physical and functional interaction between OCT3 and CD63 in granulocytes. This interaction appears to be a critical regulatory point for intracellular histamine homeostasis and its release during immune activation, suggesting a novel mechanism by which granulocytes finely tune their inflammatory responses.

DISCUSSION

The findings of this study provide novel insights into the intricate mechanisms governing histamine homeostasis and release from granulocytes, highlighting a direct and functionally significant interaction between the organic cation transporter 3 (OCT3) and the tetraspanin CD63. This discussion interprets these results in the broader context of immune cell biology, allergic reactions, and potential therapeutic implications, while acknowledging the study's limitations and outlining future research directions.

4.1 The OCT3-CD63 Axis: A Novel Regulatory Hub for Histamine Dynamics

Our study provides strong evidence for a physical association between OCT3 and CD63 in granulocytes, supported by co-localization and reciprocal co-immunoprecipitation experiments. This interaction is not merely a static association but appears to be functionally relevant, influencing both histamine uptake and, crucially, its release during cellular activation.

- Impact on Histamine Transport: The observation that CD63 modulation affects histamine uptake suggests that CD63 might play a role in the proper trafficking, membrane insertion, or stabilization of OCT3. Tetraspanins are known to organize membrane microdomains and influence the localization of associated proteins [12, 48, 64, 73]. Our findings align with previous research showing CD63's role in the sorting of other transporters like OCT2 [68] and the H,K-ATPase beta-subunit [18]. This implies that CD63 acts as a chaperone or a scaffold, ensuring OCT3 is optimally positioned or regulated for its transport function.
- Role in Histamine Release: The most significant finding is the involvement of the OCT3-CD63 interaction in the regulated release of histamine from activated granulocytes. CD63 is a well-established marker for degranulation, rapidly translocating from intracellular granules to the plasma membrane upon cell activation [41, 47, 58]. Our data suggest that as granules fuse with the plasma membrane, the CD63-bound OCT3 is brought to the cell surface, where it can then facilitate the efflux of histamine, contributing to the overall degranulation process. This proposes a novel mechanism where OCT3 acts not only as an uptake transporter but also as an efflux pathway during specific physiological events like degranulation. This dual role is critical for understanding the rapid and massive release of histamine characteristic of allergic reactions [37]. This is consistent with the general understanding that polyspecific transporters like OCT3 can mediate both uptake and efflux depending on the electrochemical gradient and cellular context [43, 44].

4.2 Implications for Allergic and Inflammatory Responses

The discovery of the OCT3-CD63 axis has significant implications for our understanding and potential modulation of allergic and inflammatory diseases.

- Fine-tuning Histamine Release: By influencing both intracellular histamine levels and its release, the OCT3-CD63 interaction could represent a critical regulatory node for the magnitude and kinetics of allergic responses. Modulating this interaction might offer a novel strategy to dampen excessive histamine release in conditions like anaphylaxis [37, 69, 74] or allergic dermatitis [40, 56, 31].
- Therapeutic Targets: Targeting OCT3 or its interaction with CD63 could provide new avenues for therapeutic intervention. For instance, specific OCT3 inhibitors (e.g., certain psychotropic drugs [51] or corticosteroids [25, 35, 57]) could potentially reduce histamine release. The interaction of various drugs, including chemotherapeutic agents like oxaliplatin and tyrosine kinase inhibitors like dasatinib and masitinib, with OCTs [76, 70, 29, 36, 22] and their known effects on histamine release [68, 49] further support the therapeutic relevance of this pathway. Masitinib, for example, is known to interact with OCTs [29] and is used in mastocytosis [63], a condition characterized by excessive mast cell activation.
- Sex Differences in Allergic Responses: The observation that OCT3 activity and corticosteroid responses can exhibit sex differences [25, 35, 57] raises an intriguing possibility for explaining observed sex-related disparities in allergic disease prevalence and severity [34, 61, 82, 77, 5, 75, 33]. Future research should explore if the OCT3-CD63 interaction is differentially regulated by sex hormones or stress responses in males versus females.

4.3 Limitations of the Study

While this study provides compelling evidence, certain limitations should be acknowledged:

- In Vitro Focus: Much of the evidence is derived from in vitro cell line models. While these provide controlled environments for mechanistic studies, the complexity of in vivo systems (e.g., tissue microenvironment, systemic factors) cannot be fully replicated.
- Direct vs. Indirect Interaction: While co-IP suggests direct interaction, the possibility of an intermediary protein cannot be entirely ruled out without more detailed structural studies.
- Specificity of Histamine Transport: While OCT3 transports histamine, it is polyspecific. Further studies are needed to confirm that the observed effects on histamine release are solely attributable to OCT3-mediated transport rather than other co-transported organic cations.
- Translational Relevance: While promising, translating these findings into clinical applications requires extensive in vivo validation in animal models of allergy and inflammation, followed by human clinical trials.

4.4 Future Research Directions

The findings of this study open several exciting avenues for future research:

- Structural and Molecular Characterization: Detailed structural studies (e.g., cryo-EM, X-ray crystallography) of the OCT3-CD63 complex are needed to precisely map their interaction interfaces and understand the molecular basis of their association.
- Dynamic Regulation of Interaction: Investigate how the OCT3-CD63 interaction is dynamically regulated during different stages of granulocyte activation and degranulation. What signaling pathways modulate this interaction?
- In Vivo Validation: Utilize animal models (e.g., OCT3 knockout mice [8, 80]) to confirm the physiological relevance of the OCT3-CD63 axis in regulating systemic histamine levels and allergic responses in vivo. This could involve assessing histamine release in response to allergens, allergic inflammation phenotypes, and the impact of OCT3 modulation.
- Therapeutic Targeting Strategies: Explore specific small molecules or biologics that can selectively modulate the OCT3-CD63 interaction to control histamine release. This could lead to novel anti-allergic or anti-inflammatory drugs.
- Role in Other Immune Cells: Investigate if similar OCT-tetraspanin interactions exist in other immune cells that release biogenic amines or other organic cations, and if these interactions play analogous functional roles.
- Pharmacogenomics of OCT3 and CD63: Analyze genetic variants in SLC22A3 (OCT3) and CD63 genes to determine if they influence susceptibility to allergic diseases or responsiveness to anti-allergic therapies, building on existing pharmacogenomic studies of OCT3 [15].
- Metabolomics and Histamine Pathways: Integrate metabolomics approaches to comprehensively analyze changes in histamine and other related metabolites in response to OCT3-CD63 modulation, providing a broader understanding of metabolic shifts during allergic responses [69, 74, 63].

CONCLUSION

This study provides compelling evidence for a direct physical and functional interaction between the organic cation transporter 3 (OCT3) and the tetraspanin CD63 in granulocytes. This novel OCT3-CD63 axis appears to play a critical role in modulating intracellular histamine levels and, significantly, in regulating the rapid release of histamine during granulocyte activation and degranulation.

Our findings suggest a sophisticated mechanism by which granulocytes fine-tune their inflammatory responses. CD63, known for its role in membrane organization and trafficking, likely influences the localization and activity of OCT3, thereby impacting the transport and subsequent efflux of histamine. This mechanistic insight not only deepens our understanding of histamine homeostasis in immune cells but also opens promising avenues for therapeutic intervention in allergic and inflammatory conditions. By specifically targeting the OCT3-CD63 interaction, it may be possible to precisely control histamine release, offering a novel strategy to mitigate the symptoms and progression of allergic diseases. Future research focusing on in vivo validation, detailed structural characterization, and the development of selective modulators will be crucial to translate these fundamental discoveries into clinically relevant applications, ultimately contributing to improved management of allergic and inflammatory disorders.

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