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Stefano Pozzi *

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Unlocking the Mystery of Oxyphil Cells: Their Origin, Function, and Clinical Relevance in Parathyroid Physiology

The Clinical Relevance of Oxyphil Cells

Stefano Pozzi

School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy;
s.pozzi62@campus.unimib.it

Significance Statement: This review was carried out because oxyphil cells in the parathyroid glands have long been an enigmatic cell population with unclear function and significance. By analyzing recent findings, it highlights the growing evidence that oxyphil cells may actively contribute to parathyroid hormone regulation rather than being functionally inactive. Understanding their role could improve diagnostic and therapeutic strategies for parathyroid disorders. This study provides a foundation for future research on their metabolic and pathological implications. Unraveling the biology of oxyphil cells may lead to novel approaches in endocrine and metabolic disease management.

Abstract: This paper provides a comprehensive review on oxyphil cells in the parathyroid glands, examining their origin, morphology, endocrine function, and clinical implications. Oxyphil cells, which arise through a transdifferentiation process from chief cells, exhibit an increased proliferation in response to aging and pathological conditions such as secondary hyperparathyroidism, particularly in association with chronic kidney disease. Histological analysis reveals a correlation between oxyphil cell accumulation and the severity of parathyroid dysfunctions, suggesting an adaptive role of these cells in calcium metabolism disturbances. Contrary to previous beliefs, oxyphil cells seem to show an overexpression of parathyroid hormone (PTH), implying a potential role in regulating hormone synthesis. Cellular mechanisms driving transdifferentiation are thus explored, including the role of mitochondrial mutations and the involvement of biochemical signals such as the calcium-sensing receptor (CaSR), despite conflicting evidence regarding its influence. This review then examines the associations between oxyphil cells and various pathologies, highlighting their potential use as biomarkers for monitoring hyperparathyroidism. Additionally, the autocrine and paracrine functions of oxyphil cells are discussed, along with their impact on PTH production and associated metabolic pathways. Finally, the need for further research to clarify the regulatory mechanisms of oxyphil cells and to assess their therapeutic potential is discussed. Priority is given to investigating the role of chemerin in parathyroid cells and its influence on metabolic and immune responses. The implications of these findings could prove essential for advancing the understanding and treatment of parathyroid disorders.

Keywords: chemerin; hyperparathyroidism; kidney diseases; oxyphil cells; parathyroid glands; transdifferentiation

Introduction

The parathyroid glands primarily contain two cell populations: chief cells and oxyphil cells. Whereas the former are primarily responsible for secreting parathyroid hormone (PTH), the function of the latter has long remained an enigma. Given their potential role in aging as well as in pathological

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processes such as hyperparathyroidism due to renal insufficiency (1-3), it is essential to investigate the nature and role of these cells. In recent years, a series of studies has identified certain elements that deepen the understanding of the origin and functions of oxyphil cells in the human body. However, these studies reveal data that conflict with previous hypotheses regarding the origin and functionality of oxyphil cells [1–3].

Consequently, a review is needed to highlight the conflicting elements in the literature, synthesizing and summarizing the latest information before considering and discussing aspects deemed clinically significant. After a brief description on the histological aspects of these cells, the review will address their origin, their relationship to certain pathologies, and their endocrine activity. A better understanding of oxyphil cells could offer various benefits both clinically and scientifically. Such knowledge may facilitate earlier diagnosis of parathyroid diseases, enable the development of targeted therapies that improve treatment efficacy and reduce side effects, enhance insights into calcium-regulating mechanisms and other metabolic pathways, advance the study of aging processes, and aid in the identification of biomarkers valuable for diagnosing specific pathological conditions or monitoring treatment response.

Materials and Methods

The research was conducted using databases accessible through the Prometeo catalog of the University of Milan-Bicocca, which has access to several databases such as The Cochrane Library, Pubmed, Embase, Ovid, Scopus, Web of Science. The search strategy used the keyword “oxyphil cells”. Since this term is sometimes also used to refer to a thyroid cell population, a targeted selection was carried out to include only studies related to oxyphil cells in the parathyroid glands. From the selected studies, information was extracted regarding the following aspects: histology, cellular origin, associated pathologies, and endocrinology of oxyphil cells, in order to provide a clear and coherent synthesis of current knowledge on this cell type. Grey literature was not considered and only articles published in English were included.

Results

Histological Overview

Oxyphil cells are absent at birth, appearing in the first decade of life, with a marked increase in number observed after the age of 40, showing a strong positive correlation between cell count and individual aging; conversely, there is no correlation with the number of thyroid C cells [4]. Oxyphil cells are distributed irregularly within the parathyroid parenchyma, occurring singly or in clusters [5]. There is a tendency for increasingly larger clusters or nodules to form with advancing age [4] or in the presence of excessive functional stress. These cells are larger than chief cells and are circular or oval in shape. Their cytoplasm is highly acidophilic, due to the substantial presence of mitochondria. Within this cytoplasm—and in the parathyroid gland as a whole—the highest levels of parathyroid hormone-related peptide (PTHrP) can be detected [6]. A study conducted on parathyroid hyperplasia revealed that tissue samples containing a higher quantity of oxyphil cells have a lower weight compared to those with fewer oxyphil cells [7]. These cells test positive in Baker’s phospholipid test, showing similarities to acidophilic cells in the pituitary gland [8]. X-ray analysis and the ultrastructural localization technique using potassium pyroantimonate have shown that calcium-containing precipitates in oxyphil cells are primarily located in the mitochondria, as well as in the nucleus [9].

Cellular Origin

The origin of oxyphil cells has been identified as a transdifferentiation from chief cells, based on two key findings [10]:

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1. The presence of transitional cells that partially exhibit characteristics of both cell types, serving as intermediates: they have small sizes like chief cells but possess an acidophilic cytoplasm similar to oxyphil cells.
2. Both transitional and oxyphil cells express parathyroid hormone (PTH) and the gene glial cells missing transcription factor 2 (GCM2), a parathyroid-specific transcription factor crucial for gland development [11].

Several hypotheses have been proposed to explain why this transformation occurs:

- The need for a defensive mechanism (represented by oxyphil cells) capable of managing significant electrolyte imbalances associated with chronic kidney disease [12].
- The advantage held by oxyphil cells in effectively responding to increases in extracellular calcium concentration, thereby ensuring better regulation under parathyroid hyperfunction conditions [13].
- The need for a defense mechanism against hyperparathyroidism, involving the transdifferentiation of highly secretory chief cells into oxyphil cells with lower secretory activity. This strategy, while not preventing the onset of the disease, could delay its progression [10]. However, it should be noted that this last hypothesis is currently unsustainable. In light of both earlier evidence [11] and further confirmation from recent research [2], it is clear that the secretory activity of oxyphil cells is not low or inferior to that of chief cells, as was once commonly believed. In fact, oxyphil cells show not only the presence of additional cellular products but also an overexpression of PTH.

The specific cause driving cellular transformation has been identified as mitochondrial mutations [14], which are also responsible for cytochrome-c oxidase deficiency in the parathyroid glands. This deficiency does not appear to be related to altered expression of DNA polymerase gamma or the human mitochondrial transcription factor A (h-mtTFA) [15]. The high number of mitochondria in oxyphil cells is thus attributed to a compensatory proliferation mechanism in these organelles, counteracting the adverse effects of respiratory chain dysfunction. This mitochondrial multiplication is observable even in the absence of pathological processes, such as during aging, and is more pronounced under conditions of glandular hyperfunction [16].

Another potential role in the transdifferentiation process, according to some authors, is played by the calcium-sensing receptor (CaSR) and, consequently, by calcimimetics (e.g., cinacalcet), given that CaSR appears to be more highly expressed in oxyphil cells than in chief cells [11]. This hypothesis is supported by a positive association between serum calcium concentration and oxyphil cell count in cases of primary hyperparathyroidism [17]. Notably, CaSR activation occurs directly through cinacalcet use and indirectly via calcitriol, which affects calcium levels. This hypothesis is further substantiated by experiments in rats: incubation of normal parathyroid glands in a calcium-rich environment led to oxyphil cell formation [18]. Additionally, cinacalcet treatment significantly increases oxyphil cell count [19,20], whereas paricalcitol (a vitamin D receptor agonist) does not have this effect [21]. Indeed, no significant differences are observed in vitamin D receptor (VDR) expression between chief and oxyphil cells [22]. However, the literature does not unanimously support higher CaSR expression in oxyphil cells. Several studies have reported similar CaSR levels in both oxyphil and chief cells [1,3,13] or even lower levels in oxyphil cells [2]. Consequently, CaSR quantity alone may not determine oxyphil cells' enhanced responsiveness to calcium variations; rather, other potential mechanisms have been suggested by various authors, including increased biochemical opposition to CaSR signaling, altered CaSR protein trafficking, or a calcium sensitivity that is entirely independent of CaSR [13].

Furthermore, based on the finding that despite morphological differences between chief and oxyphil cells, analysis of a population of healthy, PTH-positive parathyroid cells showed no distinct clusters—neither with the tSNE (t-distributed Stochastic Neighbor Embedding) algorithm nor with the UMAP plot dimensionality reduction technique—some researchers have suggested that these may not be two distinct cell types, but rather two different states of the same cell type [3].

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Associated Pathologies

If the number of oxyphil cells depends on parathyroid gland activity levels, anything causing excessive function (e.g., chronic kidney disease leading to secondary hyperparathyroidism, or SHPT) will result in an increase in their count. This phenomenon, likely related to renal damage as a secondary complication, has also been observed in primary hyperparathyroidism (PHPT) [23]. Furthermore, differences in gene expression and cellular pathway activation in tissue samples from PHPT patients—correlated with the patient's sex—seem to stem primarily from the oxyphil cells themselves [24].

In SHPT, recent single-cell RNA sequencing (scRNA-seq) studies [25] have confirmed:

- a substantial increase in oxyphil cells among uremic patients with SHPT;
- a gradual mitochondrial enrichment in the transdifferentiation of chief cells into oxyphil cells, driven by the uremic environment;
- that this uremic environment serves as the key factor initiating cellular transformation, as shown by the significant decrease in both cellular proliferation and mitochondrial enrichment in transplanted oxyphil cell nodules from diseased mice into healthy mice.

In SHPT, increased oxyphil cell count is also associated with dysregulated vitamin D transport (down-regulation of vitamin D-binding protein, or DBP) and altered Wnt, TGF-β, and ubiquitin-mediated proteolysis signaling pathways, with a notable role played by the Migration inhibitory factor - Cullin 1 (MIF-CUL1) axis [26]. In general, low vitamin D levels have been linked to an increase in oxyphil cells [27].

Elevated PTH production in chronic kidney disease is mitigated by increased activity of 25-hydroxyvitamin D3-1 alpha-hydroxylase. This increase can be triggered by fibroblast growth factor 23 (FGF-23), induced by hyperphosphatemia from kidney disease, by calcimimetics, or by oxyphil cell proliferation, as these cells produce more of the enzyme than chief cells. Considering the hydroxylase activity increase, lower levels of BDP in oxyphil cells, and vitamin D degradation promoted by calcitriol (possibly secreted by oxyphil cells), nutritional vitamin D support (cholecalciferol) is crucial in SHPT treatment to prevent further PTH elevation. This approach may also help slow SHPT progression in both early and late stages of chronic kidney disease, including in dialysis patients [28].

Bioinformatics and machine learning analyses have identified biomarkers that could predict SHPT progression [29]. One such marker, Procollagen C-Endopeptidase Enhancer 2 (PCOLCE2), enhances reactive oxygen species (ROS) generation in neutrophils, supporting innate immune defense [30]. This is significant given the high mitochondrial content in oxyphil cells, where ROS production is considerable [31]. Additionally, both parathyroid cell types contain interferon-alpha [32], a regulator of innate immunity.

Raman microscopy enables highly accurate differentiation between adenomas composed of chief versus oxyphil cells [33]. It is now established that oxyphil cell content does not affect Tc-99m sestamibi radiopharmaceutical absorption [34–36].

Mitochondrial mutations underpin the oxyphil phenotype and may confer a selective advantage, potentially contributing to the molecular pathogenesis of parathyroid adenomas [14]. Proto-oncogenes, like C-erbB-2 protein, are often present in patients with these hyperproliferative conditions [37]. An increase in oxyphil cells could thus serve as a morphological indicator of tumor-prone cellular stress [27]. In reference to mitochondrial mutations that cause the transdifferentiation of chief cells into oxyphilic cells, the types of mutations should be investigated: mutations in genes encoding the subunits of NADH dehydrogenase (ND), which are predominantly found in oxyphilic tumors, appear to be essential for tumor progression itself rather than merely serving as factors inducing the oxyphilic cell phenotype; conversely, mutations in cytochrome c oxidase seem to inhibit neoplastic progression [16,38].

Interestingly, autoantibodies against both parathyroid cell types have been observed in some idiopathic hypoparathyroidism cases [39]. In such cases, inhibited cell proliferation results in

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insufficient gland function, representing a mirror image of the hyperparathyroidism situation described above.

Endocrine Function

Some studies have focused on the autocrine-paracrine role of oxyphil cells [11]. Notably, these cells show overexpression of PTH [2], CaSR, GCM2, PTHrP, and 25-hydroxyvitamin D3-1 alpha-hydroxylase relative to chief cells [40], with intact PTH (iPTH) levels [2]. Parathyroid adenoma samples further demonstrate oxyphil cells' greater responsiveness to changes in extracellular calcium concentration [13].

Regarding PTHrP, some studies suggest that oxyphil cells not only express but also secrete it in an autocrine/paracrine manner, potentially regulating parathyroid cell proliferation and differentiation. This could promote metaplastic transformation into oxyphil cells due to lower proliferation levels—demonstrated by reduced expression of proliferating cell nuclear antigen (PCNA) and cyclin D1—compared to chief cells [2,6,41].

Given the potential role of CaSR in transdifferentiation, oxyphil cells may also produce calcitriol in response to CaSR activation, which could reduce PTH synthesis in an autocrine/paracrine manner, representing an additional PTH regulation mechanism through calcimimetics [11]. The ability to control and regulate the primary function of chief cells—the synthesis of PTH—would imply the capacity to also regulate the proliferation of the chief cells themselves, considering that the growth of the cell population represents a classic response to the need for increased hormonal synthesis [10]. However, as mentioned earlier, increased CaSR expression in oxyphil cells has been disputed in numerous studies [1–3,13], challenging the existence of this control system.

Another potential control mechanism for PTH synthesis by oxyphil cells involves the correct regulation of cyclooxygenase expression. Some researchers propose that oxyphil cells, rich in mitochondria, are the sole site of demonstrable cyclooxygenase activity, suggesting a key role in prostaglandin metabolism and thus PTH synthesis [42]. A strong positive correlation has been observed between cyclooxygenase-2 (COX2), PTH, and PCNA expression. Aberrant COX2 production is linked to cell proliferation and, consequently, parathyroid hyperplasia; targeting this enzymatic pathway could be a therapeutic goal [43].

Finally, a recent study identified the protein RARRES2 (chemerin) abundantly expressed in PTH-producing cells, including oxyphil cells, in parathyroid adenomas, suggesting a potential new role for this protein in parathyroid endocrine function [44].

Discussion

The genesis of oxyphil cells has been identified in the transdifferentiation process of chief cells [10–13], caused by mitochondrial genetic mutations [14]. Some studies previously suggested that the activation of CaSR also plays a role in this transformation [11,17–20], but this assumption is currently refuted by various studies [1–3,13]. Therefore, unless further evidence emerges, it is reasonable to exclude any certainty regarding both the potential role of CaSR in the cellular transdifferentiation process and the possible mechanism of control of PTH synthesis exerted by oxyphil cells in response to mere CaSR activation.

The metaplasia in question gives rise to various benefits. Oxyphil cells:

- show a stronger ability (compared to chief cells) to effectively respond to increased extracellular calcium concentrations, demonstrating better control during parathyroid organ hyperfunction [13]; however, the exact mechanism underlying this increased capability has not yet been specifically identified—thus, further research in this area is crucial;
- display lower levels of secretory activity, resulting in a delay in the progression of both primary and secondary hyperparathyroidism [10]; however, this is now to be excluded in light of the observed overexpression of a series of cellular products, including PTH, by oxyphil cells [2,11];
- are capable of attenuating the pathological increase in PTH production through specific strategies that have been identified over time: in regulating the activity of chief cells by

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producing calcitriol in response to CaSR activation [11] (a mechanism that has been questioned, as mentioned above), possible control of chief cell proliferation [10], and increased production of 25-hydroxyvitamin D3-1 alpha-hydroxylase [28]—further investigation in this regard is also warranted.

That the purpose of establishing a defensive mechanism by the organism is the function performed by this metaplastic phenomenon is confirmed by the slowing and cessation of the phenomenon itself upon removal of the uremic environment [25]. However, as is often the case with metaplasia [45], the alteration of the physiological situation and the appearance of a new cell type does not only produce positive effects. The presence of new cellular products [11,42], variations in the production of original secretions [2,40], and the different gene expression (dysregulations/alterations in signaling pathways) [26] of oxyphil cells entail potential and significant disadvantages:

- the oxyphil phenotype, due to the mitochondrial mutations from which it derives, may acquire a selective advantage and contribute to the molecular pathogenesis of parathyroid adenomas [14];
- oxyphil cells exhibit aberrant expression of cyclooxygenases, whose excess promotes the onset of parathyroid hyperplasia—inhibiting the COX2 pathway has been suggested as a method for regulating PTH synthesis [42,43];
- the increase in the number of oxyphil cells (a morphological indicator of the presence of tumor-predisposing cellular stress) is often associated with a greater presence of proto-oncogenes [37];
- mutations in genes coding for NADH dehydrogenases (ND) appear to significantly favor tumor progression (unlike those related to cytochrome-c oxidase, which instead impede such progression) [16,38].

Given the dual impact of oxyphil cell proliferation, it is necessary to analyze in detail, for each relevant pathology, if and how it is possible to act on these cells to mitigate and minimize the potential negative consequences for the parathyroids and for the entire organism, while safeguarding the effectiveness of the defensive mechanism they establish. Thus, research and studies oriented in this direction are required.

Regarding the recent identification of chemerin in different cell populations of parathyroid glands, it is also important to conduct investigations to identify any specific functions associated with this protein in this organ. Given the current and established evidence regarding this multifaceted adipokine [46], it is possible to hypothesize that:

- it could have a direct impact on calcium metabolism or even just an indirect impact (acting on other metabolic pathways that interact with the former);
- it might be involved in modulating local inflammatory responses, interacting or not with other mediators present locally, such as interferon-alpha, or it could act as a bridge between the innate and adaptive immune systems [47];
- it could play a role in autoimmune diseases, given its role as a chemoattractant [48] for immune cells such as monocytes and lymphocytes;
- it could have a function in lipid metabolism within parathyroid glands.

All these points warrant thorough investigation to understand the specific role of chemerin in parathyroid cells.

Regarding the limitations of this narrative review, it should be noted that:

- a search was not conducted across all existing databases, but only in those accessible through the Prometeo catalog of the University of Milan Bicocca and only in published literature, not in grey literature. Only articles in English were analyzed;
- the review was conducted by a single person, which may introduce interpretation biases in the data;
- there appear to be few articles on the subject, particularly concerning humans, which reduces both the interpretability of the data and the clinical applicability of the reported study results, especially given the complexities of the diseases considered.

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Conclusions

After highlighting the main characteristics of oxyphil cells, the metaplastic process leading to their genesis, their role in various pathologies, their endocrine activity, and the advantages and disadvantages derived from their defensive mechanism, this review has highlighted that further research is needed with the following objectives:

- identifying the exact mechanism underlying the greater sensitivity of oxyphil cells, compared to chief cells, in perceiving and effectively responding to increased extracellular calcium concentrations;
- elucidating the strategies implemented by oxyphil cells themselves to regulate PTH synthesis at the parathyroid organ level as a whole;
- assessing whether it is possible to minimize the disadvantages arising from the increased number of oxyphil cells and, should it be the case, developing appropriate strategies to address this;
- defining the role of chemerin and identifying the specific functions it performs within oxyphil cells and, in general, within PTH-secreting cells.

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