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Acinar-to-Ductal Metaplasia in Chronic Pancreatitis: A Critical Link Between Inflammation and Pancreatic Carcinogenesis

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Abstract: Chronic pancreatitis (CP) is a progressive fibroinflammatory disorder that results from the interplay of genetic, environmental, immune, and pathogenic factors. Traditionally characterized by irreversible pancreatic injury, CP is now recognized as an important precursor to pancreatic ductal adenocarcinoma (PDAC), a deadly form of pancreatic cancer. The persistent inflammatory microenvironment of CP promotes the accumulation of genetic mutations and cellular reprogramming, which can lead to acinar-to-ductal metaplasia (ADM), a precursor lesion of PDAC. ADM represents a reversible cellular reprogramming process, wherein pancreatic acinar cells transform into duct-like cells in response to inflammatory stress. This process is critical in both tissue repair and, under sustained inflammatory or oncogenic conditions, the progression to neoplasia. The molecular drivers of ADM include inflammatory cytokines, oxidative stress, extracellular matrix remodeling, and transcriptional reprogramming. Notably, the activation of signaling pathways such as Notch, EGFR/RAS/MAPK, and Wnt/β-catenin play pivotal roles in regulating ADM and its progression toward pancreatic cancer. Furthermore, the AKT/GSK3β signaling axis emerges as a central regulator in the modulation of ADM and its subsequent transition to malignancy. Understanding the molecular mechanisms of ADM and its interplay with pancreatic stellate cells provides valuable insights into therapeutic targets that could interrupt the progression from chronic pancreatitis to pancreatic cancer. This review highlights the pathophysiology of CP, the role of ADM in inflammation-driven pancreatic carcinogenesis, and the signaling networks involved in this process. By examining the regulatory pathways that govern ADM, this article aims to provide a framework for future therapeutic strategies that could target ADM and delay the progression of CP to PDAC. Early intervention in the ADM process, particularly in its reversible stages, presents a promising approach for preserving acinar cell function, preventing fibrosis, and ultimately reducing the risk of pancreatic cancer.

Keywords: Chronic pancreatitis; Acinar-to-ductal metaplasia; Kaempferol; Signaling pathway

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1. Introduction

Chronic pancreatitis (CP) is a progressive fibroinflammatory disorder of the pancreas caused by the interplay of genetic susceptibility, environmental exposure, immune dysregulation, and other pathogenic factors [1]. It has traditionally been defined by irreversible pancreatic injury, characterized by acinar cell loss, activation of pancreatic stellate cells, excessive extracellular matrix deposition, and gradual impairment of both exocrine and endocrine function [2]. Contemporary clinical guidance also emphasizes the progressive structural and functional nature of this disease [3]. From a clinical perspective, CP should therefore be understood as a chronic, evolving disorder rather than a purely static fibrotic lesion [4].

The clinical importance of this transition lies in the persistent inflammatory and fibrotic microenvironment established during CP [5]. Chronic inflammation exposes pancreatic epithelial cells to repeated cycles of injury and regeneration, and acinar cell dysfunction itself can further reinforce fibrogenic remodeling [6]. Epidemiological and mechanistic studies indicate that hereditary CP markedly increases lifetime PDAC risk and can cooperate with oncogenic KRAS in early pancreatic carcinogenesis [7]. Morphologic work on ADM has further shown that chronic injury can drive a continuum from acinar dedifferentiation to PanIN formation [8]. This concept is consistent with broader models of ductal metaplasia in pancreatic disease [9]. Human transcriptomic profiling has likewise identified ADM-associated gene programs that connect inflammatory injury with neoplastic evolution [10].

2. Acinar-to-ductal metaplasia: Definition and pathological significance

Acinar-to-ductal metaplasia (ADM) is a reversible process of cellular reprogramming in which pancreatic acinar cells, in response to injury or inflammatory stress, lose their highly specialized secretory phenotype and acquire duct-like morphological and molecular characteristics [8]. During this transition, acinar markers such as amylase and carboxypeptidase A1 are downregulated, whereas ductal markers, including cytokeratin 19 (CK19) and SOX9, are upregulated [10]. Histologically, the normal acinar architecture is progressively replaced by pseudotubular structures with duct-like features [9].

The pathological significance of ADM is dual. Under physiological or transient injury conditions, ADM represents an adaptive regenerative response that temporarily increases epithelial plasticity [8]. Once the injurious stimulus is removed, these metaplastic cells may redifferentiate into mature acinar cells [9]. In contrast, under sustained inflammatory stimulation or in the presence of oncogenic events such as KRAS activation, ADM may become stabilized and evolve into a precursor lesion of neoplasia [7]. This inflammation-metaplasia-neoplasia sequence has been consistently supported by experimental and conceptual studies of pancreatic tumor initiation [8].

Thus, ADM occupies a pivotal position in the progression from CP to PDAC. It is both a regenerative response to injury and a potential gateway to inflammation-associated pancreatic tumorigenesis [7].

3. Inflammatory cytokines as direct inducers of ADM

Among the inflammatory cell populations present in CP, immune-cell remodeling is now recognized as a key determinant of disease progression [11]. Macrophages appear to play a particularly important role because they do not simply clear damaged tissue; they also actively shape epithelial cell fate [12]. Activated macrophages secrete pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which can directly stimulate acinar cells to undergo duct-like reprogramming [12]. This macrophage–epithelial crosstalk provides a

mechanistic basis for the idea that anti-inflammatory strategies may limit or reverse metaplastic transformation [11].

4. Core signaling networks governing ADM

ADM is not regulated by a single molecular pathway. Developmental pathway reactivation is a major component of the metaplastic program [13]. Metabolic rewiring is also an early event that helps acinar cells enter an injury-adapted state [14]. Wnt/β-catenin signaling contributes to regeneration-associated plasticity and expansion of metaplastic cells [15]. Inflammatory transcriptional programs mediated by STAT3 further stabilize this transition under chronic stress [16].

4.1. Notch signaling as a determinant of cell fate

Notch signaling plays an essential role in pancreatic lineage specification during development, and its reactivation in the adult pancreas is considered a major driver of ADM [13]. In experimental CP, the expression of Notch ligands such as Dll1 and Dll4, as well as downstream effectors such as Hes1, is markedly increased [13]. Following ligand binding, the Notch intracellular domain (NICD) translocates to the nucleus and interacts with RBP-Jκ to activate transcriptional programs that promote ductal identity while suppressing acinar differentiation. Inflammatory cytokines and macrophage-derived signals can further reinforce Notch activity, thereby creating a feed-forward mechanism that stabilizes ductal reprogramming [12].

4.2. EGFR/RAS/MAPK signaling as a hub of inflammatory reprogramming

The epidermal growth factor receptor EGFR/RAS/MAPK pathway is another central regulator of ADM. Experimental work has shown that early metabolic reprogramming and stress adaptation can cooperate with growth-factor signaling to facilitate acinar cell plasticity [14]. In genetically engineered mouse models, Kras-driven plasticity is sufficient to induce ADM and PanIN formation, and chronic pancreatitis strongly accelerates this process [7]. These observations support the view that EGFR/RAS/MAPK signaling links inflammatory stress to epithelial plasticity and early neoplastic transformation [8].

4.3. Wnt/β-catenin signaling in stemness and metaplastic expansion

The Wnt/β-catenin pathway is a key regulator of pancreatic development, regeneration, and cellular plasticity [15]. Under basal conditions, β-catenin is phosphorylated by the destruction complex composed of Axin, APC, and GSK3β, resulting in its degradation. Upon Wnt activation, this complex is disrupted, allowing β-catenin to accumulate, translocate to the nucleus, and activate genes associated with proliferation and progenitor-like features, including cyclin D1 and c-Myc [15]. In CP and early neoplastic remodeling, aberrant Wnt/β-catenin activity has been linked to metaplastic expansion and maintenance of plastic cell states [14].

4.4. NF-κB and STAT3 as inflammation-associated transcriptional effectors

NF-κB and STAT3 are key transcriptional regulators linking chronic inflammatory signaling to cellular reprogramming. In pancreatic neoplasia, persistent STAT3 activation promotes survival and dedifferentiation programs that are highly relevant to ADM [16]. Recent reviews have further emphasized that STAT3 signaling supports cell-state transitions and tumor-promoting inflammation in pancreatic disease [17]. Experimental evidence also indicates that a STAT3/integrin signaling axis can accelerate pancreatic cancer initiation, highlighting how

inflammatory signaling helps stabilize early metaplastic and neoplastic states [18].

5. The AKT/GSK3β signaling axis in ADM

5.1. Activation of the AKT/GSK3β pathway in chronic pancreatitis

The AKT/GSK3β axis is a key signaling node linking extracellular stress signals to intracellular changes in survival, metabolism, and cell fate. In CP, oxidative stress can potentiate this pathway by perturbing redox homeostasis and weakening phosphatase-dependent inhibitory control [19]. In addition, inflammatory mediators and stromal cues may reinforce PI3K-AKT signaling during chronic pancreatic injury.

Once activated, AKT phosphorylates multiple downstream substrates, among which GSK3β is particularly important. Phosphorylation of GSK3β at Ser9 inhibits its kinase activity and thereby alters the stability and function of several proteins involved in differentiation, proliferation, and β-catenin turnover [15].

5.2. GSK3β as a regulator of cell fate

GSK3β is a multifunctional serine/threonine kinase that remains constitutively active under basal conditions and regulates many substrate proteins. In ADM, its importance lies in the way it connects Wnt-driven plasticity with broader changes in cell-state control [15].

One major substrate of GSK3β is β-catenin. Under normal conditions, GSK3β-mediated phosphorylation targets β-catenin for proteasomal degradation. When GSK3β is inhibited by AKT, β-catenin becomes stabilized and accumulates in the nucleus, where it drives gene-expression programs associated with cell proliferation and progenitor-like features [15].

GSK3β may also influence the persistence of metaplastic signaling by regulating transcriptional and cell-cycle effectors. Loss of GSK3β activity can prolong ductal reprogramming and support stabilization of the ADM state [14].

5.3. Crosstalk between AKT/GSK3β and other pathways

The AKT/GSK3β axis is deeply integrated with other pathways involved in ADM. By inhibiting GSK3β, AKT can activate β-catenin signaling independently of canonical Wnt ligand stimulation [15]. AKT also cooperates with oxidative-stress responses that favor cell survival and plasticity during chronic pancreatic injury [19]. These interactions position AKT/GSK3β as a central signaling hub in CP-associated ADM, making it a highly attractive target for therapeutic intervention [14].

6. Molecular basis for the maintenance and loss of acinar cell identity

The identity of pancreatic acinar cells is maintained by a coordinated transcriptional network that supports secretory specialization, epithelial polarity, and lineage stability. Disruption of this network is a prerequisite for ADM and for the emergence of broader pancreatic cancer cell plasticity [20].

6.1. PTF1 and MIST1 in acinar cell identity

PTF1 serves as a central transcriptional regulator of acinar cell differentiation. By governing the expression of genes encoding digestive enzymes while concurrently repressing ductal lineage-associated programs, this

transcription factor complex is essential for sustaining acinar cell identity. MIST1 likewise preserves secretory organization, apical–basal polarity, and normal acinar function. When this acinar-specific transcriptional network is disrupted, cells become more vulnerable to injury-induced dedifferentiation and metaplastic conversion [10].

6.2. Epigenetic reprogramming during ADM

ADM is likewise accompanied by profound epigenetic reprogramming. Under conditions of chronic inflammation, acinar cells undergo substantial alterations in chromatin accessibility and DNA methylation. Increasing evidence indicates that this remodeling can be retained as a form of transitional cellular memory, thereby rendering cells more prone to re-enter plastic states and engage PI3K-linked tumor-promoting signaling pathways [21].

7. Bidirectional interaction between ADM and pancreatic stellate cells

ADM does not occur in isolation. It is closely linked to pancreatic stellate cell activation and fibrotic remodeling during CP [22]. Pancreatic stellate cells are now recognized as key players in both pancreatic homeostasis and disease progression [23]. Fibroblast heterogeneity further shapes the inflammatory and stromal landscape in pancreatitis and pancreatic cancer [24]. Gene-expression studies also suggest that stellate-cell programs evolve during the progression from acute to chronic pancreatitis [25].

7.1. Stellate cell-derived signals promote ADM

In CP, pancreatic stellate cells (PSCs), which normally remain in a quiescent state, are stimulated by inflammatory signals and undergo activation into a myofibroblast-like phenotype characterized by α-SMA expression [22]. Once activated, these cells produce abundant extracellular matrix components as well as a variety of soluble factors that remodel the epithelial niche [23]. More recent studies have shown that exosomal cargo derived from PSCs can directly regulate ADM and pancreatic regenerative responses, underscoring the complexity of stromal–epithelial crosstalk [26].

7.2. ADM cells sustain fibrotic remodeling

In contrast, metaplastic cells themselves also participate in sustaining the fibrotic microenvironment. ADM cells can release chemokines and cytokine-related mediators that recruit inflammatory cells and amplify stromal activation [27]. Through this reciprocal interplay, metaplasia, inflammation, and fibrosis become interconnected in a self-amplifying feedback loop during CP [24].

8. Reversibility of ADM and its therapeutic implications

One of the most important biological features of ADM is that it is, at least in early stages, reversible. When injurious stimuli are removed and the inflammatory microenvironment improves, metaplastic cells can redifferentiate into functional acinar cells [8]. Rebuilding a less fibrogenic stromal niche, including through retinoic-acid-related signaling, may support this reversal [28]. This reversibility has major therapeutic implications for early intervention in CP [29].

8.1. Signaling switches and redifferentiation

The balance between metaplasia and redifferentiation is controlled by multiple signaling pathways. In the context of persistent inflammation, sustained AKT activation and GSK3β inhibition favor maintenance of the ADM state [15]. When inflammatory signaling declines and stromal activation is restrained, acinar differentiation can be re-established more effectively [28]. This dynamic regulation highlights the stromal-inflammatory network as a practical therapeutic target [29].

8.2. A therapeutic window in early disease

The reversibility of ADM also suggests the existence of a therapeutic window in early CP. At this stage, metaplasia may still reflect an adaptive and potentially reversible response to injury [8]. In contrast, once ADM becomes fixed or is coupled with oncogenic alterations such as KRAS mutation, the potential for redifferentiation is likely to diminish substantially [7]. Identifying molecular markers that distinguish reversible from irreversible ADM will therefore be essential for precision therapy [29].

9. Conclusion

Taken together, current evidence supports a revised view of chronic pancreatitis as more than a fibrotic disorder. CP is a dynamic inflammatory disease in which persistent tissue injury, epithelial plasticity, stromal activation, and signaling reprogramming converge to promote both fibrosis and cancer susceptibility [1]. Within this framework, acinar-to-ductal metaplasia represents a central pathological event. It marks the loss of acinar identity, reflects the impact of the inflammatory microenvironment, and may serve as an early bridge between chronic injury and neoplastic transformation [30].

Among the signaling pathways involved in this process, the AKT/GSK3β axis is particularly important because it integrates inflammatory, oxidative, stromal, and growth-related signals with transcriptional and epigenetic mechanisms that determine cell fate [19]. A deeper understanding of reversible and irreversible ADM states may therefore provide a stronger basis for targeted strategies to interrupt the progression from chronic pancreatitis to pancreatic cancer [21].

Disclosure statement

The authors declare no conflict of interest.

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