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1 **Editorial on “A heterogeneous subtype of biliary epithelial senescence may**
2 **be involved in the pathogenesis of primary biliary cholangitis”.**

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4 **Title: Catching the STING: Unlocking Senescence and PD-L1 in PBC.**

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18 **Key words:** Cholangiocytes; Bile duct injury; Cellular senescence; Senescence-associated
19 secretory phenotype (SASP) ; Immune checkpoint inhibitors (ICI).

20

21 Primary biliary cholangitis (PBC) presents a persistent challenge in Hepatology, characterized
22 by its complex pathophysiology, autoimmune nature, and significant unmet therapeutic needs.
23 Although first-line treatments like ursodeoxycholic acid (UDCA) have improved outcomes
24 for many patients, up to one-third fail to respond adequately, underscoring the need for novel
25 therapeutic strategies [1]. Recent work by Sasaki *et al.* has shed light on the intricate
26 mechanisms driving PBC progression, revealing critical associations between biliary
27 epithelial cell (BEC) senescence, the cGAS-STING pathway, and programmed death-ligand 1
28 (PD-L1) (**Figure 1**). The cGAS-STING pathway plays a pivotal role in innate immunity by
29 detecting cytosolic DNA, typically arising from cellular stress or damage, and triggering
30 inflammatory responses [2]. This pathway induces the release of pro-inflammatory cytokines
31 and interferons, which contribute to chronic inflammation. In PBC, activation of cGAS-
32 STING in biliary epithelial cells (BECs) appears to contribute to cellular senescence and the
33 production of inflammatory mediators, exacerbating bile duct damage [3]. Notably, BECs in
34 the small bile ducts of PBC patients, especially those with chronic nonsuppurative destructive
35 cholangitis, frequently express senescence-associated markers such as beta-galactosidase,
36 p16(INK4), and p21(WAF1/CIP1) [4, 5]. These markers are rarely found in the bile ducts of
37 control livers, highlighting their pathological relevance to PBC. Furthermore, cellular
38 senescence in PBC is closely linked to the infiltration of myeloperoxidase-positive
39 inflammatory cells into the biliary epithelial layers [6], reinforcing the connection between
40 chronic inflammation and senescence-driven bile duct injury. PD-L1, an immune checkpoint
41 molecule, suppresses T cell activation by binding to the PD-1 receptor, enabling PD-L1-
42 expressing cells to evade immune-mediated destruction [7]. Senescent cells, which are central
43 to age-chronic inflammation (inflammaging), heterogeneously express PD-L1 [8]. PD-L1+
44 senescent cells are resistant to immune clearance, even in the presence of senescence-
45 associated secretory phenotypes (SASP), which amplify inflammation [9]. In mouse models,
46 blocking PD-1 significantly reduces PD-L1+ senescent cell populations, alleviates

47 inflammation, and improves age-related phenotypes, demonstrating the therapeutic potential
48 of immune checkpoint inhibition [10]. In the context of PBC, the study of Sasaki *et al.*
49 hypothesizes that activation of the cGAS-STING pathway plays a pivotal role in inducing
50 PD-L1 expression in senescent biliary epithelial cells (BECs). This mechanism may lead to
51 the accumulation of PD-L1+ senescent BECs, which evade immune surveillance and create a
52 pro-inflammatory microenvironment. Such a process could drive chronic inflammation and
53 progressive bile duct damage, hallmark features of PBC. The findings suggest that targeting
54 the cGAS-STING pathway to mitigate senescence, or employing immune checkpoint
55 inhibitors to specifically eliminate PD-L1+ senescent cells, represents a promising avenue for
56 innovative therapeutic strategies in PBC.

57 This research identifies a unique subtype of senescent BECs that express programmed
58 death-ligand 1 (PD-L1). These cells are predominantly found in damaged small bile ducts
59 associated with chronic nonsuppurative destructive cholangitis, while they are notably absent
60 in ductular reactions. This localization underscores the site-specific nature of their emergence
61 and suggests a direct role in PBC pathogenesis. Furthermore, the study reveals that the cGAS-
62 STING pathway acts as a crucial regulator of both cellular senescence and PD-L1 expression
63 in these cells. PD-L1 expression was found to be significantly elevated in senescent BECs
64 within damaged bile ducts in PBC. This expression is closely linked to senescence markers
65 such as p21 (WAF1/Cip1), indicative of acute senescence, rather than p16 (INK4a), which is
66 associated with chronic senescence [11]. Alongside this, the cGAS-STING pathway was
67 markedly upregulated in senescent BECs, not only in damaged bile ducts but also in ductular
68 reactions. This upregulation correlates with an increase in SASP such as interferon and CCL2,
69 which are known to drive chronic inflammation.

70 The therapeutic implications of these findings are promising. *In vitro* experiments
71 demonstrated that siRNA-mediated knockdown of STING significantly reduced PD-L1
72 expression, cellular senescence, and SASP production in BECs. This positions the cGAS-

73 STING pathway as a potential therapeutic target in PBC, offering a novel approach to
74 modulating senescence and immune evasion. However, the application of immune checkpoint
75 inhibitors (ICI) targeting PD-1 or PD-L1 in autoimmune diseases like PBC requires careful
76 consideration due to their critical role in maintaining immune tolerance. For instance, PD-1
77 and PD-L1 are essential for protecting against type-1 diabetes (T1D). In non-obese diabetic
78 (NOD) mice, PD-1 deficiency accelerates the onset and frequency of diabetes, promoting T
79 cell infiltration into pancreatic islets [12, 13]. Additionally, blocking PD-1 or PD-L1 (but not
80 PD-L2) in NOD mice rapidly induces diabetes, driven by the expansion of glutamic acid
81 decarboxylase (GAD)-reactive T cells [12, 13]. These findings underscore the delicate
82 balance PD-1/PD-L1 maintains between preventing autoimmune attacks and enabling
83 immune surveillance. In the context of PBC, disrupting this axis might risk exacerbating
84 autoimmunity or triggering additional autoimmune conditions, particularly in patients with
85 pre-existing immune dysregulation. Consequently, while ICI may hold promise for targeting
86 PD-L1+ senescent cells in PBC, their potential to impair immune tolerance demands rigorous
87 evaluation. Strategies to mitigate such risks, including selective targeting of PD-L1+
88 senescent cells or combination therapies that preserve systemic tolerance, must be explored to
89 ensure safe and effective treatment options.

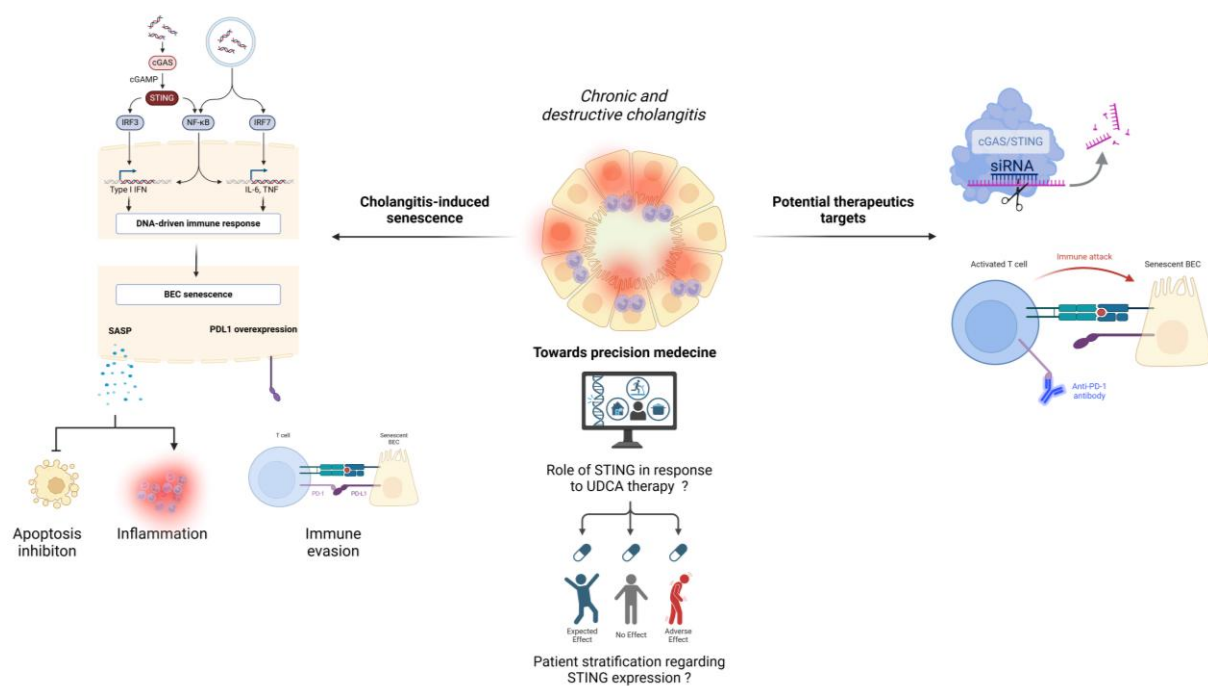
90 The discovery of PD-L1-positive senescent BECs introduces a new layer of
91 complexity to our understanding of PBC. By evading immune surveillance, these cells may
92 perpetuate chronic inflammation and bile duct damage. Moreover, senescent cells are resistant
93 to programmed cell death, such as apoptosis, rendering them virtually immortal while
94 avoiding malignant transformation (*i.e.*, cancer) [14]. This unique characteristic allows
95 senescent cells to persist in the tissue microenvironment, continuously secreting SASP.
96 Through the SASP, these cells profoundly influence disease progression by amplifying
97 inflammation, disrupting tissue homeostasis, and recruiting immune cells that further
98 contribute to chronic damage. In the context of PBC, this combination of immune evasion,

99 resistance to apoptosis, and SASP-driven inflammation likely represents a central mechanism
100 underlying bile duct injury and progressive fibrosis. Furthermore, the localized activation of
101 the cGAS-STING pathway in senescent BECs underscores its critical role in driving disease
102 progression through SASP-mediated inflammation and PD-L1 upregulation. Looking ahead,
103 several questions remain unanswered. The heterogeneity of senescent BECs in PBC warrants
104 further investigation, as understanding the drivers of this diversity could unlock new
105 therapeutic possibilities.

106 An important avenue for future research is to explore whether non-responders to
107 UDCA exhibit distinct levels of STING expression or activation compared to responders.
108 Since STING plays a key role in modulating both senescence and inflammation, differential
109 expression or activity of this pathway could underlie the variability in treatment responses.
110 Investigating this could provide valuable insights into the molecular basis of UDCA
111 resistance and help stratify patients based on their molecular profiles. Such stratification
112 might enable the identification of patients who could benefit from therapies targeting STING
113 or PD-L1+ senescent cells, potentially improving treatment outcomes for those who do not
114 respond to current therapies.

115 Translating these molecular insights into effective treatments while minimizing
116 adverse effects represents a critical next step. Moreover, the broader implications of this
117 research for other cholangiopathies, such as primary sclerosing cholangitis (PSC) or biliary
118 atresia, merit exploration. Sasaki *et al.* have provided compelling evidence linking PD-L1-
119 positive senescent BECs and the cGAS-STING pathway to PBC pathogenesis. This study not
120 only advances our understanding of the disease but also identifies actionable molecular targets
121 with significant therapeutic potential. As the field of Hepatology moves toward precision
122 medicine, these findings lay the groundwork for developing more tailored and effective
123 interventions for PBC and other related conditions.

124



125
 126 **Figure 1. The cGAS-STING pathway and PD-L1 in PBC: mechanisms and therapeutic**
 127 **perspectives.** On the left, the cGAS-STING pathway is activated by cytosolic DNA,
 128 triggering downstream signaling through IRF3, NF-κB, and IRF7, leading to the release of
 129 type I interferons (IFN) and pro-inflammatory cytokines such as IL-6 and TNF. These signals
 130 contribute to biliary epithelial cell (BEC) senescence, characterized by the production of
 131 senescence-associated secretory phenotypes (SASP) and overexpression of PD-L1. This
 132 combination promotes immune evasion, resistance to apoptosis, and inflammation. On the
 133 right, therapeutic approaches are highlighted. The use of siRNA to inhibit the cGAS-STING
 134 pathway reduces senescence and SASP production, while immune checkpoint inhibitors
 135 targeting PD-1 or PD-L1 restore immune surveillance by enabling T-cell-mediated clearance
 136 of senescent cells. At the bottom, the figure emphasizes the need for precision medicine,
 137 suggesting that stratification of patients based on STING expression and molecular profiling
 138 could help predict responses to therapies such as UDCA or targeted treatments. This approach
 139 could optimize treatment outcomes and minimize adverse effects in PBC patients.

140

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142

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147

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155

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157

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