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Research Progress on the Role of the Constant Region of Immunoglobulin γ-1 Heavy Chain in Chronic Respiratory Diseases

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Abstract: *Immunoglobulin gamma-1 heavy chain constant region (IGHG1) forms the scaffold of IgG1, governing complement fixation, Fc-γ-receptor cross-linking and glycosylation-dependent effector programming. Despite divergent triggers, chronic obstructive pulmonary disease, asthma, bronchiectasis and lung cancer converge on three core pathobiological pillars: small-airway occlusion, recurrent exacerbations and deranged mucosal immunity. Whether and how IGHG1 orchestrates this shared trajectory remains enigmatic. Here we synthesise pre-clinical and clinical datasets to chart a unifying IGHG1-centric roadmap that links humoral dysregulation to disease onset , progression and exacerbation across the chronic respiratory spectrum, and outline how precision engineering of the IGHG1–Fc axis may deliver pan-disease immunomodulatory therapeutics.*

Keywords: *Immunoglobulin γ-1 heavy chain constant region; Chronic obstructive pulmonary disease (COPD); Bronchial asthma; Bronchiectasis; Lung cancer*

1. Introduction

The human respiratory tract filters more than 10,000 liters of dust- and microbe-laden air every day, yet it sustains a state of "near-sterility and low-grade inflammation" for decades. The first line of defense is the intact mucosal immune system (MIS) that blankets the nose, pharynx, trachea and bronchi[1]. When the numerical or functional integrity of the MIS is compromised, acute infections smolder into chronicity, harmless antigens are misread, and self-tissues are inadvertently injured—culminating in chronic respiratory disease. Among MIS constituents, immunoglobulin G (IgG) serves as "distal reinforcement" [2]. IgG1, the most abundant subclass (60–65% of serum IgG), circulates as a monomer. Bronchial epithelium bidirectionally shuttles IgG1 via the neonatal Fc receptor (FcRn): continuous luminal secretion confronts pathogens, while retrograde retrieval of antigen–IgG1 complexes bridges humoral and cellular immunity and safeguards airway homeostasis[3]. The gene encoding the IgG1 heavy-chain constant region, IGHG1, simultaneously dictates expression level, half-life and effector repertoire, acting as a molecular on/off switch for this defense axis [4].Although chronic obstructive pulmonary disease (COPD), bronchial asthma, bronchiectasis and lung cancer have distinct etiologies, they share the phenotype of persistent airflow limitation and recurrent exacerbations—≥70 % of which are infection-driven and traceable to MIS dysfunction [5]. IGHG1 is reproducibly skewed in expression or function across these disorders: viral challenge elicits an early surge followed by a gradual decline in transcript abundance. In COPD, lower IGHG1 expression correlates with more frequent exacerbations in the preceding year [6]. Yet the continuum from IGHG1 transcription to functional IgG1 remains fragmentarily mapped. Here we provide a systematic dissection of this regulatory cascade.

2. Structure of IGHG1

IgG is the "field marshal" of humoral immunity, circulating in serum, interstitial fluid, lymph, placenta, saliva and colostrum. Each molecule is a canonical "Y-shaped" monomer assembled from two identical γ-heavy chains and two κ/λ-light chains [7]. Four subclasses exist—IgG1, IgG2, IgG3 and IgG4—of which IgG1 is the most abundant in serum and displays the highest affinity for all Fc-γ receptors (FcγRI, II and III) [8]. The gene encoding the IgG1 heavy-chain constant region, IGHG1, resides at 14q32.33 within the immunoglobulin heavy-chain super-locus. Its constant region is linearly arranged

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as follows: the N-terminal CH1 domain clamps the CL domain [9]; a flexible hinge permits independent Fab and Fc movement; the CH2 domain carries the Asn297 glycan that forms the core interface for both Fc-γ receptors and C1q [10]; the C-terminal CH3 domain recognizes FcRn and dictates antibody persistence in serum. Together, CH2 and CH3 constitute the functional Fc segment—the command center of immune regulation [11]. IgG1 is secreted as a pre-assembled monomer and exerts its effector functions immediately upon reaching the airway lumen, without further maturation or processing [12].Recent studies reveal an unexpected twist: beyond its canonical production after V(D)J recombination in B cells, IGHG1 can be hijacked by epithelial-derived tumors. Oncogenic STAT3/NF-κB and IL-6/JAK signaling directly engage the IGHG1 promoter, bypassing V(D)J recombination to drive full-length transcription of CH1-hinge-CH2-CH3 [13]. The resulting cancer-derived IgG (cIgG) carries a unique glyco-signature: CH1-Asn162 is hyper-sialylated and hyper-fucosylated, yet galactose-deficient. This aberrant glycan is precisely targeted by the monoclonal antibody RP215; once RP215 locks on, the pro-tumorigenic signaling of cIgG is extinguished and tumor growth is restrained [14]. Thus, IGHG1 can switch from immune guardian to tumor-specific Achilles' heel.

3. Biological Functions of IGHG1

IGHG1 (Immunoglobulin Heavy Constant Gamma 1) is a double-edged sword: it is both an antibody and a signaling molecule. Virus neutralization is initiated by the Fab domain [15], and meta-analyses now list viral neutralization as the prime effector function of IgG1 [16]. Thandeka et al. showed that, even when the variable region is identical, swapping the constant domain alone can markedly alter protection against HIV, proving that the IGHG1 scaffold intrinsically encodes neutralizing capacity [17]. In murine pneumonia models, boosting IGHG1 titers against either Streptococcus pneumoniae or SARS-CoV-2 directly attenuates lung injury [18], and tetanus toxoid-elicited IgG1 neutralizes the toxin by locking onto its C-terminal domain [19].Beyond neutralization, the Fc segment engages Fc-γ receptors (FcγR) on leukocytes, orchestrating opsonophagocytosis. As early as 1965 Rowley et al. demonstrated that virtually all phagocytic signals evoked by anti-Salmonella Adelaide IgG mapped to the Fc portion [20]. Among the four subclasses, IgG1 displays the highest affinity for FcγRI, FcγRIIa and FcγRIIIa, rapidly recruiting neutrophils, macrophages and NK cells to execute antibody-dependent cellular phagocytosis (ADCP) and cytotoxicity (ADCC) [21]. Winkler et al. found that the more IgG1 a COVID-19 convalescent serum contained, the stronger its RBD-specific ADCP; introducing the LALA mutation that ablates FcγR binding erased ADCP/ADCC without affecting neutralization [22]. Likewise, after ChAdOx1-nCoV-19 vaccination, peripheral IGHG1 transcript levels rise in lockstep with monocyte phagocytic scores[23]. Renal-tubular epithelial cells engineered to over-express IGHG1 in mice trigger macrophage influx, whereas IGHG1 silencing down-regulates the phagocytic genes Mrc1 and Cd68 [24].IgG1 also dominates classical complement activation. Residues D270, K322 and P329 within the Fc pocket bind C1q with high affinity, igniting the C4→C3→MAC cascade and lysing target cells; the vigor of this interaction directly sets the magnitude of complement-dependent cytotoxicity (CDC) [25]. Luminex assays show that microspheres coated with IgG1 capture far more C1q than those decorated with IgG2 or IgG4, reaffirming IgG1 as the subclass of choice for complement ignition [26]. Trastuzumab exemplifies the clinical payoff: its Fc engages FcγRIIIa on NK cells, erasing HER2-positive tumor cells via ADCC, and the magnitude of lysis is tightly modulated by the FcγRIIIa-V158 polymorphism [27].Yet IGHG1 is no longer exclusive to plasma cells. Within the tumor microenvironment, epithelium-derived "cancer IgG" (cIgG) can subvert immunity. Wang et al. showed that cervical carcinoma cells secreting cIgG proliferate faster, release more inflammatory cytokines and resist apoptosis [28]. Hypersialylated cIgG can also block CDC and paralyze T cells, facilitating immune escape [13]. Thus, in anti-infectious immunity IGHG1 is a loyal sentinel, whereas in cancer it may morph into an accomplice. How—and when—this Jekyll-to-Hyde switch occurs in chronic lung disease remains a critical open question.

4. Roles of IGHG1 in chronic respiratory diseases

4.1 Chronic Obstructive Pulmonary Disease

Persistent airflow limitation is the pathological hallmark of COPD. Cigarette smoking remains the dominant risk factor; cessation can partially restore lung function in mild-to-moderate disease, but once the stage is severe inflammation progresses even after quitting [29]. The root cause is a skewed B-cell program and an IgG1 deficit. In smokers who develop COPD, peripheral memory B cells shift toward IgG production, whereas healthy smokers retain an IgA-dominant profile ; Ma et al. further documented a net increase in total IgG protein [30]. Multi-centre studies consistently show that serum IgG1 is lower in

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COPD than in controls during both stable phases and exacerbations, and the level is inversely related to annual exacerbation frequency and hospitalisation risk[31]. Alen and Thomash et al. found that, in ex-smokers with severe disease, bronchial epithelial IGHG1 mRNA and BALF IgG1 fall in parallel and correlate weakly with FEV1 %pred, implying that the lower the IGHG1, the tighter the airflow limitation [32]. Conversely, sputum IgG1 protein is elevated in the emphysematous phenotype, suggesting a compartmental "leak" or compensatory local secretion [33]. Roughly one-third of patients with asthma–COPD overlap harbour an IgG1/IgG3 deficiency and experience more frequent hospital admissions and faster FEV1 decline [34].The underlying control circuits involve class-switching stimuli and glycosylation defects. The BAFF–APRIL–CD40L axis is amplified, driving B cells toward IgG1 [35]; CpG-ODN acting via TLR9–MyD88–STAT3 can induce the switch directly [36]; cigarette smoke delivers microbial DNA that chronically engages TLR7/9 on pulmonary B cells, again up-regulating IgG1 [37]. During exacerbations IFN-γ surges, and via STAT1 suppresses IL-4–STAT6 signalling, biasing the response toward IgG3 and leaving functional IgG1 short [38]. COPD plasma IgG1 carries a glycan signature of "low galactose, high core fucose, low sialic acid" that tilts the balance toward pro-inflammatory engagement and away from anti-inflammatory signalling, creating antibodies that "miss the mark but hit hard" [39]. Specifically, agalactosylated IgG1 binds activating FcγRIIIa more avidly, amplifying neutrophil respiratory burst, whereas the lack of sialic acid deprives the molecule of the anti-inflammatory activity characteristic of IVIG [40]. Zhou et al. showed that this glyco-signature is a sensitive and stable early biomarker of COPD [41].Therapeutically, re-instating "healthy" glyco-IgG1 is already showing promise. IVIG—rich in naturally glycosylated IgG1—reduces moderate-to-severe exacerbation rates without increasing sputum retention [42]; enzymatic "re-glycosylation" of patients' own IgG1 with B4GalT1 plus ST6Gal1 achieves an anti-inflammatory potency comparable to IVIG [43]. Collectively, the abundance, glycan profile and functional activity of IGHG1 are not only predictive of COPD progression but also actionable targets for precision immune intervention.

4.2 Bronchial asthma

Asthma is no longer a single entity but a clinical syndrome woven from multiple inflammatory endotypes whose shared features are chronic airway inflammation, airway hyper-responsiveness (AHR) and reversible airflow limitation. The dogma of IgE-driven type-I hypersensitivity cannot explain why IgE-knockout mice develop AHR and pulmonary eosinophilia equivalent to wild-type, while displaying markedly elevated IgG1. Clinical and cohort studies repeatedly show that house-dust mite [44], cat dander [45] and ovalbumin [46] specific IgG1 are higher in serum, sputum and BALF than in controls, and correlate positively with the incidence and intensity of the late asthmatic response (LAR) [47]. During acute attacks serum IgG1 rises step-wise with symptoms and falls rapidly after treatment; its concentration is inversely related to FEV1/FVC and FEV1 %pred . Out et al. reported an increased IgG1/IgG ratio in asthmatic BALF [48]; Robinson et al. further demonstrated that IGHG1 peptide abundance in sputum and BALF increases in parallel with eosinophil counts [49]. Hales et al. pointed out that different epitopes of the same allergen can induce "high-affinity" or "low-affinity" IgG1; only the former triggers eosinophil degranulation via FcγRII, thereby amplifying inflammation [50].Thus, in asthma IGHG1 displays an "acute surge–remission decline" dynamic governed by a three-tier control module. First, quantity is set by germline polymorphisms and the IL-4/STAT6–NF-κB axis. The G1m allotype sets the upper limit: children with G1m(f/f) express higher total and allergen-specific IgG1 than G1m(a/a) carriers [51]. IL-4/IL-13 signal through STAT6 to induce class switching, a process that also requires concurrent JAK–STAT and NF-κB inputs ; inhibition of either arm synchronously down-regulates pulmonary IGHG1 transcription [52]. Second, function is calibrated by glycosylation. During exacerbations the fraction of low-galactosyl IgG1 rises, favouring engagement of activating FcγRIIIA and granulocyte influx; during remission high-galactosyl IgG1 predominates, shifting the signal toward inhibitory FcγRIIB and creating negative feedback . Finally, FcγR cross-talk sustains an eosinophil forward loop. High-affinity IgG1–immune complexes cross-link FcγRIII on eosinophils, driving degranulation and IL-5 release that reinforces the Th2 milieu and keeps IGHG1 transcription high [52]. In short, IGHG1 operates as a positive tuner of asthmatic inflammation through a "gene–glycan–receptor" triad.

4.3 Bronchiectasis

Data on IGHG1 in bronchiectasis (BE) are sparse. The essence of BE is irreversible destruction of bronchial wall elasticity and supporting structures, producing permanently dilated airways locked in an "infection–inflammation–tissue destruction–re-infection" cycle . Sputum IgG1 is only ~10 % of paired serum levels, yet total IgG1 output from inflamed segments is significantly higher than in controls, indicating that mucosal plasma cells remain active [53]. Serum IgG1, however, is lower in BE than in

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healthy subjects, and a subset of patients have absolute IgG1 deficiency [54]. Stenlander et al. confirmed that low serum IgG1 tracks with both lung-function decline and increased exacerbation frequency [55]. Vendrell et al. further showed that some patients mount a sub-normal antigen-specific IgG1 response despite normal total IgG, implying a functional IgG1 defect [56], a mechanism De Gracia already in 1996 listed as an independent driver of recurrent infection in BE [57].Pseudomonas aeruginosa (PA) and Acinetobacter baumannii are independent risk factors for exacerbations over the next year in severe BE [58]. During exacerbations PA type-III secretion system effectors ExoS/ExoY are highly expressed and their levels are inversely related to IgG1 [59]. Li-Yan et al. demonstrated that PA auto-inducers amplify the IL-10/STAT3 axis via lasR/rhlR, skewing B cells toward IgG2/IgG4 . Once inflammation becomes chronic, TGF-β docks Smad2/3 onto the IGHG1 enhancer while recruiting FOXP3+ regulatory T cells that release granzyme B to prune plasma cells, again silencing IGHG1 [60]. Collectively, BE is characterised by compensatory local over-production of IgG1 within the airway mucosa, systemic shortfall, and antigen-specific hypo-functionality.

4.4 Lung Cancer

Lung cancer leads global and Chinese cancer statistics for both incidence and mortality. Pathologically it is split into non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). Classical immunology dictates that IgG is produced only by B cells, yet accumulating evidence over the past decade shows that tumor cells can “autonomously” generate cancer-derived IgG (cIgG). Unlike native antibodies, cIgG is largely cytoplasmic or membrane-bound and chronically activates MAPK/ERK, PI3K/AKT and allied signaling axes to promote proliferation, suppress apoptosis and re-shape the immune micro-environment. Huang first documented high IGHG1 expression in lung adenocarcinoma specimens that was positive for recombinase enzymes but negative in paired normal tissue, establishing the “non-B-cell” identity of cIgG. Tumor IGHG1 levels are consistently higher than in matched adjacent lung and correlate positively with TNM stage, nodal metastasis and poor survival; multivariate Cox analysis identifies IGHG1 as an independent prognostic risk factor [61]. Yang identified an IGHG1$^+$ sub-population in SCLC that associates with high MYC expression and liver metastasis, implying pro-metastatic potential .Post-translational modifications endow cIgG with even stronger tumor-promoting activity. Lung adenocarcinomas are enriched in sialylated IgG (SIA-cIgG) to a far greater extent than normal lung, providing a cancer-specific molecular signature [62]. In a lung squamous-cell PDX model, RP215-mediated neutralization of cIgG reduced tumor volume; mechanistically, cIgG promotes proliferation by inhibiting NO generation and activating the MEK/ERK/c-Myc axis, prompting the inclusion of RP215-IGHG1 staining in post-operative risk stratification [63].Multiple layers of regulation drive IGHG1 over-expression. At the transcriptional level, HIF-1α [64], Wnt/β-catenin [65], NF-κB/STAT3 [66] and THBS2 directly occupy the IGHG1 promoter to launch a non-B-cell transcriptional programmer. Post-transcriptionally, hypersialylation at Asn162 (SIA-cIgG) enables novel binding to Siglec-7/9 and thereby suppresses CD8$^+$ T-cell cytotoxicity [62]. Functionally, IGHG1 enhances DNA-break repair via PI3K/AKT/DNA-PKcs to mediate radioresistance, promotes migration/invasion through the FAK/Src–MTA1–EMT axis, and re-models the micro-environment via chemokine–receptor circuits. In hIgG1-G396R humanized mice, cIgG1 cross-linked to FcγRIV activates DC cross-presentation, increases CD8$^+$ T-cell infiltration and reduces M2-TAM abundance [18]. Xiaolu Cui showed that responders to neoadjuvant PD-1 blockade undergo class-switching from IgA to IgG1/3 within intratumorally B cells; IGHG1$^+$ plasma cells co-localize with CD4$^+$IL-21$^+$ T cells in mature tertiary lymphoid structures, driving M2→M0 repolarization, indicating that IGHG1 is a key molecular switch for the “cold-to-hot” transition[67]. Prazanowska likewise found high IgG1 and low IgA in the major pathological response (MPR) group, whereas non-responders displayed the opposite pattern [68]. In vitro and in vivo interference experiments demonstrate that silencing or neutralizing IGHG1 simultaneously down-regulates the aforementioned pathways and markedly suppresses tumor proliferation, metastasis and immune evasion, establishing a causal role for the first time [64].Collectively, IGHG1 in lung cancer displays the “triple-high” signature of high expression, high modification and high prognostic value, moving the field from the “whether it is expressed” stage to the “how it drives disease” stage, and positioning IGHG1 as a key molecular marker of malignant phenotype and a promising therapeutic target.

5. Conclusion

In summary, IGHG1 safeguards pulmonary homeostasis through multimodal mucosal immune functions that include pathogen neutralization, immune exclusion and immunomodulation, yet its contributions to lung disease remain incompletely defined. Four critical gaps persist: (i) whether IGHG1

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in the airways originates from local B-cell secretion or simply reflects plasma transudation; (ii) whether it actively drives—rather than merely accompanies—inflammatory or oncogenic processes; (iii) whether pathways beyond the MTA1 axis govern cell migration and immune evasion; and (iv) whether IGHG1 can serve as a disease-specific or prognostic biomarker for COPD, lung cancer and related disorders. Given its therapeutic potential, mechanistic dissection of IGHG1 in pulmonary pathobiology warrants intensified investigation.

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