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From Inherited Risk to Rare-Cell Networks: 11q23.1, POU2AF2 and Tuft-Cells in Colorectal Cancer

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Abstract

Common genetic variation has transformed the understanding of colorectal cancer (CRC) susceptibility, but biological mechanisms linking most risk loci to tumour initiation remain unresolved. The 11q23.1 locus illustrates how inherited variation can implicate a rare epithelial population: colonic tuft-cells. Recent work has identified rs3087967 as a prioritised candidate eQTL variant at 11q23.1 and implicated altered expression of *POU2AF2*, which encodes a tuft-cell-associated transcriptional co-activator. Integration of bulk RNA sequencing, single-cell transcriptomics, chromatin accessibility, human tissue imaging and mouse models supports a model linking 11q23.1 variation to altered tuft-cell abundance and transcriptional programmes. This mini-review discusses the enigmatic context-dependent roles of tuft-cells, evidence supporting the 11q23.1-*POU2AF2* model, and the broader possibility that inherited CRC-susceptibility involves rare colonic cell types that influence epithelial homeostasis before tumour initiation.

Inherited CRC-susceptibility and rare colonic cells

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide, with twin and family studies estimating that inherited genetic factors account for ~12-40% of variation in CRC-risk[1–4]. Over the past decade, genome-wide association studies (GWAS) and large-scale trans-ancestry meta-analyses have identified over 200 independent CRC-risk associations, transforming our understanding of the genetic architecture of disease risk[5–7]. Yet, despite the scale of these discoveries, the biological mechanisms through which most risk variants influence tumour initiation remain unclear. A major challenge in post-GWAS interpretation is that most CRC-associated risk variants reside within non-coding regions of the genome. While this suggests that disease susceptibility is frequently mediated through subtle alterations in gene regulation, cellular state and tissue homeostasis rather than disruption of protein-coding sequences, the identity and contextual relevance of disease-effector genes remain unclear.

Previous efforts to interpret CRC-risk loci have largely relied on bulk-tissue analyses, potentially obscuring biologically important effects occurring within rare or highly specialised epithelial cell populations. This is increasingly relevant in cancer biology, where rare cell types can exert disproportionate effects on tumour initiation, progression, therapy response and post-treatment adaptation[8–10]. Recent advances in single-cell transcriptomics, spatial-profiling and increasingly granular human datasets are reshaping this landscape, enabling risk loci to be studied at unprecedented cellular resolution.

Rather than acting uniformly across all epithelial compartments, genetic susceptibility may preferentially perturb certain epithelial cell types that influence nutrient sensing, immune modulation and intercellular communication. Among these, tuft-cells have come into focus as a poorly understood epithelial population within the colon.

Tuft-cells are rare, chemosensory epithelial cells, with established roles in immune function within the small intestine[11]. However, the functional significance of colonic tuft-cells remains considerably less defined. While tuft-cell-associated transcriptional programmes have been implicated in inflammatory responses, epithelial repair and tumorigenesis, it remains unclear whether these cells actively suppress CRC initiation or instead represent an adaptive response to epithelial injury and remodelling[12–14]. Interpretation is further complicated by the inconsistent use of tuft-cell markers across studies[15–17]. Reliance on single markers, rather than overlapping expression of multiple tuft-cell defining markers, complicates interpretation of what constitutes a true 'tuft-cell' in both normal and neoplastic tissue.

Post-GWAS mechanistic understanding of the 11q23.1 CRC-risk locus

Evidence linking inherited CRC-susceptibility to tuft-cell biology has emerged from the 11q23.1 locus, initially identified by our group through GWAS. Variation at 11q23.1 has consistently been associated with CRC-risk across multiple population cohorts[18], yet the biology underlying this remained unclear. This locus contains several linked tagging variants, including the widely reported rs3802842 and additional candidates such as rs11213801, rs7130173, rs10891245 and rs3087967[19]. High linkage disequilibrium across this region complicates identification of the most informative variant. Expression quantitative trait loci (eQTL) analyses showed local cis-effects on neighbouring genes, including *POU2AF2, POU2AF3* and *COLCA1*, but their proximity and correlated expression complicated efforts to disentangle which gene or regulatory region is most relevant to CRC-risk[19–22].

Our recent work investigated rs3087967, located in the 3'-untranslated region of *POU2AF2*, as a candidate variant at 11q23.1. Colocalization analysis, assessing whether gene expression and CRC-susceptibility share a causal variant, supported shared genetic associations between CRC-risk and expression of *POU2AF2*, *POU2AF3* and *COLCA1*. Although several linked variants have been proposed as candidates, rs3087967 was the only variant shared across the colocalization-derived 95% credible sets for all three cis-eQTL targets. Here, 95% denotes cumulative posterior support under the shared-causal-variant hypothesis; the shared-association prior was $p12=10^{-4}$. Conditioning on rs3087967 removed evidence for additional independent cis-eQTL effects, supporting its prioritisation as a marker of the regulatory association. Although this does not experimentally prove that rs3087967 is the causal variant, these analyses support it as the strongest statistical representative of the CRC-risk signal at 11q23.1[19,21,22].

POU2AF2 and the tuft-cell transcriptional programme

The 11q23.1 association also extended beyond local genes. Across independent human colonic mucosa datasets, rs3087967 acted as a trans-eQTL, influencing a wider network of distant genes highly enriched for tuft-cell markers, including *TRPM5, SH2D6, SH2D7, HTR3E, LRMP, PLCG2* and *POU2F3*, all except the latter of which reside on distant chromosomes. Summary-data-based Mendelian Randomisation (SMR v1.3.1) linked decreased expression of 21 refined trans-eQTL target genes to CRC-risk. These findings support the potential relevance of the 11q23.1-associated tuft-cell transcriptional programme in CRC-susceptibility, and further work is required to establish that altered expression of these genes mediates risk[19,21,22].

While these associations help nominate additional disease-relevant genes, their regulatory mechanisms and specific context of dysregulation remained elusive. Integrating bulk RNA-sequencing, single-cell transcriptomic and chromatin accessibility datasets showed that refined 11q23.1 trans-eQTL targets were identified as preferentially expressed in tuft-cells, correlating most strongly with *POU2AF2* expression. Analysis of publicly available, single-cell ATAC sequencing of healthy human colonic epithelium also demonstrated cell clusters with chromatin accessibility enriched for both refined trans-eQTL targets and putative tuft-cell marker genes. Genomic regions bound by POU2AF2/POU2AF3 in tuft-like lung cancer cell lines showed greater chromatin accessibility in colonic tuft-cells, while trans-eQTL targets showed enrichment for *POU2F3*-associated motifs. Together, these findings support a model in which inherited variation at 11q23.1 may alter a *POU2AF2*-associated tuft-cell transcriptional network involving *POU2F3*-regulated genes[19,21,22] (**Figure 1**).

This interpretation is strengthened by orthogonal work defining the *POU2F3-POU2AF2/POU2AF3* axis as a core regulatory complex of tuft-cells. *POU2F3* is an established master regulator of tuft-cell differentiation, while *POU2AF2* and *POU2AF3* function as transcriptional co-activators that are recruited to chromatin through *POU2F3*-associated regulatory complexes. Newer mechanistic studies show that *POU2AF2* can regulate enhancer activity in a *SWI/SNF*-dependent manner, suggesting how altered *POU2AF2* expression could reshape tuft-cell-associated transcriptional programmes[23–25].

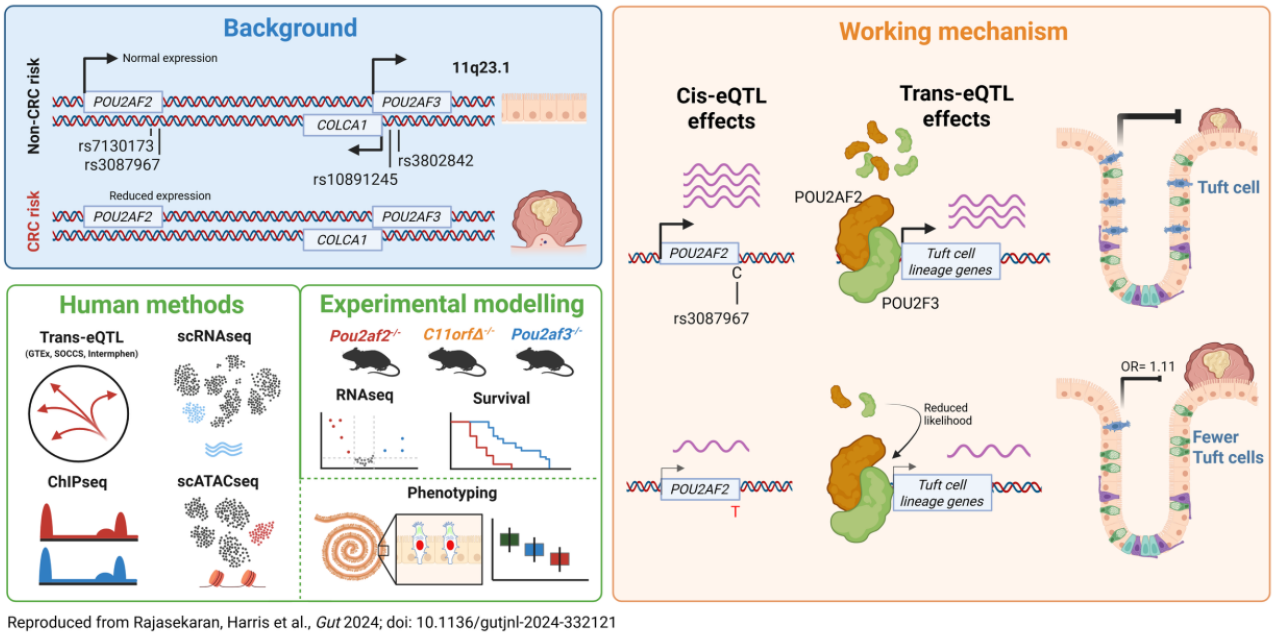

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Figure 1: Proposed links between genetic variation at 11q23.1, colorectal cancer risk and *POU2AF2*-dependent dysregulation of colonic tuft-cells: Schematic summary of a proposed mechanism by which inherited variation at the 11q23.1 CRC-risk locus alters colonic tuft-cell biology. CRC-associated variants at this locus are associated with expression of cis-eQTL target genes including *POU2AF2*, *POU2AF3* and *COLCA1*. Evidence from trans-eQTL mapping, single-cell RNA sequencing, ChIP-seq and single-cell ATAC-seq, considered alongside experimental mouse modelling of *Pou2af2* and *Pou2af3*, prioritises *POU2AF2* as a candidate effector gene. The model proposes that rs3087967-associated changes in *POU2AF2* expression may influence a broader trans-eQTL network enriched for tuft-cell lineage genes through *POU2F3*-regulatory programmes, though the causal pathway linking inherited variation, tuft-cell biology and CRC-susceptibility remains unresolved.

Defining the colonic tuft-cell

In the small intestine, tuft-cells coordinate type 2 immune responses, microbial metabolite sensing, and epithelial repair[11,26]. In the colon, however, their abundance, marker profile and function appear less defined and more context dependent. This raises the question of whether tuft-cells are dynamic specialised signalling cell types that become more relevant when the mucosa is exposed to stress and injury.

This question is critical because tuft-cell biology involves several processes relevant to early tumorigenesis. Tuft-cells can be viewed as epithelial sentinels that integrate luminal and tissue-derived cues, translating them into immune, neuronal, and epithelial responses. A small shift in tuft-cell transcriptional state could therefore have amplified consequences for microbial or metabolite sensing, epithelial repair, inflammatory tone, prostaglandin-related signalling, and adaptation to genotoxic stress[27–29].

Tuft-cell identity cannot be inferred reliably from a single marker. POU2F3 is a sensitive indicator of tuft-cell differentiation, but recent pathology studies suggest that it is not fully specific across tumour contexts, whereas co-expression of POU2F3 with POU2AF2 may provide a more robust readout of tuft-cell-like identity. Recent single-cell studies also suggest that human colonic tuft-cells may comprise multiple transcriptional subsets, reinforcing the need to distinguish stable lineages from context-dependent 'tuft-like' states. This supports the need for more stringent, multi-marker definitions of tuft-cells in normal, inflamed, and neoplastic tissue, particularly when attempting to infer function from cell abundance or transcriptional state[10,17,30–32].

If tuft-cells are simply treated as DCLK1-positive, POU2F3-positive, or TRPM5-positive cells, studies may conflate mature tuft-cells with 'tuft-like' cells within regenerative, inflammatory, or tumour-associated epithelial states. Conversely, overly restrictive definitions may miss transitional or context-dependent tuft-like states that are biologically meaningful. A more useful framework is to consider both tuft-cell identity and the signalling programmes these cells engage with across homeostasis, inflammation, repair, and early neoplasia.

Cancer relevance of tuft-cells

Accumulating evidence prioritises tuft-cells as

a candidate effector cell type for the 11q23.1 CRC associations. However, their precise contribution to susceptibility remains unresolved. Findings from other cancer contexts suggest that tuft-cell-associated states may have differing roles in tumorigenesis. In the intestine, DCLK1-positive cells have been linked to tumour initiation and tumour maintenance in some models, whereas other studies suggest that tuft-cell differentiation may restrain tumorigenesis or reflect protective epithelial responses. In pancreatic cancer, tuft-cell-like differentiation has also been associated with altered immune signalling and tumour behaviour. Although tuft-like transcriptional programmes have also been described in POU2F3-positive malignancies such as small-cell lung cancer, these tumour-associated states should not be assumed to be equivalent to normal colonic tuft-cells[16,17,23,33,34]. These apparently divergent findings argue against assigning tuft-cells a uniformly tumour-promoting or protective role. Their effects may depend on tissue context, inflammatory conditions, disease stage and whether the cells represent mature tuft-cells or tumour-associated tuft-like states. For the 11q23.1 model, altered tuft-cell abundance or transcriptional programmes could contribute to susceptibility, but could also reflect a broader change in epithelial homeostasis or repair. Establishing whether these changes drive tumour susceptibility or reflect other disease-relevant processes, or both, remains a focus of our future studies.

Human and mouse evidence linking *POU2AF2*, tuft-cells and tumour susceptibility

Human colonic mucosal 'Swiss-Rolls' enables extensive sampling and improve detection of rare tuft-cells. Individuals homozygous for the CRC-risk allele at rs3087967 (TT, n=4) had a lower relative abundance (p=0.042; unpaired Wilcoxon rank-sum test) of PTGS1/POU2F3 and ChAT/POU2F3 double-positive tuft-cells compared with individuals homozygous for the non-risk allele (CC, n=7), supporting a genotype-associated difference in marker-defined abundance[19,22]. Millions of counted cells improve within-donor sampling, demonstrating significant differences in tuft-cells between genotypes, but do not increase independent biological replication. While the modest number of donors provides an initial assessment, confirmation in larger cohorts is required to allow more robust assessment of inter-individual variability and other potential confounding factors (sex/age/anatomical sampling site).

Mouse models provided experimental support for the functional relevance of this pathway. CRISPR-mediated deletion of the murine homologous 11q23.1 cis-eQTL target regions reduced expression of multiple tuft-cell-associated trans-eQTL homologues, including *Trpm5, Sh2d6, Sh2d7, Pou2f3, Ccdc129, Rgs13* and *Avil*, and recapitulated depletion of colonic tuft-cells. Single-gene perturbation further showed that this phenotype was specifically dependent on *Pou2af2*, rather than *Pou2af3*. *Pou2af2*-deficient mice showed reduced abundance of Dclk1/ac-α-tubulin and Pou2f3/ac-α-tubulin double-positive tuft-cells, whereas *Pou2af3* deficiency did not produce the same phenotype[19,22].

The functional consequences of *Pou2af2* loss were most apparent in the $Apc^{Min/+}$ model of intestinal tumorigenesis. Loss of *Pou2af2*, but not *Pou2af3*, exacerbated tumour-associated phenotypes. $Apc^{Min/+}Pou2af2^{-/-}$ mice showed markedly reduced overall survival, while $Apc^{Min/+}Pou2af3^{-/-}$ mice showed no comparable survival effect. *Pou2af2* loss was also associated with increased polyp burden and size, including increased distal small intestinal polyp number in $Apc^{Min/+}Pou2af2^{+/-}$ mice and larger colonic polyps in $Apc^{Min/+}Pou2af2^{-/-}$ mice. These findings support a tumour-modifying role for *Pou2af2* and raise the possibility that altered colonic tuft-cell biology may contribute to this effect[19,22].

Although the human cis-eQTL and colocalization analyses implicate *POU2AF2*, *POU2AF3* and *COLCA1*, the mouse functional evidence prioritises *POU2AF2* but does not exclude context-dependent contributions from *POU2AF3* or effects mediated by *COLCA1*.

Furthermore, it remains unresolved whether the 11q23.1-associated CRC-risk is mediated by reduced tuft-cell abundance, altered function within the remaining tuft-cells, or broader effects of *POU2AF2* dysregulation. These possibilities are not mutually exclusive: reduced expression of tuft-cell-associated genes in bulk tissue could reflect changes in cell abundance, expression within individual cells, or both. Similarly, the occurrence of both tuft-cell depletion and altered tumour phenotype following *Pou2af2* loss does not establish that reduction in abundance mediates the tumour phenotype. Dysfunction in residual tuft-cells or secondary changes in the tissue microenvironment are possible explanations that remain to be tested. Complete germline deletion of *Pou2af2* also differs from the subtler regulatory effects associated with common human variation. Our current experiments demonstrate that *Pou2af2* can modify tumour-associated phenotypes in this model but do not establish the magnitude or mechanism of the human risk allele's effect.

Future studies should distinguish changes in tuft-cell abundance from function and determine their contributions to tumour susceptibility. This requires consideration of tuft-cell heterogeneity, including how distinct populations or functional states differ in sensing, repair, communication, and responses to tumour-promoting stresses.

The main experimental and analytical evidence supporting this model, together with key caveats and future directions, is summarised in **Table 1**.

Table 1: Evidence linking the 11q23.1-*POU2AF2* axis to colonic tuft-cell biology and inherited CRC susceptibility: Summary of the experimental and analytical evidence supporting a model in which common genetic variation at 11q23.1 influences CRC risk through dysregulation of *POU2AF2* and tuft-cell associated transcriptional programmes.

Experimental/ Analytical approach	Main findings	Interpretation of data	Caveats	Future direction
CRC GWAS, cis-eQTL fine mapping and colocalization at 11q23.1.	11q23.1 is associated with CRC risk. Cis-eQTL effects in bulk colonic tissue samples implicate *POU2AF2*, *POU2AF3* and *COLCA1.* Fine mapping/colocalization refined rs3087967 as the prime eQTL variant.	Supports 11q23.1 as a regulatory risk locus. Shifts interpretation from broad locus association to rs3087967-linked gene regulation.	rs3087967 is the strongest statistical representative, though not definite proof of causality. Earlier work nominated linked variants, including rs7130173 and rs10891246.	Future work: allele-specific reporter assays, CRISPR/Prime editing.
Trans-eQTL and SMR analysis.	rs3087967 acts as a trans-eQTL hub influencing distant tuft-cell enriched genes. Reduced expression of refined trans-eQTL targets is associated with CRC risk.	Suggests 11q23.1 risk may be mediated through disruption of a broader tuft-cell transcriptional programme.	Strengthens causal inference but does not prove mechanism.	Perturbation of prioritised downstream genes/pathways to test effects on repair, metabolite sensing, immune signalling and tumour susceptibility.
scRNAseq, WGCNA and tuft-cell cluster enrichment.	11q23.1 trans-eQTL targets clustered into a *POU2AF2*-correlated module. Strongest expression was seen in a tuft-cell epithelial module. Multiple markers replicated across datasets.	First evidence that 11q23.1 risk may act through rare tuft-cells. Supports tuft-cell signalling as the context of the trans-eQTL network.	Primarily inferential and based on existing and publicly available scRNAseq datasets.	Larger genotype-linked human datasets to resolve tuft-cell subtype, state and spatial localisation.
POU2F3/ POU2AF2 regulatory axis, chromatin evidence and SWI/SNF dependency.	POU2AF2 is implicated in regulation of tuft-cell specific trans genes through POU2F3-associated regulatory architecture. Small cell lung carcinoma (SCLC) studies show the POU2F3/POU2AF2 axis can act as a lineage-defining transcriptional module. POU2AF2 can regulate enhancer activity through SWI/SNF-dependent chromatin remodelling.	Provides a plausible route linking rs3087967, altered POU2AF2 expression and tuft-cell transcriptional programmes. Supports POU2AF2 as a functional co-regulator, not just a tuft-cell marker.	Most chromatin and SWI/SNF evidence come from SCLC models, not normal colonic tuft-cells.	Validate POU2AF2-POU2F3-SWI/SNF mechanisms in colonic epithelial organoids/ ex-vivo tissue using ATAC-Seq, enhancer assays and co-occupancy mapping.
Human colonic tissue imaging.	Human Swiss-Roll immunofluorescence showed reduced PTGS1/ POU2F3 and ChAT/POU2F3 double positive tuft-cells in rs3087967 TT risk-genotype carriers.	Provides tissue-level evidence that inherited genotype is associated with measurable tuft-cell depletion in normal colon.	Number of human samples remains modest despite large cell counts.	Larger genotype stratified cohorts, spatial profiling and standardised multi-marker tuft-cell quantification across site, age, inflammation and neoplastic context.
Mouse 11q23.1 region and single gene deletion models.	Deletion of murine homologues of 11q23.1 cis-eQTL region reduced tuft-cell abundance and trans-eQTL homologues. Single-gene models implicated *Pou2af2*, not *Pou2af3*, as the key driver.	Supports *POU2AF2* as the primary regulator linking 11q23.1 to tuft-cell transcriptional abundance.	Germline deletion and complete knockout mouse models may not represent the more subtle human variation.	Conditional, inducible, tuft-cell specific and allele-specific *Pou2af2* perturbation models, including inducible epithelial-specific deletion using *Villin-CreER* and tuft-cell focused perturbation using *Pou2f3-CreER* or *Dclk1-CreER* systems where feasible.

Experimental/ Analytical approach	Main findings	Interpretation of data	Caveats	Future direction
Apc$^{Min/+}$ tumour susceptibility models.	*Pou2af2* loss, but not *Pou2af3* loss, heightened tumour phenotypes in *Apc*$^{Min/+}$ mice. Effects included reduced survival and increased tumour burden and size.	Provides functional evidence that *POU2AF2*-dependent biology modifies intestinal tumour susceptibility. Supports a tumour-protective role for the tuft-cell axis.	Does not prove that tuft-cell depletion alone causes CRC susceptibility.	Test whether restoring *Pou2af2* expression, tuft-cell state or downstream signalling modifies tumour risk. Use carefully titrated AOM/DSS and DSS only models culled at early-time points, ex vivo models and spatial profiling to separate primary tuft-cells effects from secondary injury responses.
Tuft-cell regulation of immune responses.	Tuft-cells act as epithelial sensory cells coordinating type 2 immune responses. IL-25 activates ILC2s, promoting IL-13 production and tuft-cell expansion. Pou2af2 isoforms regulate tuft-cell differentiation and innate type 2 immunity. Tuft-cell derived acetylcholine can promote epithelial chloride secretion and helminth clearance.	Shows that tuft-cells are active signalling cells that regulate epithelial and immune physiology. Supports the idea that 11q23.1 variation could influence mucosal resilience, immune coordination and epithelial homeostasis.	Most immune function data come from small intestine and not colon.	Test whether genotype linked tuft-cell disruption alters IL-25 signalling, ILC2 activation, epithelial secretion and repair in preclinical models and human colonic tissue.

Data Source: Evidence summarised from Rajasekaran et al., 2025; Harris et al., 2022.

A tuft-cell model of inherited CRC-susceptibility

The broader implication is that inherited CRC-susceptibility may not solely act through direct effects on epithelial proliferation or canonical tumour suppression pathways. Instead, genetic variation may also selectively perturb rare epithelial populations whose importance lies in their capacity to coordinate tissue-level responses. Even subtle changes in tuft-cell abundance or function could influence how normal colonic mucosa senses and responds to inflammatory or tumour-promoting stress, although whether these effects mediate 11q23.1-associated CRC-risk remains unresolved.

This model suggests that inherited variation may influence tumour susceptibility by altering the abundance or function of specialised epithelial populations, potentially disrupting homeostasis and reducing mucosal resilience. This framing also shifts the value of post-GWAS functional studies. The goal is not simply to assign each susceptibility locus to a nearest gene, but to understand how inherited variation changes the cellular composition of the normal tissue in which cancer arises. At 11q23.1, integration of genetic and functional evidence implicates a rare epithelial cell population whose contribution may be difficult to resolve through bulk-tissue analysis alone. This supports a broader model in which inherited CRC-risk may be mediated through altered epithelial communication, niche organisation, injury response and stress adaptation before overt neoplasia develops.

Future directions: moving from genetic risk prediction to prevention biology

Although rs3087967 genotype has already been interrogated in relation to transcriptomic and clinical data, larger and more comprehensive resources are still needed to allow more robust testing of whether rs3087967 genotype alters tuft-cell abundance, transcriptional state, or spatial organisation across larger and more diverse populations. Such datasets would also allow the proposed 11q23.1 mechanism to be examined in relation to tumour site, inflammatory states, gut microbiome, and CRC molecular subtypes. Integrating genotype information with scRNA-seq, spatial transcriptomics, microbiome profiles and data from human colonic tissue would help assess whether 11q23.1 variation is associated with tuft-cell states across clinically relevant contexts.

Functional models, such as the *Pou2af2* tuft-cell specific mouse models, could be used to distinguish whether tumour susceptibility is driven directly by the loss of tuft-cell function or indirectly by broader consequences of altered *Pou2af2* expression. Inflammation- and injury-associated models, may be particularly informative because tuft-cells are likely to be more relevant when the epithelium is required to sense damage, coordinate repair and facilitate communication with immune/microbiome pathways. However, injury models also need to be interpreted carefully as models including DSS can substantially disrupt the epithelium, making it important

to distinguish effects on tuft-cell biology from secondary consequences of epithelial stripping, inflammation, and repair.

The clinical relevance of tuft-cell biology remains uncertain. Current evidence does not yet support tuft-cells as clinical biomarkers but suggests they may provide an experimental readout of mucosal resilience, the capacity of normal colonic epithelium to respond to injury, inflammation, or tumour-promoting stress. Once confirmed in larger human datasets and functional models, genotype-linked tuft-cell programmes could help identify individuals whose normal mucosa is less able to adapt to inflammatory, microbial, or genotoxic stress, opening a route towards stratified prevention strategies based on epithelial cell states.

Conclusion

The 11q23.1 locus provides a compelling example of how integrating genetic and functional evidence can connect a CRC-associated GWAS signal to altered gene expression and the abundance of a rare intestinal epithelial cell type, tuft-cells. Linking rs3087967, *POU2AF2* dysregulation, a tuft-cell enhanced trans-eQTL network, reduced tuft-cell abundance, and altered tumour susceptibility in preclinical models, this work suggests that CRC-risk may be shaped at the level of specialised epithelial cell populations that coordinate tissue level responses. More broadly, this work illustrates how post-GWAS studies can prioritise cellular mechanisms through which inherited susceptibility may influence normal colonic mucosa before malignancy develops.

Abbreviations

ac-α-tubulin: Acetylated α tubulin; $Apc^{Min/+}$: Adenomatous polyposis coli multiple intestinal neoplasia mouse model; AOM: Azoxymethane; ATAC-seq: Assay for transposase-accessible chromatin sequencing; Avil: Advillin; Ccdc129: Coiled-coil domain containing 129; ChAT: Choline acetyltransferase; ChIP-seq: Chromatin immunoprecipitation sequencing; COLCA1: Colorectal cancer associated 1; CRC: Colorectal cancer; CRISPR: Clustered regularly interspaced short palindromic repeats; DCLK1: Doublecortin-like kinase 1; DSS: Dextran sodium sulphate; eQTL: Expression quantitative trait locus; GWAS: Genome-wide association study; HTR3E: 5-hydroxytryptamine receptor 3E; IL-13: Interleukin-13; IL-25: Interleukin-25; ILC2: Group 2 innate lymphoid cell; LD: Linkage disequilibrium; LRMP: Lymphoid-restricted membrane protein; PLCG2: Phospholipase C gamma 2; POU2AF2: POU class 2 associating factor 2; POU2AF3: POU class 2 associating factor 3; POU2F3: POU class 2 homeobox 3; PTGS1: Prostaglandin-endoperoxide synthase 1; Rgs13: Regulator of G protein signalling 13; scATAC-seq: Single-cell assay for transposase-accessible chromatin sequencing; scRNA-seq: Single-cell RNA sequencing; SCLC: Small-cell lung cancer; SH2D6: SH2 domain containing 6; SH2D7: SH2 domain containing 7; SMR: Summary-data-based Mendelian randomisation; SNP: Single nucleotide polymorphism; SWI/SNF: Switch/sucrose non-fermentable chromatin-remodelling complex; TRPM5: Transient receptor potential cation channel subfamily M member 5; WGCNA: Weighted gene co-expression network analysis

Conflict of Interest

The authors declare no competing interests.

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Authors' Contributions

VR conceptualised the review and drafted the manuscript. SMF and BH contributed to critical revision and approval of the final manuscript.

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