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Perspective

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Defining and using immune archetypes to classify and treat cancer

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Abstract

Tumours are surrounded by a host immune system that can suppress or promote tumour growth. The tumour microenvironment (TME) has often been framed as a singular entity, suggesting a single type of immune state that is defective and in need of therapeutic intervention. By contrast, the past few years have highlighted a plurality of immune states that can surround tumours. In this Perspective, we suggest that different TMEs have 'archetypal' qualities across all cancers — characteristic and repeating collections of cells and gene-expression profiles at the level of the bulk tumour. We discuss many studies that together support a view that tumours typically draw from a finite number (around 12) of 'dominant' immune archetypes. In considering the likely evolutionary origin and roles of these archetypes, their associated TMEs can be predicted to have specific vulnerabilities that can be leveraged as targets for cancer treatment with expected and addressable adverse effects for patients.

Sections

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Introduction

The past decade has seen a revolution in cancer treatment owing to a shift from traditional chemotherapy and radiation-based therapies towards the use of antibody-based immunotherapies (also known as immune checkpoint blockade (ICB) therapies) that modulate immune response against tumours. However, clinical responses to immunotherapy have been highly variable, with some patients entering remission and others receiving no clinical benefit. Therefore, a deeper understanding of the diversity of the immune microenvironment across human malignancies is crucial to expand the reach of immunotherapy. As we consider how tumours live together with immune systems, and frequently avoid ICB therapies, it is likely that individual tumours engage common patterns of the immune system — what we have termed 'archetypes' — creating prototypical non-destructive tumour microenvironments (TMEs) and modulating tumour targeting. Hereafter, we use the term 'dominant archetypes' to describe the most prevalent of these cellular networks and gene programmes across solid tumours. Each dominant archetype is assumed to be composed of distinct cellular networks that interact with and promote tumour growth differently and predispose in one way or another to defective antitumour responses. We highlight the emerging dominant types of immune composition and gene programmes and provide a perspective on the likely tissue biology that tumours might co-opt, providing a framework to direct immunotherapies to the most relevant tumour biology.

The concept of immune archetypes

Burnett, Medawar and Owen[1] are widely credited with the concept of immune tolerance — the conceived process by which the immune system accepts an antigen as self, typically as a result of clonal deletion of B cells and T cells. This paradigm has been fundamental in the development of ICB strategies, including anti-CTLA4 (refs. 2,3) and anti-PD1 (ref. 4). In studying tumour immunity, many researchers have considered the 'goal' to be one of reversing tumour tolerance, including overcoming tolerance to self-antigens, and promoting reactivity to tumour neoantigens.

In most mouse studies of ICB strategies, and since the approval of ipilimumab (anti-CTLA4) and multiple anti-PD1/PDL1 drugs for use in patients, ICB therapy has shown various levels of efficacy in eliciting tumour rejection. Efficacy profiles are different within a single cancer indication and even within genetically inbred cohorts of animal models. This variability has been suggested to result from those individuals having a combination of poor tumour antigenicity leading to sparse T cell ability to detect the tumour[5] and/or to an unreceptive immune TME that somehow prevents or suppresses the benefits of T cell enhancement produced by the ICB[6–8]. Although preclinical models using inbred mice and standardized tumour cell lines have supported the vast majority of ICB therapies that have already been approved, these approaches have clear limitations with respect to their ability to be informative regarding genetic heterogeneity, T cell receptor (TCR) variability and TME diversity[9]. To better characterize and understand the wealth of resistance mechanisms to ICB, defining and studying TMEs across human cancer is crucially important.

How might we understand and classify such variability within cancer TMEs? Here, basic research comes to the rescue. In the background to the excitement of ICB success, the field of immunobiology has made a series of seemingly unrelated discoveries that force fundamental reconsiderations of the breadth of function of the immune system as envisioned in the era of Medawar, Burnett and Owen. In their model of immunity based on clonal selection theory, B cells or T cells bearing receptors against anything designated as self are eliminated. However, the past 20 years has demonstrated the existence and formative power of TCRs that recognize self and then direct T cells into an alternative fate, best exemplified by regulatory T (T_{reg}) cells[10]. T_{reg} cells are responsible not only for downregulating other T cell responses but also for driving wide-ranging immune system behaviours that influence lipid metabolism and adiposity[11,12] and tissue repair[13,14], as well as providing immunomodulatory curation of microbiota[15]. That latter role also extends to other T cell subsets[16]. Thus, instead of seeing the immune system as simply a friend or foe detector, it can be viewed as a system that achieves 'accommodation'[17] and encourages tissue health, even in the absence of overt insults.

In the same window of time, other studies have revealed additional forms of tissue accommodation through the innate immune system. For example, in the absence of tissue macrophages and complement components, memory formation in the brain is impaired owing to the role of immune cells in pruning neurons and maintaining neuronal health[18,19]. Likewise, macrophages and T cells have been found to be essential for initiating the branching morphogenesis of mammary tissue in anticipation of lactation[20] and subsequently for its involution[21]. To varying extents, 'accommodation'[17] functions of the immune system can thus use combinations of adaptive immunity and/or innate immunity elements (that is, receptors, cells and gene-expression programmes).

Cancers display significant heterogeneity with respect to tissue of origin, driver mutations and other features of the surrounding tissue. Individual tumours probably engage specific patterns of the immune system — what we term archetypes — creating prototypical non-destructive TMEs and modulating tumour targeting. A crucial point made in this Perspective article is that there is not just one kind of TME with random selection of cell types or pathways; instead, at least a dozen reasonably common and archetypal bulk-level collections of immunobiology exist, probably owing to the gene and cell cooperativity hardwired into the human immune system. Because these networks can be found and characterized from the total composition of a tumour — and notably without yet a full accounting of how these assemble into spatial neighbourhoods — we refer to these as the dominant archetypes of TMEs.

We have previously introduced the idea that tumour-promoting dominant archetypes can also contain small niches of 'reactive' immune archetypes[17]. The immune compartment can display significant spatial heterogeneity, and a TME can potentially harbour multiple archetypes in a mosaic fashion. These rare reactive niches (containing, for example, rare conventional dendritic cells (cDCs)[22], non-exhausted $CD8^+$ T cells[23,24] and natural killer (NK) cells[25,26]) seem to represent the biology that we are seeking to enhance with ICB therapies. The dominant archetypes represent the opposition to antitumour immunity but can variably permit reactive archetypes to coexist in the TME.

The yin and yang between the dominant and reactive archetype of a tumour is illustrated in Fig. 1 for conceptual purposes. We presume that the therapeutic goal can be conceived of as both enhancing a 'reactive' immunity and defeating the oppositional (pro-tumoural) function of the dominant state.

The existence of many kinds of TME

Tumours have long been categorized as inflamed or non-inflamed, or via the terms 'hot' versus 'cold' or occasionally 'rich' versus 'desert'[27–30] (Fig. 2, outside ring). Those broad categories rely mostly on the frequency but sometimes also on the spatial localization[30] of

tumour-infiltrating T lymphocytes (TILs) with respect to the tumour nest and non-immune stromal compartments quantified on histological sections. Inflamed tumours have also been subdivided to denote 'infiltrated' tumour (defined by close proximity of TILs with tumour cells), immune-excluded tumours (associated with TILs embedded in the surrounding tumour stroma away from tumour cells) and immune deserts (associated with tumours devoid of TILs)[30]. This low-resolution classification of the TME — derived mainly from specific analysis of colorectal cancer (CRC) tumours but also from bladder urothelial carcinoma[31] — led to the development and implementation of a consensus, standardized scoring system. This scoring system is based on the quantification of only two lymphocyte markers (CD3 and CD8) both at the tumour nest and the invasive margin[32]. A clear clinical translation of this 'Immunoscore' into a prognostic marker in CRC tumours at baseline has been demonstrated[33]. However, its utility in other tumour types is still under investigation, and it is already clear that its strong dependence on $CD8^+$ T cells represents an important limitation. Indeed, it is now well appreciated that not all tumour-infiltrating $CD8^+$ T cells are equal[24,34], and intratumoural accumulation of certain subsets (defined by high expression of co-inhibitory molecules) is associated with poor survival across multiple solid tumours both at baseline[35–37] and after ICB therapies[24]. This finding indicates that although the number of infiltrating $CD8^+$ T cells provides essential information on the state of the antitumour response, this single parameter cannot fully capture the breadth of tumour ecosystems and their association with disease outcome.

Conserved immune archetypes

Variation in immune systems in patients has pushed us and many others to approach this topic systematically using multiparametric immune monitoring technologies, including flow cytometry and immune gene-signature scores, in total tumour data sets across various tumour types to enumerate cell and gene-expression frequencies (Table 1). Some groups have used deconvolution algorithms such as CIBERSORT[38], EcoTyper[39] and other machine learning frameworks based on bulk, single-cell and spatially resolved gene-expression data[40] on The Cancer Genome Atlas (TCGA) bulk RNA data, whereas others have directly isolated and performed a holistic and multidimensional profiling of immune systems from TMEs across one[23,35,41–44] or many tumour types in parallel[45]. Both methods have their own limitations. For instance, deconvolution methods are limited by the number of cell types and cell states they can resolve from bulk RNA sequencing (RNA-seq)[45,46], whereas methods that directly isolate cell types might be limited by the number of populations they can profile. Nevertheless, both approaches share the same overarching goal of developing a standardized and unequivocal definition of these immune-based tumour classifications across tumour types.

In our 2022 study, we leveraged a unique data set composed of both cell type compositional and transcriptomic data from hundreds of fresh surgical specimens across 12 tumour types to uncover dominant archetypes across cancers[45]. This UCSF Immunoprofiler (IPI) data set was clustered using just ten independent cell compositional features, covering T cell and mononuclear phagocyte (MNP) subsets, as well as non-immune $CD90^+CD44^+$ cancer-associated fibroblasts (CAFs). Unsupervised clustering revealed 12 distinct clusters spanning various cancer types and a spectrum from immune-rich to immune-desert TMEs (Fig. 3a, Table 2 and Supplementary Table 1); notably, ten independently assorting binary variables might have produced 2^{10} (1,024) groups or archetypes, thus indicating the strong selection for specific

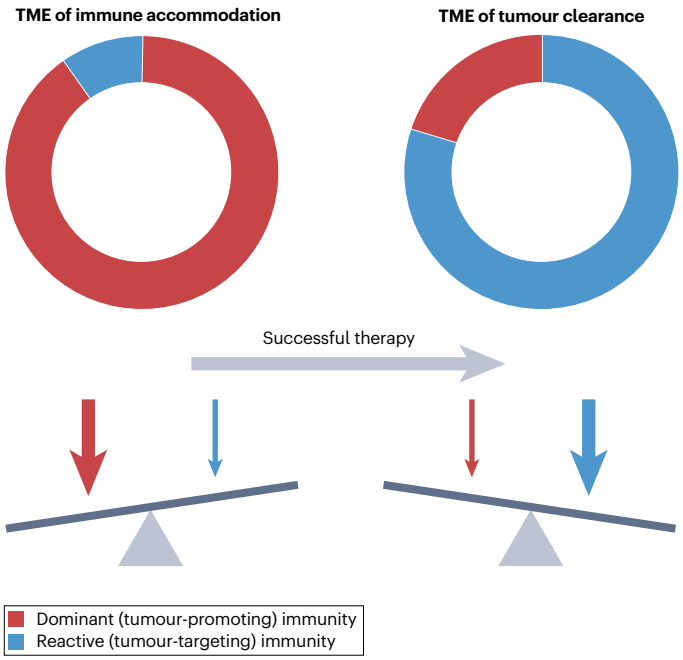

Fig. 1 | The yin and yang of dominant and reactive archetypes. This illustration depicts the concept that tumour microenvironments (TMEs) comprise collections of cells that fall into two distinct categories. In tumours, the 'dominant' tumour immune archetype (red) creates a prototypical non-destructive TME that opposes tumour targeting. Less-prevalent 'reactive' tumour immune archetypes (blue) can also live within the TME, and these are the collections of cell types that we believe are the seeds of a productive immune response. Successful immune checkpoint blockade therapy will transform the TME from one that contains abundant 'dominant' tumour-promoting immunity (left) towards one in which reactive tumour-targeting immunity prevails (right).

combinations of these cell populations. Importantly, the 12 archetypes derived from these ten features (Figs. 2 and 3) were also associated with chemokine gene expression, the frequency of additional cell types and gene expression within immune populations. Undoubtedly, this analysis will be refined as yet more samples and analytical tools[46] are applied, but at present when survival analysis was performed across tumours using a multivariate survival regression, we detected significant outcome differences between archetypes that have similar T cell subset enrichment regardless of the cancer type analysed[45].

Although the IPI study and associated work directly measured immune cell frequencies along with gene expression by compartment, we note that TCGA-based studies using CIBERSORT, although they failed to differentiate key archetypes, also found some of the key distinctions between archetypes. This includes the distinction that $CD90^+CD44^+$ CAF density splits immune-rich from immune-stroma-rich, as well as splitting the immune-poor deserts[40]. Moreover, work using EcoTyper (a deconvolution method that probes 69 transcriptionally defined cell states using single-cell RNA-seq references across 16 tumour types)[39] identified ten recurrent multicellular communities spanning cancer types. Among these communities were TMEs mainly enriched in MNPs and CAFs, which might correspond to those identified by direct cell counting as myeloid-centric archetypes (see later). This finding again highlights the key role of this population in subdividing different TMEs. As a general result, going from the most infiltrated

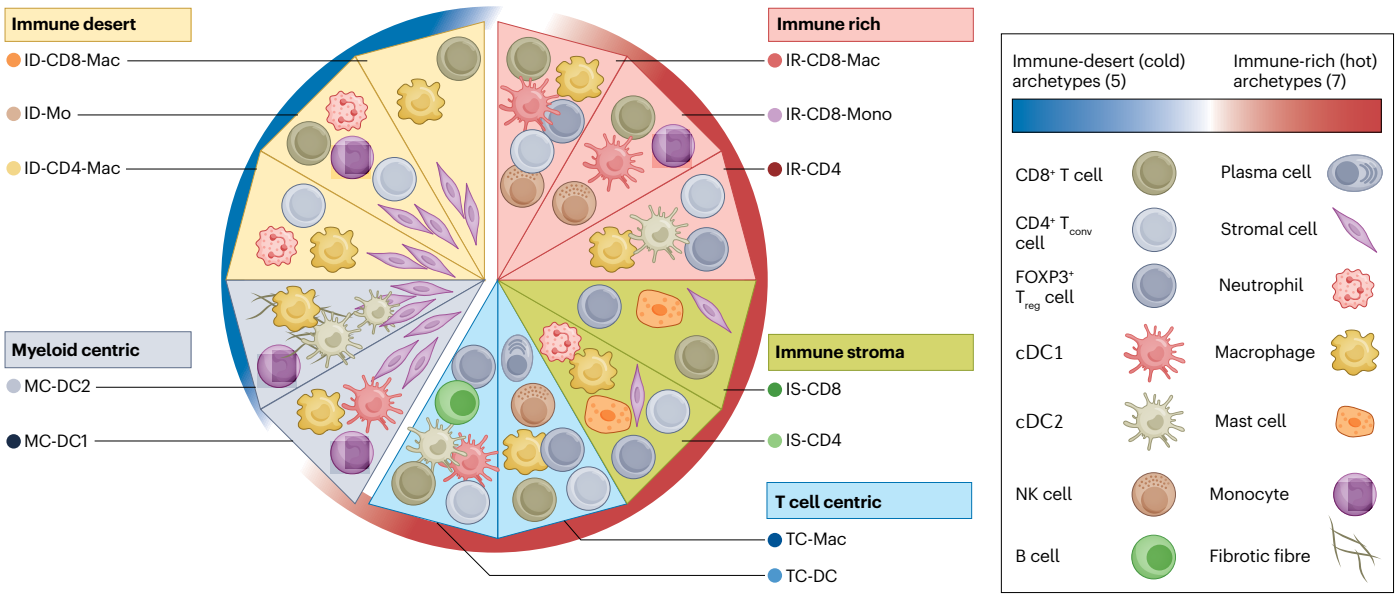

Fig. 2 | Pan-cancer census of TMEs across solid tumours. Wedges together represent the spectrum of tumour microenvironments (TMEs) that have been found in solid tumours. Coarse TME descriptors are indicated from immune 'hot' to immune 'cold' classification based on Galon and colleagues[30], as well as the more recent finer-detailed classification that emerges from our work[45] as it intersects with parallel studies by others[23,30,35,38,41–44]. The first classification is represented by the outside ring with gradient from red to blue representing the degree of tumour-infiltrating T lymphocytes (TILs), the second one is represented by each 'slice' of this pie chart representing the 12 common and archetypal bulk-level collections of immunobiology grouped by immune-rich (IR), immune-stroma-rich (IS), T cell-centric (TC), myeloid-centric (MC) and immune-desert (ID) TMEs. The major compositional elements of each of the 12 TMEs are represented inside each slice. cDC, conventional dendritic cell; NK cell, natural killer cell; T_{conv} cell, conventional T cell; T_{reg} cell, regulatory T cell.

to the least, the 12 archetypes are spread across five main subgroups with unique relationships between cell densities, chemokine networks and tumour and immune gene expression (Fig. 2).

Immune-rich TMEs

Immune-rich TMEs are highly infiltrated by immune cells and have limited $CD90^+CD44^+$ CAF accumulation. Immune cell accumulation includes conventional T cells, T_{reg} cells and MNPs. Substantial interferon-stimulated gene (ISG) expression is typical in the tumour cells[45], indicating a pivotal role of the interferon pathway in those tumours. Immune-rich archetypes are highly enriched in samples from kidney tumours and to a lesser degree in melanoma, head and neck squamous cell carcinoma (HNSCC), lung adenocarcinoma and breast cancer[41] samples (Fig. 3a, right).

Immune-rich archetypes come in three subvarieties, two in which $CD8^+$ T cells are the dominant T cell subset (IR-CD8-Mac and IR-CD8-Mono) and one in which $CD4^+$ T cells are enriched (IR-CD4). The former two show concomitant enrichments in the CXCL9, CXCL10, CXCL11–CXCR3 and/or XCL1, XCL2–XCR1 chemokines, whereas the $CD4^+$-biased archetype is more enriched in the CCR4–CCR8 axis[45]. IR-CD8-Mac has more macrophages than IR-CD8-Mono, and this distinction also coincides with the latter containing more NK and cDC1 cells. Monocytes are known to rapidly differentiate into macrophages in tissue, including in solid tumours; however, we[45] and others[47] have shown that certain tumours are highly enriched in monocytes. The combination of NK and cDC1 cells has been shown to correspond to better overall survival, as well as response to checkpoint blockades[25,26]. Moreover, mouse studies have shown that endogenous cancer cell-derived type I interferons control monocyte functional polarization by promoting immunostimulatory function associated with anti-PD1 immunotherapy response in mice[48]. As interferon signalling has a pleiotropic role on both NK cells[49] and DCs, including promoting differentiation of monocytes towards a DC-like phenotype[50], it is tempting to postulate that this pathway has an important role in the cellular network observed in the IR-CD8-Mono TME.

By contrast, IR-CD8-Mac has more tumour-associated macrophages (TAMs) than IR-CD8-Mono, which correlates with higher signatures of T cell exhaustion[45], consistent with studies showing that these two cell types reinforce one another in mouse models[51] and in human kidney[43,51] and breast tumours[41]. Those two biases (towards TAMs and exhausted T cells) are consistent with the observation that the IR-CD8-Mono subvariety, taken either across multiple indications[45] or when analysed just in one cancer type (kidney)[43,44], correlates with better overall survival even in the absence of treatment.

T_{reg} cell abundance is variable across the immune-rich archetypes as a whole, with the most prominent frequencies being found in the IR-CD4 archetype; the frequencies of T_{reg} cells correlate with increased numbers of macrophages[44,52] and cDC2 cells[42,45].

Immune-stroma TMEs

Immune-stroma archetypes are highly infiltrated by T cells and MNPs (similar to immune-rich TMEs) but are characterized by a high abundance of $CD90^+CD44^+$ CAFs. Immune-stroma TMEs are divided into two subclasses based on distinct accumulation of $CD8^+$ versus

$CD4^+$ T cell subsets, respectively IS-CD8 and IS-CD4. The presence of $CD90^+CD44^+$ CAFs corresponds to an enrichment in the TGFβ pathways in our IPI data set, as well as other studies[53–55] (Fig. 2, Table 2 and Supplementary Table 1). Immune-stroma TMEs are prominent in bladder cancer, HNSCC, lung cancer, kidney cancer and CRC in the IPI data set (Fig. 3a) and have been documented both in mouse models and in single-indication human tumour biopsy samples of bladder[56], HNSCC[57], lung[58], breast[59] and pancreatic tumour (where they are enriched in spatial subdomains)[60]. A wealth of evidence has shown that TMEs strongly enriched in $CD90^+CD44^+$ CAFs and featuring cancer cells with a strong TGFβ transcriptomic programme are highly refractory to ICB treatment despite having substantial numbers of T cells[40,55,61]. Owing to the resemblance to these TMEs, it is tempting to hypothesize that immune-stroma archetypes are poorly responsive to ICB therapy.

T cell-centric TMEs

Variations of the immune-rich tumours are those that have high frequencies of T cells but an overall relatively low density of MNPs. Indeed, although both immune-rich and T cell-centric TMEs are highly infiltrated by immune cells, immune-rich TMEs have a high proportion of both T cells and MNPs, whereas the immune fraction of T cell-centric TMEs is mainly made up of T cells with very few MNPs present (Fig. 2). Both T cell-centric archetypes, denoted TC-Mac and TC-DC, are CD4 biased within the T cell compartment, with TC-DC having the higher $CD4^+$ T cell density of the two. A prominent distinction is that whereas TC-Mac has a macrophage bias within the MNP compartment, TC-DC has higher densities of less-mature monocytes and cDC1 and cDC2. As with IR-CD8-Mac versus IR-CD8-Mono, monocyte and cDC1 infiltration are once again coincident, which seems to be an emerging theme. Although the IPI clustering that identified T cell-centric archetypes did not use B cell frequencies for its elaboration, both T cell-centric archetypes are unique in having high densities of either resting B cells (TC-DC) or plasma cells (TC-Mac), and TC-Mac TMEs express substantial levels of CXCL13, which is associated with B cell zones in lymph nodes. Although experimental validation is lacking, both of these archetypes notably have a compositional character that resembles tertiary lymphoid structures (TLSs)[55–57] with the TC-DC perhaps appearing more like resting lymph nodes or TLSs at a more immature stage[62] (containing more DCs, as well as resting B cell infiltration, but also increased expression of CCR7 on both myeloid and T cells and CD86 on myeloid cells)[39].

Expression of CXCL13 in $CD8^+$ T cells (as noted in TC-Mac) has been shown to be prognostic across five tumour types for ICB response[63]; cDC1 prevalence in TC-DC is also a positive prognostic marker for overall outcome and ICB response in mice[22,64,65] and humans[25,26]. Both archetypes are highly enriched in melanoma and lung adenocarcinomas[45], which are the most prominent indications for ICB response. Beyond the IPI data, we note that a study found substantial B cell characteristics in a single-indication study of lung tumours[66], and resting B cell infiltration has been associated with ICB responsiveness in sarcoma[67] and mammary tumours[68]. Plasma cell infiltration was associated with ICB responses in kidney cancer[69]. Thus, even though these two dominant archetypes have very high densities of T_{reg} cells (which oppose T cell activation) and they differ from one another in some significant respects, the bulk of the analyses suggest that these archetypes are among the most permissive for the co-existence of key components of reactive immunity that license ICB responses.

Myeloid-centric TMEs

In contrast to the T cell-centric archetypes, IPI analysis also revealed that across many cancer types some immune-infiltrated tumours contain substantial numbers of MNPs but are largely devoid of T cell populations and have a slight enrichment in neutrophils (Fig. 2). These TMEs might sometimes be confused with cold or immune-desert TMEs when only viewing the T cell compartment but are actually distinct owing to their substantial MNP accumulation. Two subsets have been revealed: MC-DC2 and MC-DC1, in which the former is more biased

Table 1 | High-dimensional approaches to characterize tumour microenvironment diversity across solid tumours

Data used	Tumour type	Number of immune subtypes identified	Association with overall survival	Association with response to immunotherapy	Ref.
Microarray probing 81 cell-type-specific genes	Colorectal cancer	2	Yes	Not tested	163
Bulk RNA-seq from TCGA	Bladder urothelial carcinoma	2	Not tested	Not tested	31
Bulk RNA-seq from TCGA probing 160 immune expression signatures	Pan-cancer (33 cancer types)	6	Yes	Not tested	38
Bulk RNA-seq from TCGA probing 29 knowledge-based functional gene-expression signatures	Pan-cancer (20 cancer types)	4	Yes	Yes (melanoma, lung adenocarcinoma and bladder urothelial carcinoma)	40
Single-cell RNA-seq, probing 88 cell subsets and their 204 associated gene-expression programmes	Colorectal cancer	7	Not tested	Not tested	23
Bulk RNA-seq from TCGA probing 69 transcriptionally defined cell states, defined using bulk RNA-seq from sorted population or single-cell RNA-seq	Pan-cancer (16 cancer types)	10	Not tested	Yes (melanoma and bladder urothelial carcinoma)	39
Paired flow cytometry and sorted bulk RNA-seq probing 10 features on a discovery cohort and validated on TCGA	Pan-cancer (12 cancer types)	12	Yes	Not tested	45
Decision-tree machine learning deconvolution using 51 cell type gene signatures from tissue and blood applied on TCGA data	Pan-cancer (31 cancer types)	NA	Not tested	Yes (melanoma and bladder urothelial carcinoma)	46

NA, not available; RNA-seq, RNA sequencing; TCGA, The Cancer Genome Atlas.

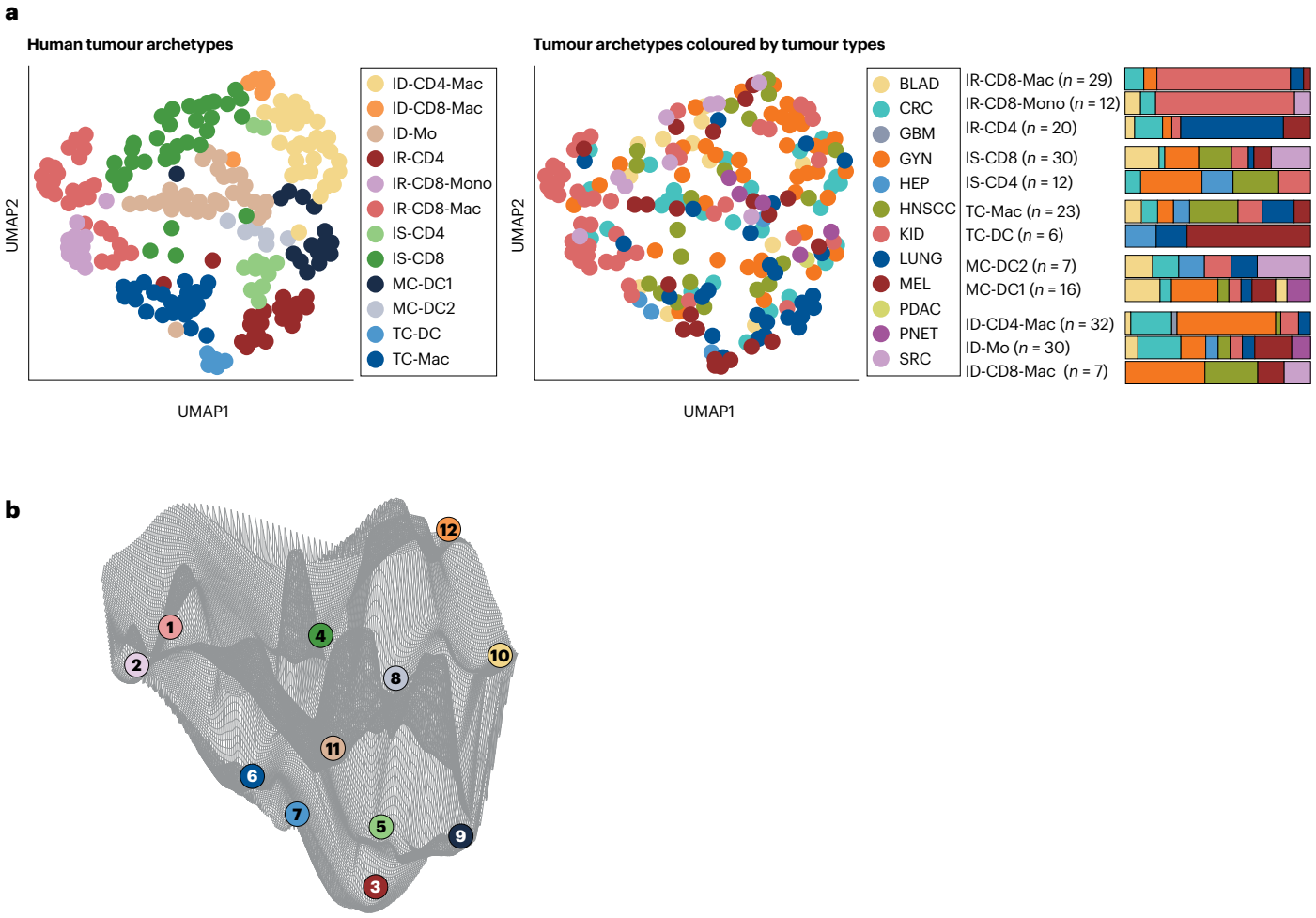

Fig. 3 | Tissue distribution and potential 'distance' between dominant immune archetypes. a, Uniform manifold approximation and projection (UMAP) display and graph-based clustering of tumour immune archetypes using 10-feature clustering in the UCSF Immunoprofiler cohort (left). UMAP display and graph-based clustering of tumour immune archetypes using 10-feature clustering colour-coded by tumour type. Each dot represents a single patient. Stacked bar plot of the tumour type distribution for each archetype (right). **b**, 3D representation of the left UMAP display (*x* axis, UMAP1; *y* axis, UMAP2; *z* axis, Manhattan distance between the sample and the centroids of its cluster or 'archetypes'), illustrating that some tumour microenvironments might be 'closer' to each other than others. BLAD, bladder cancer; CRC, colorectal cancer; GBM, glioblastoma; GYN, gynaecological cancer; HEP, hepatic cancer; HNSCC, head and neck squamous cell carcinoma; KID, kidney cancer; LUNG, lung cancer; MEL, melanoma; PDAC, pancreatic ductal adenocarcinoma; PNET, pancreatic neuroendocrine tumour; SRC, sarcoma. Part **a** adapted with permission from ref. 45, Elsevier.

towards DC2 but also contains more monocytes, neutrophils and a distinct T helper 17 (T_H17) gene-expression pattern in the lymphoid pool[45]. Previous work seems to have documented TMEs with this characteristic MNP 'inflammation', and we note the profound presence of MNPs in some pancreatic[70] and liver[71,72] tumours, which suggests that although these tumours might typically be classified as cold or an immune desert they might in fact more closely fall into a myeloid-centric category. Notably, MC-DC2, like some but not all immune deserts, is characterized by tumour cells expressing fibrosis-associated genes, further emphasizing how higher-dimensional analysis is necessary to deconvolve these archetypes.

Immune-desert TMEs

Finally, as described by multiple groups, we also found immune-desert TMEs with extremely low frequencies of all $CD45^+$ immune cells, including T cells and MNPs. We were able to distinguish three types: ID-CD4-Mac, ID-CD8-Mac and ID-Mo. ID-CD4-Mac and ID-CD8-Mac had high numbers of $CD44^+CD90^+$ CAFs, and the few MNPs that were present were skewed towards macrophage differentiation, with further distinctions in the relative frequencies of $CD4^+$ versus $CD8^+$ T cells. ID-Mo had fewer $CD44^+CD90^+$ CAFs and the few MNPs were skewed towards monocytes. The ability to distinguish immune deserts based on CAF presence (Fig. 2, Table 2 and Supplementary Table 1) was previously noted in the CIBERSORT analysis of TCGA gene-expression signatures[40], although the CD4 versus CD8 distinction was not discernible by this method. This stromal as well as T cell distinction is a key area in which higher-dimensional immunoprofiling indicates fundamental distinctions that are not as obvious with lower-dimensional classifications. This important distinction is indicated not only in the patterns of chemokines used (Table 1)

Table 2 | Identifying features of each of the 12 archetypes of tumour microenvironment

Immune archetype	Notable additional cell types	Transcriptomic features			Potential origin
		Key transcriptional programmes in immunity	Chemokine axis	Key transcriptional programmes in non-immune cells	
IR-CD8-Mac	$CD4^+$ T_{reg} cells, NK cells	Type 1 immunity (M1 and T_H1); high exhaustion; interferon/TNFα signalling; PD1–PDL1/2	CXCL9/11/12–CXCR3/4; XCL1/2–XCR1	Interferon-stimulated genes; CSF1	Chronic viral infection I: $CD8^+$ T cell–macrophage axis; sustained by interferon signalling
IR-CD8-Mono	cDC1, cDC2, NK cells	Tissue-resident T_{reg} cells; lower exhaustion	XCL1/2–XCR1; CXCL2–CXCR1	Interferon-stimulated genes; SASP, EMT	Chronic viral infection II: NK cell–monocyte–cDC1–$CD8^+$ T cell axis; sustained by interferon/CCR2 signalling
IR-CD4	$CD4^+$ T_{reg} cells, cDC2	TGFβ signalling; enriched in active DCs; resting T_{reg} cells	CCL17/18–CCR4/8	ER stress (CH25H–ERN2)	Epithelial homeostasis: stromal cell–T_{reg} cell axis; sustained by TGFβ
IS-CD8	$CD4^+$ T_{reg} cells, mast cells, neutrophils	T_{rem} cells; high exhaustion; suppressive T_{reg} cells	CCL8/11/16–CCR3; CXCL1/5/6/8–CXCR2; CCL2–CCR2; CXCL9/11/12–CXCR3/4	TGFβ signalling; interferon-stimulated genes; prostaglandin	Chronic inflammation and tissue repair: tissue-resident $CD8^+$ T cells–T_{reg} cells; sustained by interferon and TGFβ signalling
IS-CD4	$CD4^+$ T_{reg} cells, macrophages, cDC2, mast cells, neutrophils	M2-like phenotype; interferon-stimulated genes in myeloid cells	CCL2–CCR2; CCL17/16/19/21/22–CCR6/7; CXCL9/11/12–CXCR3/4	TGFβ signalling; SASP; tissue repair	Tissue ageing (senescence): tissue resident T cells–M2-like macrophages; sustained by interferon and TGFβ signalling
TC-Mac	Plasma cells, $CD4^+$ T_{reg} cells	Interferon signalling; high exhaustion; suppressive T_{reg} cells; high antigen presentation/co-stimulation	CXCL13–CXCR5; XCL1/2–XCR1	Interferon-stimulated genes	Chronic intracellular infection: extrafollicular response; macrophage–T_{reg} cell–plasma cell axis; sustained by CXCL13 signalling
TC-DC	B cells, cDC1, cDC2	High in DCs; high in antigen–mast cell–DC presentation/co-stimulation	CCL28–CCR10	Nervous system; metastasis	Quiescent lymph node: TLSs; DC–conventional $CD4^+$ T cell–B cell axis; sustained by CCL28 signalling
MC-DC2	CAFs, neutrophils	Type 2 immunity (M2 and T_H2); T_H17 like; suppressive T_{reg} cells; very abundant neutrophils	CXCL1/5/6/8–CXCR2; CCL2/7–CCR2	Fibrosis; cell stress DNA damage	Symbiosis with commensal microbes: T_H17 cell–myeloid cell–neutrophil axis; sustained by CCR2/CXCR2 signalling
MC-DC1	CAFs, cDC2, cDC1	High in antigen presentation/co-stimulation	CX3CL1–CX3CR1; CXCl17–CCR6; CCL26–CCR3	ER stress (ATF3); PPARγ pathway; oestrogen signalling	Lipid metabolism/adipose: VAT cDCs acquire a tolerogenic phenotype; sustained by PPARγ, IL-10 and steroid signalling
ID-CD4-Mac	CAFs, neutrophils	Low-frequency T_{rem} cells; T_H17 like; IL-10/TNFα/IL-1 signalling	CXCL17–CCR6; CXCL1–CXCR2	Cell cycle (G1–S); nervous system	Neuronal inflammation: T_{rem} cell–macrophage axis; sustained by CXCR2 signalling
ID-Mo	Neutrophils	Low-frequency T_{rem} cells; IL-1β/ARG1 signalling; suppressive T_{reg} cells	NA	Cell division (G1–S, G2–M); proteasome pathway; autophagy	Mid wound healing: T_{rem} cell–suppressive T_{reg} cell–neutrophil axis; sustained by IL-1 and TGFβ signalling
ID-CD8-Mac	CAFs, neutrophils	Low-frequency T cells with PD1–PDL1 (high exhaustion); interferon/TNFα signalling	CCL26/27/28–CCR10; CX3CL1–CX3CR1	Cell division (G1–S, G2–M); fibrosis; EMT	Late wound healing: $CD8^+$ T cell–macrophage axis; sustained by CX3CR1 signalling

ATF3, activating transcription factor 3; CAFs, cancer-associated fibroblasts; cDC1, type 1 conventional dendritic cell; cDC2, type 2 conventional dendritic cell; CH25H, cholesterol 25-hydroxylase; CSF1, colony-stimulating factor 1; DCs, dendritic cells; EMT, epithelial–mesenchymal transition; ER, endoplasmic reticulum; ERN2, endoplasmic reticulum–to–nucleus signalling 2; NA, not applicable; NK, natural killer; PPARγ, peroxisome proliferator-activated receptor-γ; SASP, senescence-associated secretory phenotype; TGFβ, transforming growth factor-β; T_H1 cells, type 1 helper T cells; T_H2 cells, type 2 helper T cells; T_H17 cells, T helper 17 cells; TLSs, tertiary lymphoid structures; TNFα, tumour necrosis factor-α; T_{reg} cells, regulatory T cells; T_{rem} cells, resident memory T cells; VAT, visceral adipose tissue.

but also in the fact that the ID-CD8-Mac archetype shows substantially increased levels of fibrosis-associated gene expression in the tumour, as well as increased PDL1 expression and associated exhaustion, whereas the ID-CD4-Mac archetype has $CD4^+$ T cells with T_H17-biased gene expression[45].

Although immune-desert TMEs were identified in our clustering analysis foremost by their immune composition, namely the paucity of $CD45^+$ cells, we discovered that these archetypes were also very much defined by the expression of Ki-67 in the tumour compartment, much more than other archetypes, suggesting that their 'desertness' might be tied to the ways in which they avoid cell-cycle checkpoints. Both in our data set[45] and in TCGA data set analyses[38], melanoma and glioblastoma are highly represented in desert archetypes. Melanoma exemplifies the heterogeneity in TMEs, in which some are T cell centric (where we find evidence of reactive immunity and ICB responses) and others are immune deserts. A study of tumour gene expression across a cohort of patients with melanoma found that this distinction corresponds to therapeutic resistance to ICB and was associated with distinct patterns of tumour cell-cycle gene expression[73], perhaps consistent with the Ki-67 finding described above.

Evolutionary history of tumour archetypes

Cancers have long been thought to grow out because they trick the rest of the body, notably the immune system, into accepting them. In some cases, immunity is even specifically programmed by tumours in such a way as to decrease the fitness of non-transformed cells, creating a niche for tumours to propagate[74]. Archetypal forms of immunity in tumours were probably not evolutionarily selected to permit tumour outgrowth but instead represent patterns misappropriated by specific tumours[75] that have their origins in other kinds of biology. In this section we highlight similarities between tumour immune archetypes and other immune states (Table 2 and Supplementary Table 1). Undoubtedly, it is simplistic to think that TMEs are exact replicas of these other immune settings, but in many cases strong clues exist at the level of composition, as well as gene expression, to support this hypothesis. Notably, these ideas are hypothetical and will need to be validated by further experimental work.

Along the path of chronic viral infection

We propose that the response to chronic viral infection forms the basis for two distinct immune archetypes found in cancer. In both IR-CD8-Mono and IR-CD8-Mac, numbers of $CD8^+$ T cells are high but differ in their degree of exhaustion, as well as in their myeloid composition[45]. Tremendous recruitment of both antigen-specific and bystander $CD8^+$ T cells are found in some cancers[76], notably in renal cell carcinoma[77], which is a tumour type enriched in both IR-CD8 TMEs (Fig. 3a). Similarly, in chronic viral infection, $CD8^+$ T cells with viral specificity accumulate in large numbers, but become exhausted over time[78]. We note that both $CD8^+$ archetypes are defined by a CXCL9, CXCL10, CXCL11–CXCR3 axis, which is responsible for $CD8^+$ T cell recruitment[79] and further resembles the biology of an ongoing chronic viral infection. We propose that IR-CD8-Mono, in which T cells are less exhausted than in IR-CD8-Mac, represents a pattern taken from an early stage of viral infection.

Consistent with this idea, we note that macrophages, some of which might resemble TAMs (and are sometimes known as myeloid-derived suppressor cells) accumulate in late-stage chronic viral infections[80]. These macrophages seem to promote exhaustion and viral chronicity through IL-10 (ref. 81) and other factors (such as expression of PDL1), thus sparing the host from immunopathology[82]. Notably, chronic viral infections, but not acute viral infections, have enhanced myeloid recruitment in tissues and in the blood[80]. We consider it likely that monocytic recruitment is a feature of late-phase infection in general, and that, depending on the virus and the level of production of type I interferons, the resulting monocytes might differentiate to become macrophages in the later more-chronic stages.

As noted above, the IR-CD8-Mac archetype in cancer has lower numbers of NK and cDC1 cells than IR-CD8-Mono. NK cell populations expand in acute viral infection[83] and although absolute frequencies are difficult to assess in existing human studies, reports suggest impaired NK function in chronic HIV[84] and increased expression of IL-10 in NK cells in chronic hepatitis C virus (HCV)[85] and persistent hepatitis B virus (HBV)[86]. Similarly, human chronic HCV has been suggested to involve subversion of cDC1 biology[84]. Thus, additional links in cellular composition might exist between early versus late chronic infection and the IR-CD8-Mono versus IR-CD8-Mac archetypes.

Repair and homeostasis functions

Four archetypes of TME in human tumours — IR-CD4, IS-CD4, IS-CD8 and TC-Mac — have strong resemblance to various homeostatic tissue-repair functions that are characterized in immunobiology, and that prominently involve T_{reg} cells. A fifth, TC-DC, bears resemblance to a quiescent lymph node and together with TC-Mac are the most closely aligned with the concept that tumours can contain characteristics of TLSs.

Tissue repair and remodelling

The IR-CD4, IS-CD8, IS-CD4 and TC-Mac archetypes present a strong enrichment in T_{reg} cells, with the first three also showing enhancement in TGFβ signalling pathways (Table 2 and Supplementary Table 1). TGFβ is a well-known component of tissue remodelling[87].

The immunosuppressive functions of TGFβ and T_{reg} cells have been studied extensively[88] and their role in some cancers has been reviewed elsewhere[89]. However, several TCGA-based analyses of the immune classes in human tumours have already revealed the presence of a specific subset of TGFβ-enriched tumours that span multiple tissues of origin[38,40]. Armed with data from the higher-dimensional tools in the IPI data set, we suggest that TGFβ-enriched tumours might represent distinct modules of tissue-repair functions of the immune system.

First, TGFβ is often enriched in immune-rich CD4-skewed tumours (IR-CD4), which themselves are highly enriched for in lung adenocarcinomas in the IPI cohort (Fig. 3a). Pulmonary inflammation and fibrosis are highly regulated by the TGFβ pathway and by expression of αvβ6 or αvβ8 integrin[90,91]. In specific phases of injury and repair in experimental lung injury models, T_{reg} cells act to restrain $CD4^+$ conventional T cells from causing unregulated inflammation and alveolar epithelium destruction[92,93] by exerting their effect partially through modulation of macrophage development[94]. T_{reg} cell modulation of TAM maturation has been described in mouse tumour models[44], and TAMs are abundant in the IR-CD4 archetype (Fig. 2). Although the exact mechanistic comparisons need to be resolved, it seems plausible that the IR-CD4 archetype might represent the co-opting of a cellular network involved in epithelial homeostasis and repair, particularly as it is applied in airways.

Second, the two archetypes of immune-stroma TMEs (IS-CD8 and IS-CD4) might indicate distinct TGFβ usage and high T_{reg} cell functions of the immune system. As mentioned earlier, the IS-CD8 and IS-CD4 archetypes differ from others insofar as they are highly infiltrated by CAFs (Fig. 2, Table 2 and Supplementary Table 1). Beyond tumour immunology, fibroblasts are non-haematopoietic cells that populate all tissues and delineate the topography of organs by producing and remodelling extracellular matrix (ECM) proteins and support other tissue-resident cell types across tissues[95]. The role of the TGFβ pathway in regulating fibroblast biology in tumours has been extensively studied and reviewed[87], although distinctions were not made between CD8-rich and CD4-rich environments. We note that IS-CD8 tumours typically express genes associated with interferon signalling, as well as prostaglandins[45], which is consistent with more chronically activated fibrosis. T cells isolated from IS-CD8 tumours express high levels of genes such as *ITGAE* (encoding CD103) and *CD69*, which are typically associated with T resident memory phenotypes[96]. By contrast, in the IPI data set, IS-CD4-classified tumours expressed high levels of genes associated with cellular senescence (such as *CXCL8* and *IL1B*) and might thus be more closely associated with patterns found in aged fibrotic tissues[41]. Although the details that delineate the two immune-stroma archetypes are not clear at present, both are likely to be mimics of various forms of tissue fibrosis, perhaps parsing to chronic versus ageing-associated forms.

Persistent extrafollicular response

The TC-Mac archetype is characterized by the unique presence of plasma cells, which have been found in subsets of lung cancer

specifically[66] along with the emerging, although sporadic, reports of B cells in tumours more broadly[97]. As noted earlier, we believe that these TMEs, along with the TC-DC (discussed below) have been observed in other studies and referred to collectively as having characteristics of TLSs[98,99]. TLSs are lymph node-like structures that arise de novo in the stroma of hot tumours in response to antigens and inflammatory stimuli and were first described in lung and skin cancers[99].

The TC-Mac archetype is associated with infiltrates of B cells, plasma cells, T cells and macrophages (Table 2 and Supplementary Table 1). These cells have been observed to associate with each other in what have been termed lympho-myeloid aggregates (LMA)[97]. Such structures have profound similarities to the extrafollicular response zone, where B cell activation and maturation to form plasma cells occurs outside of the germinal centre and quenches the germinal centre response[100]. Extrafollicular responses require CXCL13 expression by $CD4^+$ T cells[101], a chemokine that is highly expressed by the T cells in the TC-Mac archetype[45] and has been described in both $CD8^+$ and $CD4^+$ exhausted T cells in other isolated tumour studies[63]. Typically, T_{reg} cells are also part of the TC–macrophage–plasma cell cellular network and function in the bone marrow where T_{reg} cells support plasma cell residency[102]. Such extrafollicular responses are found in vaccination and chronic intracellular bacterial infections[100]. They are also prominent in autoimmunity in which they again comprise activated B cells and plasma cells alongside CXCL13-expressing $CD4^+$ T cells to promote auto-reactive B cell development[100,103]. Although extrafollicular responses have not been formally described in cancer, it is tempting to propose that they represent a potential origin for these TC-Mac TMEs, in which CXCL13-expressing T cells, helped by T_{reg} cells, sustain B cell development[104]. This process might regulate peripheral B cells to target tumour antigen[105] or might generate non-tumour-specific B cells that might benefit tumour growth[106].

Quiescent immunity

Although TC-Mac TMEs (or LMAs) are probably one manifestation of highly organized TLSs, the TC-DC TMEs perhaps better resemble lymph nodes owing to the high frequency of DCs and immature B cells. (Fig. 2, Table 2 and Supplementary Table 1). This finding suggests that some tumours might co-opt the biology of a quiescent lymphoid organ in which immune responses are largely suppressed in the absence of infection, for example, by suppressive stromal elements[107,108]. We note that TC-DC tumours are also characterized by substantial expression of the CCL28–CCR10 axis[45], which is important for patterning lymphangiogenesis[109]. Thus, we suggest that tumours might co-opt lymphangiogenesis to cloak themselves as a developing lymphoid organ and thus counteract immune activation.

Two myeloid-centric archetypes (MC-DC2 and MC-DC1) and one immune-desert (ID-CD4-Mac) archetype also bear intriguing resemblance to various quiescent immune states and tissues. All of these TMEs display a relatively high abundance of CAFs but contain few T cells (thus they might all be classified as immune-poor or immune deserts in other studies). The monocyte–macrophage presence with CAFs is consistent with a central role for a fibroblast–monocyte–macrophage axis in the establishment of those poorly infiltrated environments[110].

MC-DC2 tumours contain a high infiltration of cDC2 and T_H17 cells, a pairing that has been shown to be essential for the establishment of immune tolerance towards commensal microbes in mucosal tissues such as skin[111] and gut[112] (Table 2). Relatedly, a study in mouse lung models has shown that dysregulation of local microbiota stimulates IL-17 production and other pro-inflammatory mediators to promote expansion of neutrophils – a cell type that is also enriched in this kind of TME – and tumour cell proliferation[113]. This finding suggests that the mechanisms put in place by the immune system to interact with host microbiota could be at the origin of some MC-DC2 tumours.

MC-DC1 TMEs, by comparison, have features that are reminiscent of the immunobiology of visceral adipose tissue (VAT). In VAT, resident T_{reg} cells and macrophages form an axis of interaction that regulates adiposity[12,114]. Furthermore, cDC1 cells (Table 2) harbour a tolerogenic phenotype in VAT through activation of the WNT–β-catenin pathway inducing IL-10 production, resulting in their decreased antigen presentation functions[115]. Significant expression of PPARγ genes in these tumours is also reminiscent of the role of that pathway in lipid metabolism, as well as in immune regulation in VAT[116].

Finally, ID-CD4-Mac tumours are immune deserts with macrophage and CD4 biases within the sparse immune infiltrate. They show a T_H17 bias that is reminiscent of the finding that brains under homeostasis also contain few T cells, but certain barriers, namely the epithelial blood–cerebrospinal fluid barrier, seem more permissive to T_H17 cell entry[117]. The brain contains tissue-resident microglia that are in charge of synaptic pruning[118,119], and the idea that some immune-desert TMEs arise from immune privileged environments is supported by the high proportion of brain tumours that present with TAMs with lineage and phenotypic resemblance to microglia[120]. Together, these findings suggest a possible origin for this archetype in the highly restricted surveillance and activity of the immune system in the central nervous system; however, the evidence remains difficult to assess at present.

Wound healing

Cancers have been described as 'wounds that do not heal'[121]. Two immune-desert archetypes (ID-Mo and ID-CD8-Mac) bear substantial resemblance to the immune system's participation in wound healing. Both have low overall numbers of T cells, which is consistent with wounds. One has substantial numbers of infiltrating neutrophils and immature myeloid cells (ID-Mo) the other has more mature myeloid populations (ID-CD8-Mac) (Table 2 and Supplementary Table 1). In skin wound healing, a first wave of neutrophil and monocyte infiltration driven by IL-1 and TGFβ signalling is followed by the differentiation of monocytes into macrophages, which are responsible for clearance of cellular debris and coordinate with fibroblasts and keratinocytes in tissue healing through ECM remodelling[122]. Wound healing is thus seen as a series of stages[123], with the emerging understanding that each phase has distinct space- as well as time-dependent accumulation of cell types[124]. To this extent, the two remaining immune-desert archetypes (ID-Mo and ID-CD8-Mac), with very sparse T cell infiltration, seem most like mid- and late-phase wound healing.

Further insights into origins

The idea that subsets of tumours exploit specific evolutionary immune states unlocks new possibilities, and further progress will be aided by integrating the wealth of single-cell multi-omics data generated in projects such as the Human Cell Atlas project[125], as well as individual studies that highlight variations in specific immune populations across many tissues[126,127].

Tumour archetypes and systemic immunity

The immune system is a connected network, and the composition and function of TMEs are strongly influenced by the contents and conditions in the periphery, as well as by the ability of cells in the periphery

to migrate to or from the TME[128]. The importance of systemic immunity for a successful antitumour immune response is seen in mouse experiments in which inhibition of egress from lymphoid organs or surgical resection of tumour-draining lymph nodes (TdLNs) abrogates both natural and therapeutically induced[129] antitumour immunity. Our group and others demonstrated that trafficking of cDC1 and cDC2 from the tumour to the TdLNs is required for the priming of tumour-specific $CD8^+$ T cells[22,64,130] and $CD4^+$ T cells[42,131], demonstrating that localized antitumour immune response is highly dependent upon continuous input from the periphery[129]. This fact has been emphasized by multiple preclinical studies highlighting that ICB efficacy is dependent on peripheral T cell expansion and replenishment with fresh stem-like T cell clones[132] that reside in the TdLNs[133].

Furthermore, the global immune landscape is known to be substantially altered in individuals with tumours. Human and animal model data exemplifying the range of systemic immune perturbations that occur during tumour development have been reviewed elsewhere[134]. In one pertinent example in the context of dominant archetypes of TMEs, tumour burdens can result in the expansion of immature myeloid cells such as monocytes[135] and neutrophils[136] and thus might provide positive feedback into particular myeloid-based archetypes. Additional studies demonstrate tumour-dependent altered systemic immunity in the spleen[137] and lymph nodes[138]. These systemic changes are associated with improved metastatic dissemination[138,139], which suggests that tumours preprogramme the systemic immune system to bias it towards their favoured archetypal biology in distant organs.

Modified systemic immunity also modifies the generation of reactive archetypes. For example, circulating NK cells from patients with clear cell renal cell carcinoma (ccRCC) can exhibit an 'inhibitory' phenotype characterized by high expression of CD48, CD45, CD85j and PD1 (ref. 140). The expression of this phenotype can distinguish patients with ccRCC from healthy individuals[140], and we speculate that such systemic biases in NK cells would alter the NK–cDC1–$CD8^+$ T cell reactive axis. Another study demonstrated that higher levels of circulating antigen-specific exhausted T cells (both before and after immunotherapy) correlated with worse long-term outcomes after anti-PD1 therapy[141]. Thus, what is in the periphery might well dictate what is in the tumour and therefore might be crucial for understanding ICB response mechanisms. Altogether, these data strongly support the notion that systemic corruption of immune organization occurs across diverse types of TME. The relationship between different TMEs and the peripheral immune system remains unclear. Further work is needed to fully characterize the distinct types of peripheral immune state in patients with cancer and the associations of these types of immune state with the TME, tumour tissue of origin, stage of development and patient demographics.

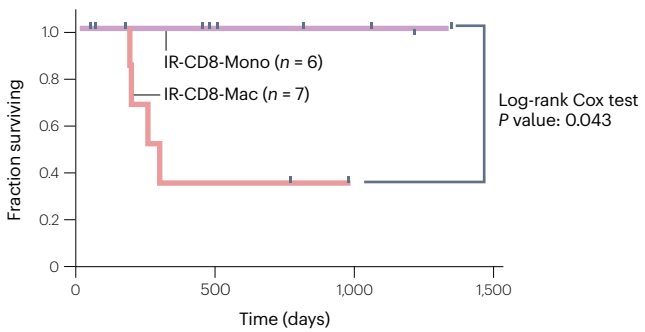

Fig. 4 | The dominant tumour immune archetype is associated with different disease outcomes in patients with kidney cancer. Survival curves of patients with kidney cancer grouped by immune archetype (which was revealed by flow cytometry analysis of the intertumoural immune composition). Part **a** adapted with permission from ref. 44, AACR.

Transitioning between archetypes

Tumour development is a dynamic process and although we and others have shown the existence of a limited number of immune classes spanning human solid tumours[38,40,45], how these classes align with stages of tumour development or, more importantly, how they might relate to each other and transition from one to another remains unclear.

Work from the Wu group using multi-modal single-cell RNA-seq in a cohort of 13 patients with ccRCC at different tumour stages showed that numbers of terminally exhausted $CD8^+$ T cells and M2-like macrophages progressively increase during tumour development[43]. This increase is associated with increased expression of ligands and receptors that support T cell dysfunction and macrophage development (CSF1), recruitment (CXCL12) and polarization (IFNγ)[43]. These cell networks represent linked cell states that vary between the two IR-CD8 archetypes (Fig. 2, Table 2 and Supplementary Table 1), so one could conclude that early tumours could start from the IR-CD8-Mono archetype and progressively transition to the IR-CD8-Mac archetype (which promotes T cell exhaustion, thus enabling tumour immune escape). Our own studies did not find a stage-specific bias in which archetypes were present across cancers, although this effect might vary within cohorts and study details[45]. A parallel study in another cohort of patients with ccRCC showed that only tumours with decreased levels of the exhausted T cell–macrophage axis (that is, more like the IR-CD8-Mono archetype) responded to ICB therapy[142], and we have noted that this archetype has higher levels of the cDC1 cells associated with reactive CD8 immunity[22,143] than IR-CD8-Mac. This finding suggests that a better understanding of the transition from one state to another could help us to improve tumour treatment and develop the next round of cancer immunotherapies.

Moreover, the question regarding the transition between archetypes is not limited to the immune-rich TMEs. Indeed, the major role of TGFβ in both immune-stroma TMEs and IR-CD4 TMEs (in which cross-talk between CAFs, macrophages and T_{reg} cells is prominent) could indicate that those TMEs are part of a common path that tumours could follow and in which they could be stopped at various steps. Therefore, delineating the transition from one state to another might reveal how tumours could evolve into different archetypes despite a shared transcriptomic pathway.

Sterile tissue wounding demonstrates that the presence or introduction of some cell types clearly inhibits the introduction of others; for example, macrophages seem to regulate the entry of neutrophils[144]. It is tempting to postulate, therefore, that modulating the correct cell type could modulate others and thus dissemble or reassemble a TME into a microenvironment capable of improved immune destruction or one that is more permissive to reactive immune archetype biology[143] (Fig. 1). Although we still lack evidence to support this theory, in Fig. 3b we illustrate the potential 'distance' between immune archetypes using published transcriptomic data sets. In this rendering, the *z* axis of this 3D plot is based on a Manhattan distance calculated between the centroid of each archetype and the sample[145]. Although we acknowledge that this figure is hypothetical, more of a cartoon than data, we hope it illustrates the idea that some of these TMEs might be closer than others, and that multi-omics data could enable computational

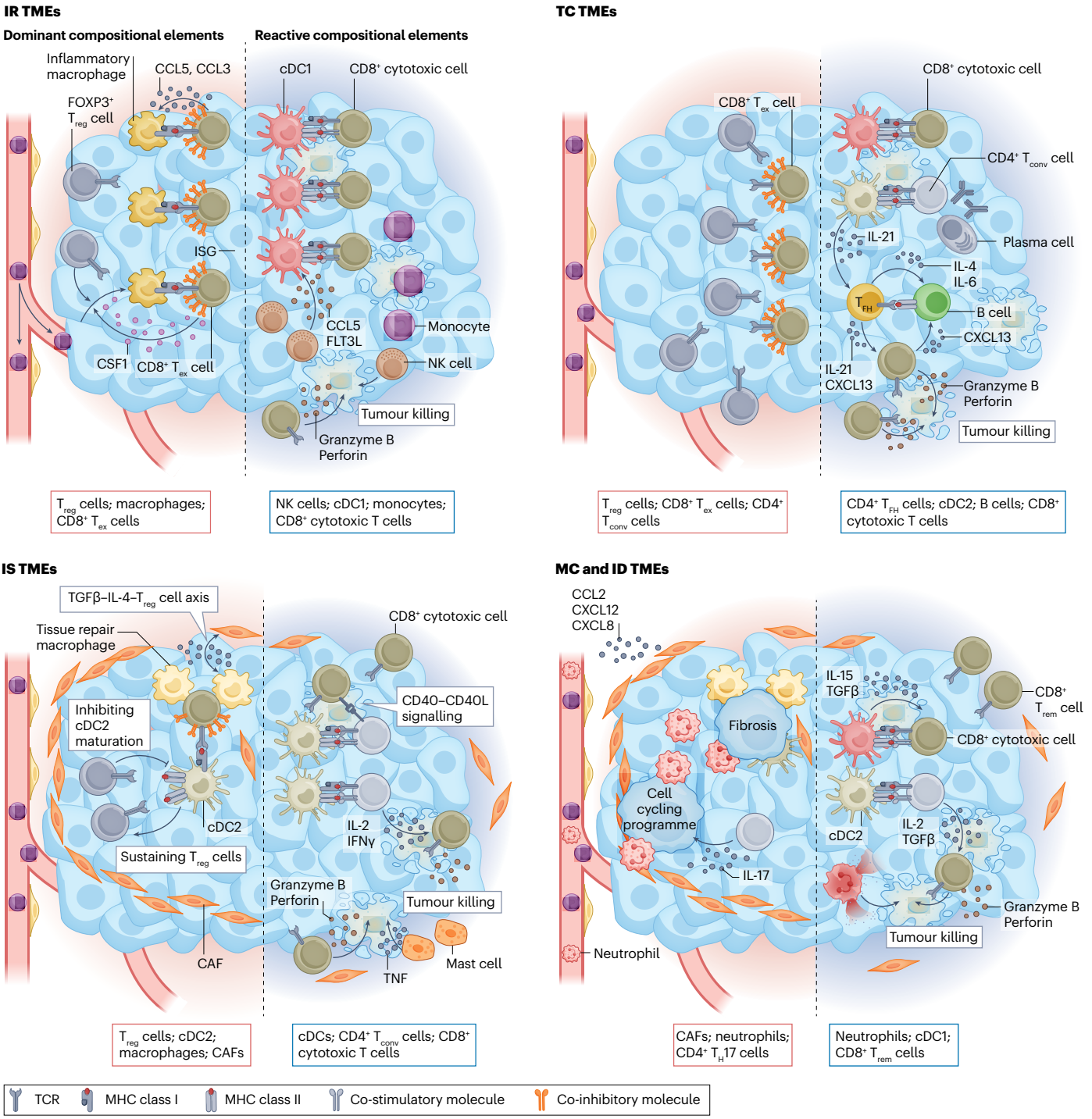

Fig. 5 | The dominant tumour-promoting immune archetype serves as a scaffold to identify the reactive tumour-eliminating cellular network. The observed relationships of dominant immune archetypes and the presence of components of reactive immunity, grouped by broad class: immune rich (IR), T cell centric (TC), immune stroma (IS), myeloid centric (MC) and immune deserts (ID). Each panel summarizes the distinct compositional elements and cellular networks that make up the dominant characteristic of the tumour microenvironment (TME) (which promote tumour growth (left)), as well as the rare reactive immune archetypes that reside within each of them (right). Co-stimulatory molecules include CD28 on $CD8^+$ and $CD4^+$ T cells, and CD86/CD80 on conventional type 1 dendritic cell (cDC1) and cDC2. CAF, cancer-associated fibroblast; ISG, interferon-stimulated gene; MHC, major histocompatibility complex; IFNγ, interferon-γ; NK cell, natural killer cell; T_{conv} cell, conventional T cell; TCR, T cell receptor; T_{ex} cell, exhausted T cell; T_{FH} cell, follicular helper T cell; T_H17 cell, T helper 17 cell; T_{reg} cell, regulatory T cell; T_{rem} cell, resident memory T cell.

identification of transcriptomic programmes shared between cell types across TMEs that could be potential vectors for these transitions. The role of the various gene programmes will need to be validated experimentally; the development of multiple single-cell technologies using CRISPR–Cas9 genetic perturbations[146,147] opens avenues for in-depth investigation.

Transcriptomic data alone will not be sufficient to understand the whole complexity of such TME transitions. Several studies have highlighted the ability of tumour cells to induce epigenetic modifications in TME-infiltrating immune cells to aid immune surveillance evasion. For instance, the lack of TILs in several human cancers is associated with DNA methylation-induced epigenetic silencing of *CCL5* (ref. 148) (which encodes a chemokine involved in exhausted T cell–macrophage crosstalk and is highly expressed in the IR-CD8 archetypes[51]). Moreover, epigenetic regulation is a key driver for T cell exhaustion in various cancers, and specific epigenetic marks are associated with immunotherapy treatment in patients with melanoma[149] or mammary tumours[68]. Undoubtedly, the use of single-cell technologies to study the epigenetic state of the immune compartment in the TME (as has already started in tumours themselves)[150] will be essential to better understand the transition between tumour immune archetypes.

Conclusions

We outline here the evidence that the TME is not invariant across tumour types, but that at least 12 reasonably common and archetypal bulk-level collections of immunobiology exist, spanning tumour types. Each of these archetypes is composed of distinct cellular networks that interact with and promote tumour growth differently. In an era of precision immunotherapies for cancer, understanding the broader context in which these therapies operate — such as the type of TME — will be essential to determine the most appropriate therapy for each patient.

We have previously described emerging variations in reactive immune archetypes (the collections of cell types that seed productive immune responses that are enhanced by ICB), and how their initial presence is deemed to be crucial[143]. Key components of reactive archetypes are rare in growing tumours, and here we note how their prevalence might depend on the dominant archetype in which they reside; for example, the prevalence of monocytes in an archetype tends to partner with higher prevalence of cDC1 and reactive immunity. A fine balance between dominant tumour-promoting archetypes and reactive tumour-eliminating archetypes can be seen in each kind of TME. This model suggests that regardless of the tissue of origin or the tumour mutational burden (TMB), the original kind of TME in which the tumour resides would be a better indicator of which immunotherapy to use or of their degree of responsiveness. For now, this model is hypothetical and will need to be tested, probably first in animal models in which the dominant archetype can be precisely defined before testing several immunotherapies, including the one that is most likely to promote tumour clearance based on the reactive features present. In that vein, we conclude by highlighting some observations.

The IR-CD8 archetypes seem to be dominated by chronic activation of the interferon pathway, which is marked by substantial ISG expression in tumours[45,69] and by the variable prevalence of a feedback loop between macrophages and exhausted $CD8^+$ T cells[43,44,52] through a CSF1 and CCL5 axis[51]. Here, exhausted T cells or T_{reg} cells drive monocyte differentiation towards a TAM phenotype, which is associated with tumour growth, poor prognosis in patients with ccRCC[44] (Fig. 4) and ICB therapy resistance[142,151]. Those same IR-CD8-Mono TMEs contained notable numbers of cDC1 and NK cells; these cells are key components of type I reactivity[143], which has been associated with tumour regression in mouse melanoma models[22,26,64,65] and ICB responsiveness in patients with melanoma[25] (Fig. 5). Therefore, therapies that promote cDC1 recruitment[64], deplete T_{reg} cells[44] or exhausted T cells[51], include engineered NK cells[152] or influence the interferon signalling pathway[153,154] might serve as candidates for sensitizing these types of TME.

For the immune-stroma archetypes, the axes of cDC2–T_{reg} cells[42] and macrophage–CAF[155] seem to be the main elements that oppose reactive immunity; these TMEs might be sensitive to therapies that target a specific subset of CAF[55] or TGFβ pathways[58,156] (Fig. 5). Although these TMEs are associated with poor response to ICB as a monotherapy[40], reactivity to ICB might be well served by first diminishing the T_{reg} cell, TGFβ and CAF axes.

The T cell-centric TMEs are dominated by a T_{reg} cell–exhausted T cell suppressing axis[45], but only the TC-Mac archetype expresses CXCL13 — a mark of TLS formation[67] and extrafollicular response, which might provide essential CD4 help (through CD40–CD40L engagement) to $CD8^+$ tumour-specific T cells[157] (Fig. 5). This idea is perhaps supported by a study describing CXCL13-expressing T cells as representing a hallmark of ICB response across various human tumours[63]. Studies have also highlighted the importance of the spatial organization for this CXCL13-dependent network[23], which underlines the need for further investigation of the spatial landscape of tumour immune archetypes and how dominant and reactive archetypes might be juxtaposed. We do note that the TC-DC archetype has a stronger resemblance than any other archetype to a resting lymph node (Table 2 and Supplementary Table 1), and it will be important in future studies when TLSs are invoked, to differentiate on the basis of plasma B cell (TC-Mac) versus resting B cell (TC-DC) prevalence in addition to their other differences.

Finally, although the myeloid-centric and immune-desert TMEs frequently feature a neutrophil–macrophage–T_H17 cell axis that is generally associated with tumour progression, bad prognosis and metastasis[158], they represent the right environment in which T resident memory cells are most enriched as a proportion of all T cells, and could serve in a prominent curative role[159,160] (Fig. 5). We also note that as these tumours have a profound paucity of overall immune cells, they are the most subject to error in our ability to resolve their key features. For similar reasons, non-immune cells are certainly essential for promoting cancer immunity and response to ICB therapy[161].

As a final note, we strongly believe that understanding the archetypal classification of immune responses can not only serve as a framework to direct immunotherapies to the most relevant biology but will also help us to better understand the adverse effects of immunotherapies[162]. Although immunotherapy is aimed at the tumour, distant tissues might have the same or distinct archetypal biology (Table 2 and Supplementary Table 1). Extending knowledge of the archetypes of immune systems beyond the tumour might ultimately be necessary to inform how disparate cancers are safely treated. We also think it is likely that these archetypes for cancer immune states represent all or a subset of the archetypes of peripheral immune tolerance more generally. In other words, we hope that by finding the classes of immune system by which tumours cloak themselves, we have also begun to map the diversity of immune-tolerant states more generally.

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