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Not all cancers are created equal: Tissue specificity in cancer genes and pathways

Joy J. Bianchi[1,2,a], **Xin Zhao**[1,2,a], **Joseph C. Mays**[1,2], **Teresa Davoli**[1,2]

[1]Institute for Systems Genetics, NYU Langone Health, New York, NY 10016, USA

[2]Department of Biochemistry and Molecular Pharmacology, NYU Langone Health, New York, 10016, USA

Abstract

Tumors arise through waves of genetic alterations and clonal expansion that allow tumor cells to acquire cancer hallmarks, such as genome instability and immune evasion. Recent genomic analyses showed that the vast majority of cancer driver genes are mutated in a tissue-dependent manner, that is, are altered in some cancers but not others. Often the tumor type also affects the likelihood of therapy response. What is the origin of tissue specificity in cancer? Recent studies suggest that both cell-intrinsic and cell-extrinsic factors play a role. On one hand, cell type–specific wiring of the cell signaling network determines the outcome of cancer driver gene mutations. On the other hand, the tumor cells' exposure to tissue-specific microenvironments (e.g. immune cells) also contributes to shape the tissue specificity of driver genes and of therapy response. In the future, a more complete understanding of tissue specificity in cancer may inform methods to better predict and improve therapeutic outcomes.

Keywords

Cancer driver genes; Tissue specificity; DNA damage response; Cancer immune evasion; Mutations; Aneuploidy

Introduction

It has long been known that cancer driver genes can have profoundly different effects in different tissues. For example, germline mutations in *BRCA1/BRCA2* increase the risk of breast and ovarian cancers much more than other types of cancer, whereas mutations in the mismatch repair (MMR) pathway contribute to colorectal cancer. At the somatic level, *KRAS* mutations are frequent in lung, colon, and pancreatic tumors but not in other cancers. Recent genomic analyses of human cancers have confirmed and expanded this notion,

Corresponding author: Davoli, Teresa (Teresa.Davoli@nyulangone.org).

Author contributions

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[a]These authors contributed equally.

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revealing that the vast majority of cancer driver genes, with a few exceptions (e.g. *MYC*), are mutated or amplified/deleted in a tissue-specific way (Figure 1) [1,2]. These data also indicate that tumor cells from different tissues often acquire similar cancer hallmarks, such as genome instability and proliferation, in a tissue type–dependent manner.

One of the cancer hallmarks that have recently received increased attention is cancer immune evasion, owing to novel outstanding therapeutic opportunities. The explosive growth of the field of immune oncology in the past few years has revealed high tissue specificity of both (1) the frequency of mutations in genes and pathways that control cancer immune evasion (e.g., *B2M* and *HLA-A/B*) and (2) the efficacy of cancer immunotherapy – current immunotherapy strategies such as checkpoint inhibitors can achieve enduring clinical benefit in a fraction of patients affected by certain tumor types (e.g. melanoma or lung cancer) but are less effective for other cancers (e.g. pancreatic cancers) [3,4].

What are the causes of tissue specificity of cancer driver genes and of therapy response? Tissue specificity of cancer genes may be explained by tissue-specific expression level (the fact that a gene is expressed at different levels across tissues), but computational analyses suggest that this is generally not the case [5]. Instead, recent studies indicate a different scenario [6–9]. On one hand, each cell in the body has a specific signaling network that depends on its developmental origin. This circuitry (cell-intrinsic) plays a role in determining the type of outcome of mutations in a certain gene (e.g. increased proliferation or genome instability) [6,7,9]. On the other hand, tumor cells interact with tissue-specific microenvironments (cell-extrinsic; e.g. immune cell composition or exposure to hormones) that can influence the way mutations in specific cancer genes and pathways are selected for during tumorigenesis [8]. Here, we will cover recent advances in the field, focusing on aspects of the DNA damage response (DDR) and cancer immune evasion. We will provide specific examples of how both tumor cell-intrinsic and cell-extrinsic factors cooperate to determine the tissue specificity of cancer driver genes and pathways.

Tissue specificity of DDR genes and genome instability

DDR genes are among the most mutated genes in cancer [10]. Although some of them are mutated also at the somatic level (such as BRCA1/2), most DDR genes are mutated mainly at the germline level and promote the development of tissue-specific cancers. For example, germline mutations in the nucleotide excision repair (NER) pathway (e.g. *XPA, XPC, XPE*) induce xeroderma pigmentosum (XP), a hereditary skin syndrome that promotes cutaneous cancers. Patients with germline mutations in the homologous recombination pathway (e.g. *BRCA1* and *BRCA2*) have an increased risk of developing breast and ovarian cancers, whereas germline mutations in the MMR pathway (e.g. *MSH2, MSH6*, and *MLH1*) contribute to hereditary nonpolyposis colorectal cancer (also known as Lynch syndrome) [11]. Despite the tissue specificity of these cancers, genes involved in DNA repair pathways are expressed at a similar level across tissues including those from which the cancer originates [5,12]. Distinct mechanisms involving cell-extrinsic and cell-intrinsic factors have been explored to explain the tissue-specific effects of DDR mutations.

First, cell-extrinsic factors such as exposure to environmental mutagens and hormones can impact the tissue specificity of mutations in DDR genes (Figure 2). Different organs and tissues are exposed to specific mutagens which give rise to specific type of DNA damage and related mutation signatures in cancer genomes [13,14]. For instance, UV light induces several types of DNA lesions including pyrimidine dimers, which can be repaired by NER. Accordingly, NER pathway genes are highly mutated in skin cancers [5]. Organs such as the mammary gland are not directly exposed to environmental mutagens but can be affected by endogenous genotoxic metabolites. For instance, excess estrogen can be metabolized into quinone radicals that induce oxidative damage in DNA; BRCA1 acts in a tissue-specific manner to regulate these estrogen-metabolizing enzymes [15]. Thus, it is possible that in the case of BRCA1, as in NER-deficient skin cancers, the tissue specificity of cancer driver genes arises from the interaction between the exposure to tissue-specific mutagens and DNA repair pathways.

A second possibility is that the outcome of DDR gene mutations depends on the interaction between cell-extrinsic factors (e.g. hormones) and cell type–specific circuitry of signaling pathways. For BRCA1, it has been proposed that the tissues where the tumors manifest may be the only ones in which complete loss of the DNA repair gene is tolerated through hormone-dependent proliferative signals [16]. Supporting this hypothesis, it has been suggested that estrogen plays a fundamental role by specifically protecting mammary (and possibly ovarian) epithelial cells (MECs) from the oxidative stress-induced cell death occurring in the absence of BRCA1 [9] (Figure 2). This effect is mediated by the binding of estrogen to its receptor (ER) that can subsequently regulate NRF2 via the PI3K-AKT pathway. Recent studies also suggest another mechanism in which mature *BRCA1*-haplodeficient MECs, expressing ER and progesterone receptor, can stimulate the progesterone receptor–dependent secretion of RANKL. Through a paracrine signaling, RANKL then activates its receptor RANK, localized on luminal progenitor cells (LPCs) that lack ER and triggers subsequent LPC proliferation through NF-κB pathway [17,18]. Interestingly, LPCs have been proposed to be the cell-of-origin of the basal-like subtype of breast cancer and BRCA1-deficient LPCs display a greater sensitivity to ionizing radiation and replication stress than wild-type LPCs. Thus, activation of NF-κB may increase the genomic instability of RLPCs by promoting their proliferation, which in turn induces additional replication-associated DNA damage and constantly activates intrinsic NF-κB activity, thereby freeing the proliferation of LPCs from hormonal influences [18].

Third, tissue specificity of DDR mutations in cancer could be explained by cell-intrinsic factors, that is, the fact that DNA repair genes can modulate cell type–specific cellular signaling pathways that are critical for tumorigenesis, such as differentiation of tissue stem cells (Figure 2). For example, apart from its involvement in DNA repair, several *in vitro* and *in vivo* studies have proposed a direct role of BRCA1 in cell fate determination. Indeed, depletion of BRCA1 impairs differentiation of MECs and maintains a stem cell–like behavior [19,20]. BRCA1 activates the NOTCH pathway by transcriptional upregulation of NOTCH ligands and receptors, in breast cells. This regulation is important for normal breast differentiation, as knockdown of NOTCH signaling components results in loss of ER (estrogen receptor) and luminal marker expression [21]. In addition, BRCA1 negatively regulates SLUG protein stability, which promotes breast differentiation, as SLUG acts by

functionally suppressing human breast progenitor cell lineage commitment and differentiation [22]. BRCA1 has also been shown, specifically in MECs, to positively regulate the transcription of SIRT1, a deacetylating enzyme involved in many functions including the regulation of telomere length and the induction of apoptosis. Accordingly, BRCA1-haplodeficient human MECs exhibit significant telomere shortening and chromosomal instability [23]. Hence, BRCA1 can contribute to tumorigenesis in hormone-sensitive and ER-negative populations through synergic interactions and a tumor-promoting environment specific to breast tissue.

Finally, other factors must be considered. Colorectal cancers arise from rapidly dividing stem cells and are also associated with mutations in MMR genes [5]. Indeed, DNA mismatches occur frequently at the replication fork of dividing cells, and thus MMR is especially crucial to prevent the fast accumulation of DNA replication errors and extensive genomic microsatellite instability in intestinal stem cells [1]. Accordingly, context-specific mutation signatures associated with replication timing were retrieved at point mutations affecting various colorectal cancer driver genes in adult stem cells of the colon, the cells of origin of this cancer [24]. Moreover, cell-of-origin chromatin and epigenomic features are the best predictors of cancer mutation rates, suggesting that variations of the epigenomic landscape across tissues may also contribute to cell type–specific mutagenesis [25]. Therefore, context-specific differences in features such as replication timing or chromatin structure can also shape the tumor-specific effects of DDR mutations and the acquisition of genome instability in human cancer.

Tissue specificity of cancer immune evasion

Evading recognition and killing by the immune system represents a crucial hallmark of cancer and is targeted by immunotherapy strategies [3,4]. Although some tumor-agnostic markers of response have been identified, such as the extent of cytotoxic immune infiltrate, there is an increasing recognition of the role of tissue- and context-specific determinants of cancer immune evasion and therapy response [8].

As with other cancer hallmarks such as genome instability (see to the aforementioned information), the mechanisms of cancer immune evasion and the likelihood of responding to immunotherapy vary across tumor types. Similarly to other cancer driver genes, the spectrum and frequency of point mutations or deletion/amplification in cancer genes that drive immune escape is highly tissue-specific. For example, genes that are crucial for antigen presentation such as *B2M, HLA-A*, and *HLA-B* act as tumor suppressors in a fraction of skin melanoma, colorectal, head and neck, or lung cancers [26,27] but not in breast, ovarian, or pancreatic cancers (Figure 3). Because antigen presentation is necessary for Tcell–emediated recognition and killing of tumor cells, a high (vs low) frequency in the inactivation of this pathway suggests a high (vs low) degree of selection to escape T cell recognition [28]. Perhaps not surprisingly, the tumor types showing the highest rate of clinical response after anti-PD1 and/or anti-CTLA-4 immunotherapies (which reactivate mainly T cell–mediated immunity) are the same tumor types that display significant inactivation of genes involved in antigen presentation. In fact, current immunotherapy strategies have demonstrated clinical benefit mainly in melanoma, lung, colorectal, head and

neck cancers but much less in other tumor types such as pancreatic or ovarian cancers [3,4,29–32].

Why do distinct tumor types display different patterns of mutations in cancer genes driving immune evasion and different response to immunotherapy? Among the possible causes are (1) how cellular pathways implicated in immune recognition are regulated in tumor cells from different tissues (cell-intrinsic factors) and (2) how tumor cells interact with tissue-specific immune microenvironments (cell-extrinsic factors) (Figure 3) [8,33].

First, among the tumor cell–intrinsic properties, different tumor types display different loads of point mutations and aneuploidy that can alter tumor immune properties. For example, owing to UV- and smoke-related DNA damage, melanomas and lung cancers have among the highest number of point mutations (and thus neoantigens) that can promote tumor immune recognition [34–36]. Although this hypothesis can in part explain why highly mutated tumor types are more likely to respond to immunotherapy, it does not explain why tumors with, on average, lower amount of mutations such as kidney tumors (and in part head and neck tumors), can still show a good response rate. Even though the total number of mutations is positively associated with T cell infiltrates in some tumor types, neoantigen and mutation burden are not always good predictors of cytotoxic infiltrate and immunotherapy response [28,37,38]. The level of aneuploidy is associated with lower amount of cytotoxic markers both within and across many cancer types and could explain in part why tumor types mainly driven by copy number alterations, such as ovarian and pancreatic cancers, tend to respond poorly to immunotherapy [39–42].

Second, in addition to the total load of point mutations or aneuploidy, alterations in specific cancer genes primarily involved in other cellular pathways can affect the cancer immune phenotype [43]. Although mutations in some cancer drivers are associated with high (e.g. *CASP8* and *EP300*) or low (e.g. *IDH1* and *APC*) level of cytotoxic markers across most tumor types, many associations between mutations and immune markers are tumor type–specific [42,44]. For example, *TP53*-mutant tumors tend to display a lower level of cytotoxic markers than *TP53*-wild-type tumors in pancreatic, colorectal, and head, and neck cancers, whereas in breast and lung cancers and in sarcomas *TP53* mutations are linked to higher immune infiltrate [43–45].

Third, re-expression within the tumor cells of cancer testis antigens or endogenous retroviruses, which are normally restricted to the germline, is associated with different cancer immune properties in a tumor type–specific manner. For example, expression of cancer testis antigens positively correlates with cytotoxic immune infiltrates in breast, lung, cervix, bladder, uterine, and stomach cancer [28,45]. In contrast, in melanoma, MAGEA antigen expression predicts resistance to CTLA4 blockade [37]. Expression of viral antigens by tumor cells positively correlates with the IFNγ level and other cytotoxic markers in cervix, kidney, and head and neck cancers (positive for human papilloma virus) and stomach cancers (positive for Epstein–Barr virus) [28,44].

Tumor-extrinsic features that characterize the tissue-and organ-specific immune microenvironment also shape the strategies used by cancer cells to evolve during tumor

development. The immune system has evolved and diversified across different parts of the body, depending on the extent and spectrum of pathogens' exposure. Thus, the composition, differentiation, and activation status of immune cells vary across tissues. Lung and gut mucosae, which are directly or indirectly exposed to exogenous viruses, have developed a strong local army of tissue-resident immune cells — especially T cells and B cells — to fight the infections locally as compared with internal organs such as ovary, breast, or pancreas, which are not as directly exposed to exogenous pathogens [33]. In addition, the level of markers of activated T and NK (Natural Killer) cells is higher in normal lung, colon, and ileum tissues than in other tissues such as brain, ovary, and kidney [28,46–48].

Overall, across tissues, the extent and spectrum of the immune infiltrate in tumors follow a trend similar to normal tissues, suggesting that the pre-existing tissue-specific microenvironment is often retained in the tumors. For example, colon or stomach cancers and brain or liver tumors display among the highest or lowest level of T and NK cell cytolytic markers, respectively [28,44,49–51], similar to their normal counterpart. However, there are notable exceptions. For example, melanoma, head and neck, and kidney cancers are among the tumor types with high proportion of IFNγ-dominant subtype, characterized by high abundance of cytotoxic markers cells (e.g. CD8 T and NK cells) [28,44,49,52], much higher than their adjacent normal tissues. Other tumor types, such as a large proportion of pancreatic adenocarcinoma, display myeloid-inflamed stroma that may contribute to a weak response to immunotherapy in these patients [53,54].

Trafficking and homing of immune cells to different organs can also vary widely and play different roles in tumorigenesis and response to immunotherapy. For example, a recent study using a syngeneic model of melanoma showed that, in the skin, melanoma cells recruit blood-derived inflammatory monocytes that contribute to antibody-dependent tumor cell killing, whereas in the lung, shrinking of melanoma metastases depends on tissue-resident macrophage populations [55]. Organ-specific microbiomes can regulate, in different ways, systemic immune responses, as in the case of the intestinal microbiome, which can not only promote systemic antitumor immune responses [56] but also the local immune microenvironment, as in the case of the lung microbiome, which promotes tumorigenesis through recruitment of γ/δ T cells [57,58].

Finally, if the local microenvironment plays a significant role in shaping the anticancer immune response, then metastatic lesions derived from the same tumors but located in different organs should undergo tissue-dependent immune response and regulation. Recent data from patients with metastatic cancer suggest that this may be the case [59,60]. Compared with metastases (from melanoma, colorectal, or lung cancer) to other sites, metastases to the liver tend to show a lower cytotoxic T cell/Treg ratio and a weaker response to immunotherapy [60–62]. This suggests that the strong immune tolerance of the liver, whose local immune system evolved to limit harmful immune response against food and microbiota, promotes immune tolerance against cancer cells and limits the efficacy of immunotherapy. Interestingly, compared with the liver, melanoma metastases to the brain, an immune privileged organ also characterized by low cytotoxic molecules, respond well to immunotherapies, similar to nonbrain lesions [63]. Although other explanations are possible, it is plausible that in brain metastases the physical disruption of the blood–brain barrier

profoundly alters the local microenvironment, promoting leukocyte infiltration in this otherwise immune privileged organ [28,50,64].

Final remarks and open questions

Recent studies highlight how the crosstalk between cell type–specific rewiring of signaling pathways [7,65] and tissue type–specific microenvironment [8] shapes the tumor type–specific mutational frequency of cancer driver genes, as well as response to therapy. Although, we have covered some aspects of tumor type–specific response to immunotherapy, tumor type often also dictates response to targeted therapies. For example, inhibition of BRAF is highly effective in *BRAF*-mutated melanoma but not in *BRAF*-mutated colon cancers [66] and recent data from a phase I clinical trial suggest that a new KRASG12C inhibitor may be more effective in lung tumors than in colorectal tumors harboring the same mutation [67].

Several outstanding questions remain to be addressed: (1) How do cancer driver genes (especially those that are ubiquitously expressed and perform core cellular functions such as DDR) interact with cell type–specific genetic networks to promote cancer initiation and progression? Our understanding, as described previously, is quite limited to a few examples and tissues. (2) How do oncogenic mutations in specific cancer drivers or aneuploidy events interact with the tumor microenvironment to promote cancer hallmarks such as cancer immune evasion and therapy response? A better understanding of tumor type specificity will allow us to decipher context-dependent roles of cancer driver genes and context-dependent therapeutic vulnerabilities.

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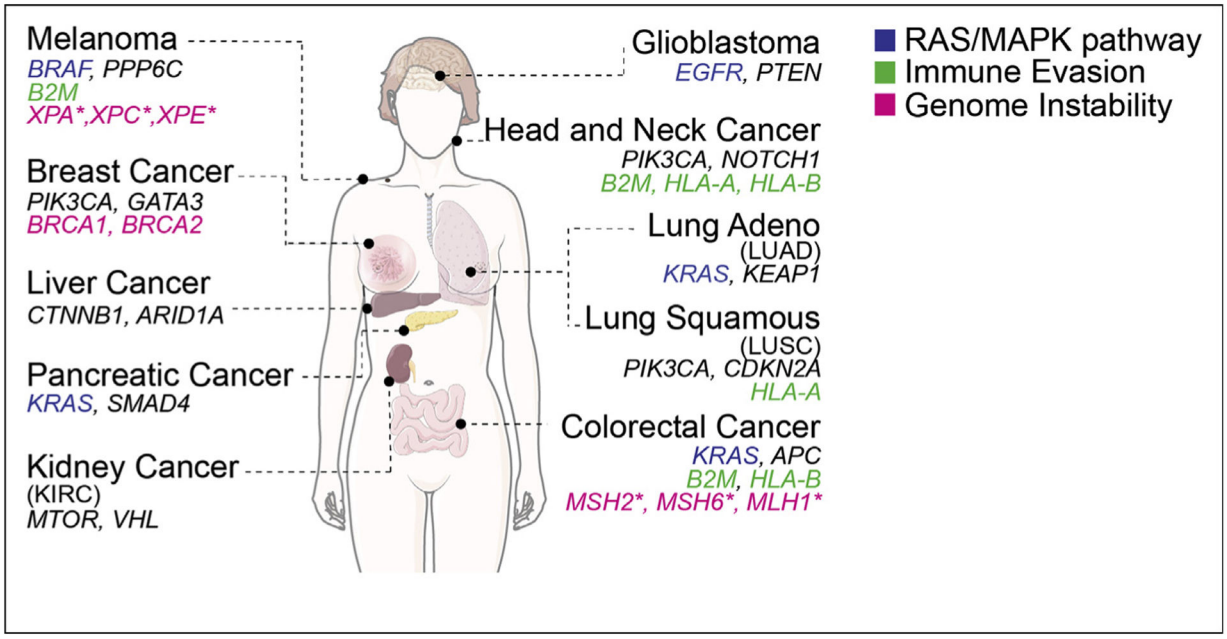

Figure 1. Tissue specificityspecificity of cancer driver genes.

For each tumor type representative mutated cancer driver genes are shown including genes acting in the RAS/MAPK pathway, immune evasion and genome instability. Lung cancers refer to NSCLC (non–small-cell lung cancer) either adeno-carcinoma (LUAD) or squamous cell carcinoma (LUSC) as indicated. *: germline only.

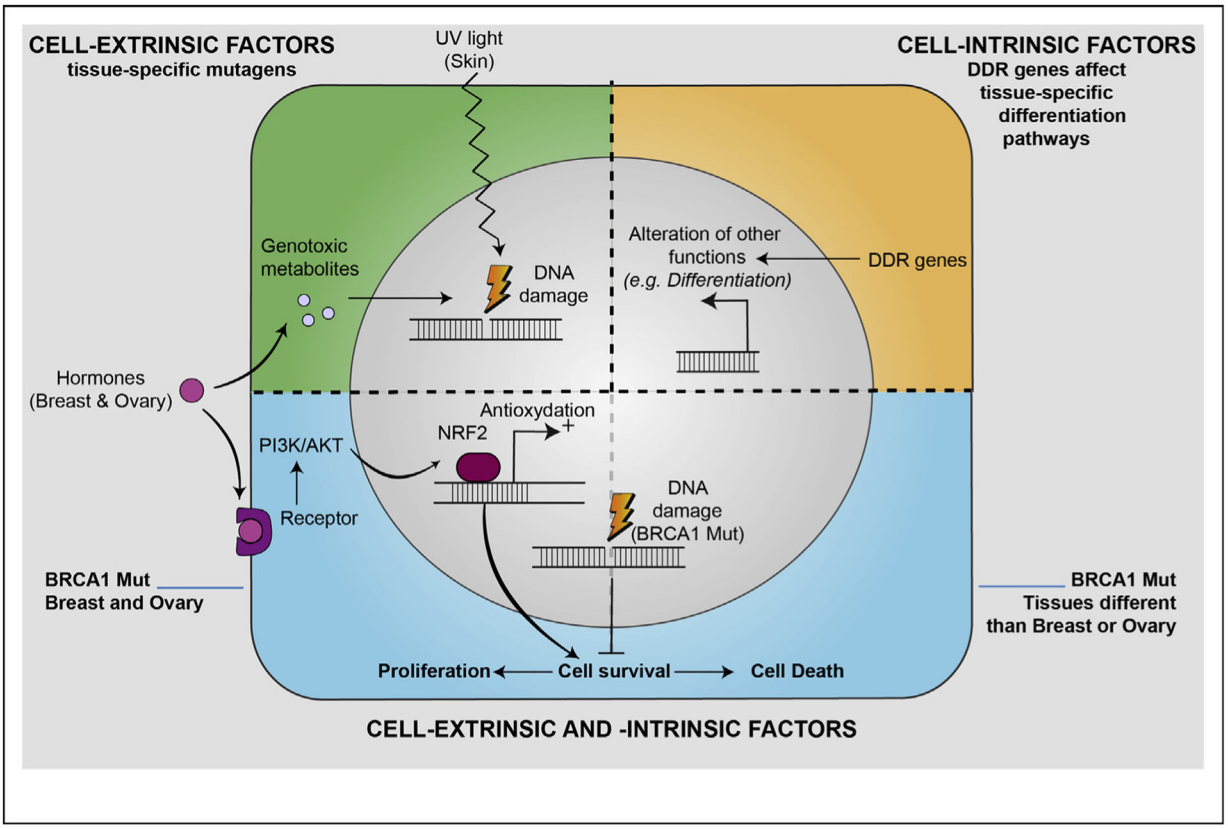

Figure 2. Model for the possible cellular and molecular interactions driving the tumor specificity of DDR genes.

Upper left: tissue-specific cell-extrinsic factors, such as UV light or hormones, can determine DNA damage and promote cell transformation. Upper right: DDR genes can affect other cellular signaling pathways, such as cellular differentiation as in the case of BRCA1 inhibition that can promote the maintenance of a stem cell–like behavior in mammary epithelial cells. Lower: cell-extrinsic and -intrinsic pathways can interact and affect cell autonomous pathways. For instance, estrogen can promote survival of *BRCA1*-mutated cells, thus protecting them from oxidative stress. DDR , DNA damage response.

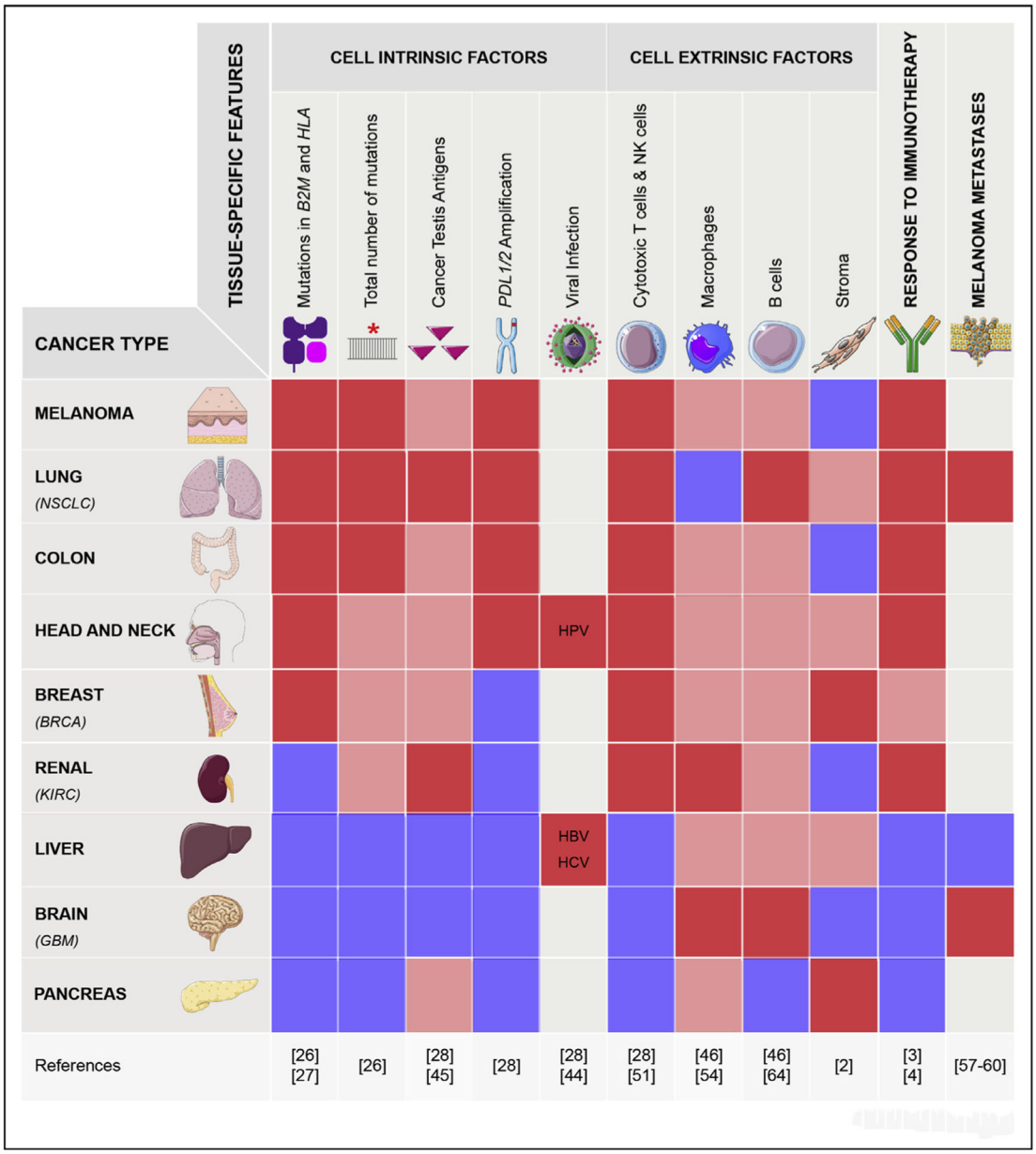

Figure 3. Tissue-specific features affecting immune response across cancer types.

The different levels of each feature are depicted as a heatmap-like system (dark red: high, light red: medium and blue: low or absent. Gray refers to information not available). For the response to immune checkpoint inhibitors, the dark red indicates that a response has been achieved in a fraction of patients and that it has been FDA approved for this tumor type. The light red for the BRCA type refers to only one immunotherapy approved by the FDA in 2019 and performed in combination with chemotherapy (Schmid et al., NEJM, 2019). For the cancer testis antigens, we show its average expression in the tumors, not its correlation with cytotoxicity or immunotherapy (see text for details). NSCLC, non–small-cell lung cancer;

BRCA, breast invasive carcinoma; KIRC, kidney renal cell carcinoma; GBM, glioblastoma multiforme.