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| Table 1 A complete list of T cell exhaustion and immune dormancy genes compiled from literature research | | | |
| Gene symbol | Proposed mechanism of action | Expected change | GeneCards symbol |
| T CELL EXHAUSTION | | | |
| 2B4  (alternative name: CD244) | 2B4 is a widespread immune regulator expressed on many immune cells in the tumour microenvironment, including NK cells, some T cells, DCs, and MDSCs [40,41]. Its role in exhaustion is well established; in LCMV infected mice, exhausted CD8+ T cells had higher expression of 2B4 [40]. In human melanoma, 2B4 was upregulated in tumour-specific T cells and its expression correlated with other inhibitory receptors, such as PD1, CTLA4, and CD160 [42]. | Upregulation | CD244 |
| BATF | It was shown *in vitro* that inhibitory receptor PD1 functions not only to inhibit T cells by reducing TCR signalling, but also by inducing the expression of genes that impair T cell function [20,43]. One of those genes is BATF, whose overexpression was sufficient to impair T cell proliferation and cytokine secretion, and a knockdown of BATF gene reduced PD1 inhibition in effector T cells [43]. In addition, genomic studies show BATF is a genomic switch which drives T cell exhaustion signature [44] and Th cell-originating leukaemias [45]. | Upregulation | BATF |
| BLIMP1 | BLIMP1 is a key transcription regulator, shown to repress normal memory CD8+ T cell differentiation and promote expression of inhibitory receptors such as PD1, LAG3, CD160, 2B4 during chronic LCMV infection [44,46]. Moreover, BLIMP1 expression seems to be controlled by IRF4, another regulator of T cell exhaustion [44]. | Upregulation | PRDM1 |
| CD160  (previous name: BY55) | CD160 binds to MHC class I molecules and delivers a co-stimulatory signal necessary for CD8+ T cell activation [47]. However, prolonged CD160 signalling seems to lead to inhibition of TCR signalling and, consequently, T cell exhaustion. CD8+ T-cell populations expressing CD160 have reduced proliferation capacity and perforin expression *in vitro*. Conversely, the blockade of CD160 interaction with its ligand restores the proliferation of CD8+ T cells [48]. | Upregulation | CD160 |
| CD39  CD103 | CD103 is an integrin and a marker of tissue-resident memory T cells [49], whereas CD39 is ectonucleotidase which produces free adenosine and forms immunosuppressive environment [50]. New data shows CD103+CD39+ TILs are enriched in multiple tumours and display an exhausted, memory T cell-like phenotype. Interestingly, they seem to be a subset of cells reactive to tumour cells, but for yet unknown reasons resident in the tumour microenvironment [51]. | Unclear | ENTPD1  ITGAE |
| EOMES  TBX21  (protein: TBET) | EOMES and TBET are paralogous transcription factors and master regulators of cytotoxic T cell lineage commitment and exhaustion programme activation [52,53]. EOMES is required for induction of effector CD8+ T cells by IFNγ induction in CD8+ T cells [52] and is upregulated, along with PD1, in chronic viral infections *in vivo* [52,54]. This points to its role in T cell exhaustion. TBET, similarly to BLIMP1, promotes differentiation of cytotoxic T cells at the early stages of infection [55]. Persistent antigenic stimulation causes downregulation of TBET, which competes for genomic binding sites with EOMES and causes exhaustion phenotype [52,55]. | EOMES: Upregulation  TBET: Downregulation | EOMES  TBX21 |
| IFNG | Interferons are important activators anti-tumour response. However, accumulation of interferon gamma tumour microenvironment leads to immunosuppression and upregulation of PD1 ligand on CD8+ T cells [56,57]. Moreover, it was shown that longstanding interferon gamma signalling in tumour cells leads to acquisition of epigenetic modifications leading to the expression of more interferon-stimulated genes as well as the expression ligands for multiple T cell inhibitory receptors [58]. | Upregulation | IFNG |
| IL-10 and IL-35  STAT1  STAT3  STAT4 | Interleukins 10 and 35 are both immunosuppressive cytokines. IL-10 was previously known to promote CD8+ T cell exhaustion in LCMV infected mice [59] and *in vitro* this exhaustion can be reversed with IL-10 blockade [60]. IL-35 promoted the expression of multiple inhibitory receptors (PD1, TIM3, LAG3) on the surface of effector T cells in mouse models of cancer [61]. IL-35 is a recently identified cytokine, and is a dimer of proteins encoded by two genes: IL12A and EBI3 [62]. However, it was only recently shown that both IL-10 and IL-35 are secreted by regulatory T cells in the tumour microenvironment, thereby driving exhaustion of TILs by activating the expression of transcription factor BLIMP1 [63].  STAT3 and STAT1/4 are transcription factors involved in signalling downstream of IL-10 and IL-35, respectively [63–65]. STAT3 seems to be a master regulator promoting the differentiation of immunosuppressive neutrophils and macrophages [16]. | Upregulation | IL10  IL12A  EBI3  STAT1  STAT3  STAT4 |
| IRF4 | IRF4 is a master regulator of effector T cells with links to exhaustion phenotype, development of memory-like T cells, and transplant tolerance *in vitro* [44,66]. Interestingly, IRF4 seems to be a master regulator of exhaustion, as stimulated *Irf*+/- T cells show reduced expression of inhibitory receptors PD1, TIM3, LAG3, 2B4, TIGIT, and CTLA4 [44].Moreover, upregulation of IRF4 represses the formation of memory T cells, further impairing the immune response [44]. | Upregulation | IRF4 |
| LAG3 | LAG3 is one of the known inhibitory receptors (IRs) expressed on the surface of the T cells. The exact signalling mechanisms downstream of LAG3 and interplay with other IRs remains unknown due to LAG3’s structure which is unique and distinct from other IRs [40,67]. However, in vivo blockade of the PD1 and LAG3 IRs together led to a greater reversal of T cell exhaustion and viral control compared to blockade of either one of those pathways alone [40]. | Upregulation | LAG3 |
| NFAT | Three NFAT proteins are present in T cells: NFAT1, NFAT2, NFAT4. All of them are regulated by Ca2+ signalling. NFAT proteins redundantly bind to AP1 cofactor, activating the expression of T-cell activating cytokines [68]. In the absence of AP1, NFAT binds promoters of inhibitory receptors (i.e. PD1, LAG3, and TIM3), therefore causing the expression of inhibitory receptors on T cell surface [69]. In addition, NFAT1 was shown recently to be part of a positive feedback loop strengthening the exhaustion phenotype [44]. | Upregulation  Structural mutation | NFATC1  NFATC2  NFATC4 |
| PD1  CTLA4 | PD1 and CTLA4 are well characterised inhibitory receptors expressed on the surface of the immune cells. Antibodies directed against those ligands are currently used in the clinic [23] | Upregulation | PDCD1  CTLA4 |
| PROCR  PDPN  cMAF | Advances in sequencing allowed recent discovery of new co-inhibiotry receptors PROCR and PDPN, as well as a co-inhibitor cMYF, using scRNAseq an CyTOF [70]. Whereas PROCR and PDPN are transmembrane proteins previously associated with tumour progression [71,72], cMAF is a transcription factor responsible for activation or repression of key cytokine loci in immune cells [73]. PROCR(+)CD8(+) TILs exhibit exhausted phenotype in mouse models, whereas PDPN-deficient mice show delay in tumour growth [70]. cMAF mice knock-outs exhibit low expression of inhibitory receptors such as TIGIT and PD1 [70], and cMAF upregulation results in increased CD8+ T cell apoptosis [74]. | Upregulation | PROCR  PDPN  MAF |
| PTPN11  (protein: Shp2) | Cytoplasmic tails of inhibitory receptor PD1 bear immunoreceptor tyrosine-based switch motif (ITSMs) which are phosphorylated upon engagement and transiently bind the Shp2 protein, which is a phosphatase [20,75,76]. Shp2 was in turn believed to dephosphorylate T cell receptors, rendering them inactive, and thus being a part of PD1-mediated signalling[77,78].  Recent *in vivo* studies show Shp2 is sufficient but not necessary to induce dysfunctional state of exhausted T cells [78]. However, it is included in this study as it is a direct regulator of another molecule responsible for T cell exhaustion, Sprouty [75]. | Upregulation | PTPN11 |
| SPRY | Sprouty (SPRY1 and 2) is a family of proteins which function as master negative regulators of the MAPK/ERK pathway [79,80]. Its deregulation has been implicated in different cancer types [79] as well as HIV infection [81]. The absence of SPRY1/2 signalling in effector T cells enhances their survival and results in the formation of more memory T cells. SPRY1/2 activity, on the other hand, limits early CD8+ T cell differentiation [82]. | Upregulation | SPRY1  SPRY2 |
| TIGIT  CD266 | TIGIT is an immunoglobulin superfamily member shown to be expressed on CD8+ tumour infiltrating T cells and natural killer cells [83]. In human cancers, TIGIT acts in conjunction with PD-1 to inhibit effector T cells, hence enabling progression of cancer [83,84]. *Tigit*–/– mice do not exhibit NK cell exhaustion and show fewer metastases and improved survival further highlighting the key role of TIGIT in regulating cancer immunosurveillance [85]. CD226 is an activator receptor which competes for a shared receptor with TIGIT, however high concentrations of TIGIT act in *cis* with CD226 and disrupt its function [83,86]. | TIGIT: Upregulation  CD226: Downregulation | TIGIT  CD226 |
| TIM3  (alternative name: HAVCR2) | TIM3 is expressed on CD8+ T cells in the tumour microenvironment in mouse models of solid tumours. They co-express PD1and exhibit a severe exhausted phenotype [87]. Moreover, TIM3 blockade restores T cell function and improves the control of bacterial infection [88]. Very recently, the TIM3 was linked to myeloid derived suppressor cells, which trigger the TIM3+CD8+ T cells through a Gal9 receptor in human studies, causing T cell exhaustion [89,90]. | Upregulation | HAVCR2 |
| TRAF1 | It is hypothesised that co- stimulatory receptors can also serve as a mechanism of T cell dysfunction during chronic infection [20]. TRAF1 is downregulated in dysfunctional T cells in HIV and LCMV infections and transfer of TRAF1(+) but not TRAF1(-) memory T cells at the chronic stage of infection reduces viral load [91]. Nonetheless, evidence on the role of TRAF1 in exhaustion is sparse with reports of its role as both a positive and negative regulator of immune signalling [92]. | Downregulation | TRAF1 |
| IMMUNE DORMANCY | | | |
| B7H  B7H1  SOCS1 | B7H and B7H1 are ligands of a well-studied receptor PD1. Dormant tumour cells upregulate these ligands and resist cytotoxic T cell mediated lysis. Human carcinomas abundantly express B7‐H1, and in mice, expression enhances tumour growth [93]. SOCS1 seems to mediate the inhibition of cytotoxic cells via an epigenetic methylation process[94].  *Limited research is available in on this mechanism.* | Upregulation | CD80  CD274 |
| CXCL9  CXCL10 | It appears that antiangiogenic chemokines released by immune cells are a bridge between immune dormancy and angiogenic dormancy [95]. CD4+ T cells were shown to release CXCL9 and CXCL10, which inhibit vascularization processes in the growing tumour, indirectly contributing to the induction of cancer dormancy [8]. | Upregulation | CXCL9  CXCL10 |
| IFNb  IFNAR  IRF7 | Type I interferons, such as interferon beta, are known regulators of cancer immunity, and immune response in general. They bind to interferon receptor (IFNAR) and activate the transcription of many genes through the activation of intracellular transcription factors, such as IRF7 [7]. It was shown that chemotherapy induces a type I IFN response in tumour cells as a result of MDSC signalling. This results in a self-sustained overexpression of IRF7 and consequently, IFNβ, which triggers dormancy programme [96].  *IFNB1 expression values are missing from the data. The expression of interferon genes is difficult to measure using RNAseq.* | Upregulation | IRF7  INFB1  IFNAR1  IFNAR2 |
| IFNG  TNF  STAT1  TNFR1 | Th1 cells express TH1 IFNγ and TNF which in turn activate cell-mediated antitumor immune response by facilitating CD8+ T cell maturation and macrophage activation [7,8], as well as inducing G0/G1 arrest in the tumour cells [8]. It was shown that through promoting TNFR1 signalling and IFNγ signalling the lifespan of mice with malignant cells doubles [97], and indispensable to this signalling pathway is STAT1 [8]. | Downregulation | IFNG  TNF  STAT1  TNFRSF1A |
| uPAR  ITGA5  ITGB1  (protein: integrin α5β1)  FAK | uPAR is a proteolytic enzyme which degrades extracellular matrix, and it has been associated with invasion and metastasis in human cancer [98]. In cell culture studies, knockdown of uPAR induced a state of tumor dormancy characterised by G0/G1 cell cycle arrest [99]. The downstream signalling proteins are α5β1 integrin and FAK, whose activation in turn leads to ERK signalling cascade. The role of both of these proteins have been implicated in cancer [100,101]. | Downregulation | PLAUR  PTK2  ITGA5  ITGB1 |
| VEGFR2  VEGF  MMP9 | MDSC can promote angiogenesis in tumour microenvironment through the release of VEGF and MMP9 while also having immunosuppressive features [102]. It was shown that inhibition of tumour angiogenesis with the anti-VEGFR-2 antibody, attenuated the inhibitory effect of MDSCs on T cell proliferation, as well as decreased the frequency of Tregs in primary tumors and lung metastases [103].  *VEGFA is used as a proxy of VEGF expression.* | Upregulation | KDR  VEGFA  MMP9 |
| ZEB1 | Zeb1 is a key regulator of the epithelial-to-mesenchymal transition and there is a limited evidence *in vitro* that it promotes metastasis in LPS-induced inflammation [104]. | Upregulation | ZEB1 |