Indian Journal of Experimental Biology
Vol. 63, February 2025, pp. 117-124
DOI: 10.56042/ijeb.v63i02.11712

Mini-review

Hypoxia manipulating infiltrating T cells in solid tumor with respect to CD5 expression

Avika Sharma & Ambak Kumar Rai*

Department of Biotechnology, Motilal Nehru National Institute of Technology Allahabad, Prayagraj 211004, Uttar Pradesh, India

Received 10 June 2024; revised 31 January 2025

Reduced levels of oxygen in the microenvironment, defined by the term hypoxia, is a feature of the growing solid tumor. The hypoxic tumor microenvironment (TME) modulates the tumor-infiltrating lymphocytes (TILs), such as T cells, favoring tumor growth and survival. This mini-review emphasizes how hypoxia affects infiltrating CD8+ cytotoxic T cells and regulatory T cells (Tregs) within the TME. CD5, a T cell marker expressed by TIL and Tregs, is a negative regulator of T cell receptor (TCR) signaling. We propose two mechanisms of loss of TIL function in TME: firstly, reduction in the CD5 expression on TIL followed by activation-induced cell death (AICD). Here, our findings showed hypoxia-inducible factor-1a (HIF-1α) binding to the promoter of a non-conventional human endogenous retrovirus (HERV) derived alternate mRNA transcript of CD5. This results in reduced surface and increased intracellular expression of CD5 protein, a phenotype that is quite common in leukemic T cells, particularly in acute T cell lymphoblastic leukemia. Secondly, hypoxia attracts Treg cells, characterized by high CD5 levels, further suppressing TIL function. This minireview highlights an interplay between hypoxia, HIF-1α, and CD5 and provides insights into tumor immune evasion and inefficacy of TILs.

Keywords: Hypoxia-inducible factor, Tumor microenvironment, Tumor-infiltrating lymphocytes, Regulatory T cells, Human endogenous retrovirus

Introduction

Hypoxia, defined by reduced oxygen levels, is a well-described feature of the tumor microenvironment and is a hallmark characteristic of solid tumors. As we move deep inside a solid tumor, there is a gradual decrease in the oxygen level. Therefore, the deep locations of a solid tumor are more hypoxic than the periphery[1]. It is primarily caused by the increased rate of cell proliferation, resulting in faster depletion of available oxygen and insufficient blood supply towards the deeper location due to overwhelming angiogenesis, blood vessel maturation, and blood vessel leakiness[2,3]. The hypoxic condition leads to the evolution of a more aggressive tumor cell, which in turn results in an invasion of other sites. Hypoxia also curtails antitumor immune response. Infiltrating immune cells enter as a part of surveillance and get manipulated by the hypoxic conditions, resulting in impaired or less effective immune response[4]. These cells are monocyte/macrophages, dendritic cells, and T cells, including CD4+ and CD8+ cells. Usually, there will be a significant influx of these cells, including cells of adaptive immune cells. Besides several other factors that may manipulate the infiltrating cells, hypoxia manipulates their cellular response primarily by the Hypoxia-inducible factors (HIF)[5]. HIF regulates the expression of genes involved in multiple vital processes such as angiogenesis, apoptosis, proliferation, cell cycle progression, cancer stem cell self-renewal and metastasis[6]. Besides, HIF-1α increases PD-L1 expression, and its inhibition abrogates PD-1 - PD-L1 mediated suppression of the tumor-infiltrating lymphocytes (TILs), resulting in tumor rejection[7]. In addition to its effect on the expression of PD-1 – PD-L1 pathway, HIF-1α can also upregulate the expression of CTLA4, LAG3 and TIM-3 in CD8+ T cells[8]. In recent years, ample evidence indicates that HIF is crucial in regulating immune responses within the tumor microenvironment (TME) through immune checkpoint inhibitors[7-9].

In this mini-review, we mainly focus on the response of infiltrating T cells and their immune regulation under hypoxic conditions. This will emphasize how hypoxia affects the tumor-infiltrating lymphocytes (TIL; effector T cells and T reg cells)[10]. Our lab focuses on CD5 biology, a pan-T cell marker and one of the prominent regulators of T cell development, maturation and function. It negatively

*Correspondence:
Phone: +91 532 2271241
E-mail ambakrai@mnnit.ac.in

regulates TCR signaling that protects tumor-infiltrating lymphocytes (TILs) from tumor-mediated activation-induced cell death (AICD). According to reports, HIF-1α of TME alters CD5 expression in solid tumors, influencing the effectiveness of effector TILs and possibly contributing significantly to the sub-optimal response by the T cells. This also helps the tumor cells to grow and sustain the immune pressure. We have demonstrated that a human endogenous retrovirus (*i.e.*, HERV) regulates the surface expression of CD5 on the surface of T cells.

Hypoxia and the basic biology of HIF

Hypoxia affects both normal and cancerous cells, and both of them try to cope by devising specific mechanisms. One is by upregulating the hypoxia-inducible factor (HIF) signaling pathways. HIF, the transcription factor, belongs to the highly conserved family of basic helix-loop-helix-PER-ARNT-SIM (bHLH-PAS) proteins[11]. One of them is a heterodimer complex with an oxygen-sensitive alpha subunit (HIF-1α) and the constitutively expressed and stable beta subunit (HIF-1β/ ARNT). Under normoxic conditions, HIF-1α is synthesized and rapidly degraded by post-transcriptional modification, which involves the hydroxylation of their proline and asparagine residues by propyl hydroxylases (PHDs)[12]. PHDs are oxygen-dependent dioxygenase proteins. PHDs-mediated hydroxylation promotes the binding of von Hippel-Lindau tumor suppressor protein, which recruits E3 ubiquitin ligase targeting HIF-1α for ubiquitination and 26S proteasome degradation (Fig.1). Under hypoxic conditions, the action/activity of PHDs is repressed due to low oxygen. This

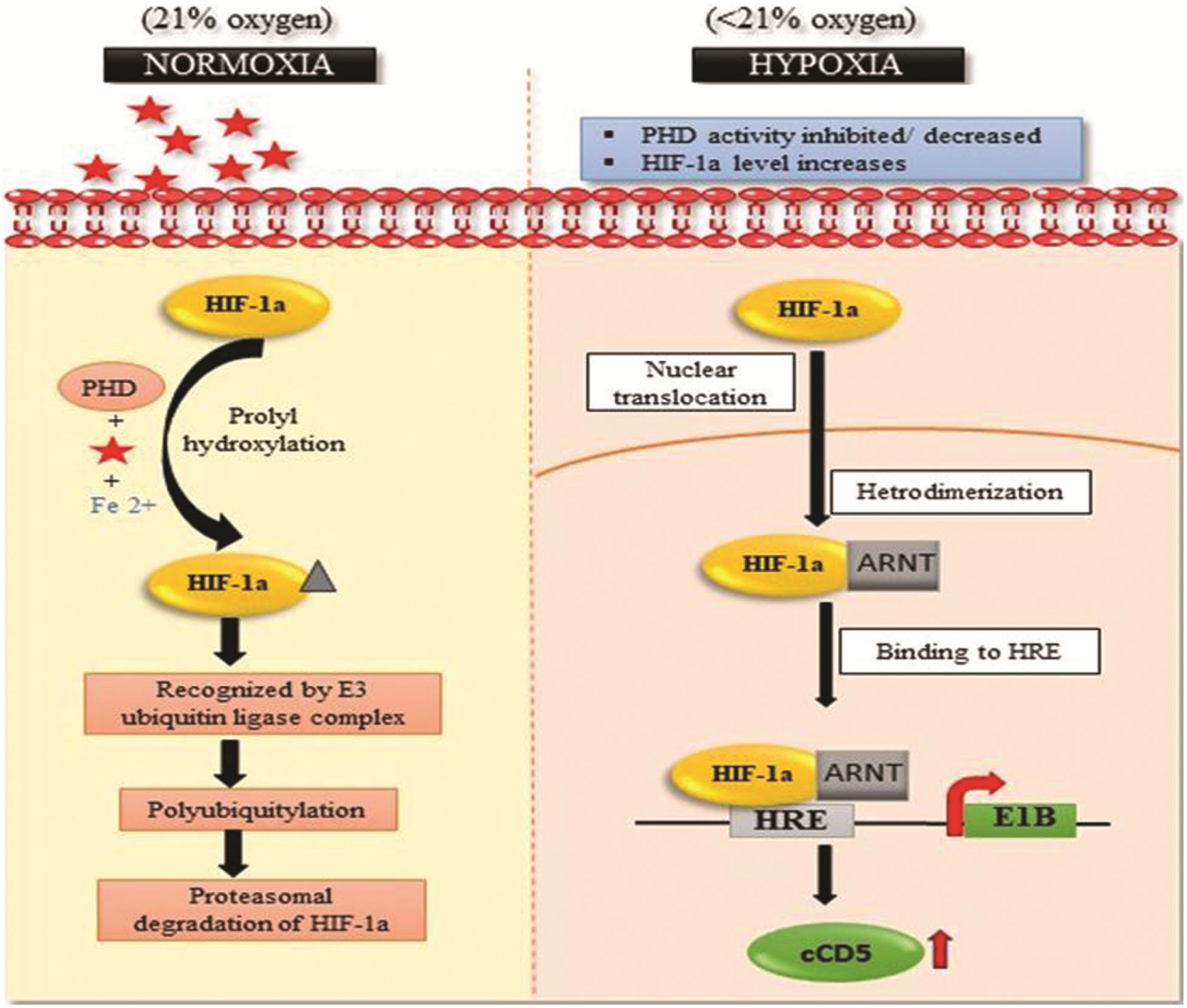

Fig. 1 — Fate of hypoxia master regulator, HIF-1α under normoxic and hypoxic condition. Regulation of CD5 expression in hypoxic condition *via* HIF-1α.

inhibition or repression causes HIF-1α to stabilize, allowing it to translocate to the nucleus where it binds to HIF-1β and regulates the transcription of the targeted gene having HIF-1α/β binding sequence known as hypoxia response element (HRE) (Fig.1)[13]. HRE sites are documented to be located upstream of the gene regulating various checkpoints of TILs, suggesting hypoxia can manipulate the action/function of TILs. One of the immune checkpoints/regulators we will emphasize in this mini-review is CD5[14,15].

CD5 and tumor infiltrating cells

Tumor microenvironment (TME) is a complex multicellular environment that includes cancerous cells, and they may vary between 5 and 100% of total cells. The remaining cells comprise infiltrating immune cells, such as lymphocytes (T cells, B cells), and antigen-presenting cells like macrophages or dendritic cells. It also includes natural killer cells, neutrophils, myeloid-derived suppressor cells, and stromal cells like cancer-associated fibroblast, pericytes, and mesenchymal stromal cells in various proportions[15-18]. Tumor infiltrating T cells, the key players in antitumor immune response and one of the main components of TME, are especially vulnerable/susceptible to various factors. A few of these factors are tumor-derived antigens, specific metabolites, and TME. Hypoxia, an important factor in TME, manipulates these infiltrated T cells and breaches the immune regulation to favor cancer progression and immune suppression. Two important and distinct cell types of TILs with opposing immunological responses are cytotoxic CD8+ T lymphocytes (CTL) and regulatory T (Treg) cells. CTLs target tumor cells in an antigen-specific manner and are essential for the antitumor response in TME. Tregs are in charge of immune regulation to favor tumor tolerance and, consequently, its growth[19,20]. Eliminating tumor cells is proportional to the overall function of CTLs, and their function is regulated by positive and negative receptors[21-23]. CD5, one of the negative regulators of T cell receptors and checks T cell activation, plays a vital role in regulating antitumor immune response.

CD5 is a 67 kDa membrane glycoprotein, expressed constitutively by all T cells (thymocytes as well as mature T cells) and a small subset of B cells (B1a)[24]. It belongs to a family of conserved scavenger receptor cysteine-rich (SRCR) superfamily, and its extracellular region is composed of three SRCR domains (type B; d1, d2, and d3). A transmembrane region and 94-aa-long intracytoplasmic region contain 11 Ser, 4 Thr, and 4 Tyr residues suitable for phosphorylation by protein kinases, further generating downstream signaling[25-27]. The intracytoplasmic region of CD5 exhibits two motifs associated with the activating and inhibiting signaling properties of CD5: pseudo-ITAM (immunoreceptor tyrosine-based activation motif) and pseudo-ITIM (immunoreceptor tyrosine-based inhibitory motif). ITAM, which is located at the cytoplasmic tail, serves as a docking site for some signaling molecules such as Lck, Fyn, Ras, GTPase-activating protein (Ras-GAP), and c-Cbl, while ITIM is positioned close to the membrane, interacts with SHP-1 (Src homology region two domain-containing phosphatase-1)[28]. CD5 is reported to be associated with various malignancies like chronic lymphocytic leukemia (CLL), T-ALL (T cell acute lymphoblastic leukemia), and mantle cell lymphoma[29]. Initially, its role was only considered as a negative regulator of T cell function in the periphery[30], but gradually its role is explored in the development and maturation of thymocytes[31], survival, and tolerance[32,33], and calcignaling in activated T cells[34]. It plays a vital role in the antitumor T cell response, as it protects TIL from antigen-driven AICD by inhibiting caspase-8 activation and downregulating FasL expression[35]. Our findings showed the role of hypoxia in TME in manipulating CD5 expression on TIL. Loss of CD5 may unleash the T cell function and show enhanced response, which may efficiently target tumor cells. However, this may not last long as CD5 deficient ag-specific CTLs become more susceptible to tumor-mediated AICD, ultimately losing CTLs and boosting tumor cell survival (Fig. 2)[36].

How do TME affect immune regulators expression and, in turn, the functional consequences of TILs?

The response is centered on the heterogenic nature of TME and the roles performed by its defining characteristics such as ischemia, hypoxia, acidic pH, and nutrient deficiency, etc. (Fig. 2). However, in the present concise review, the hypoxia was the one factor which has been discussed in the context to immune regulation. Recent studies have revealed complex relationships between hypoxia signaling pathways and CD5 expression on TILs in the hypoxic tumor microenvironment. The master regulator of

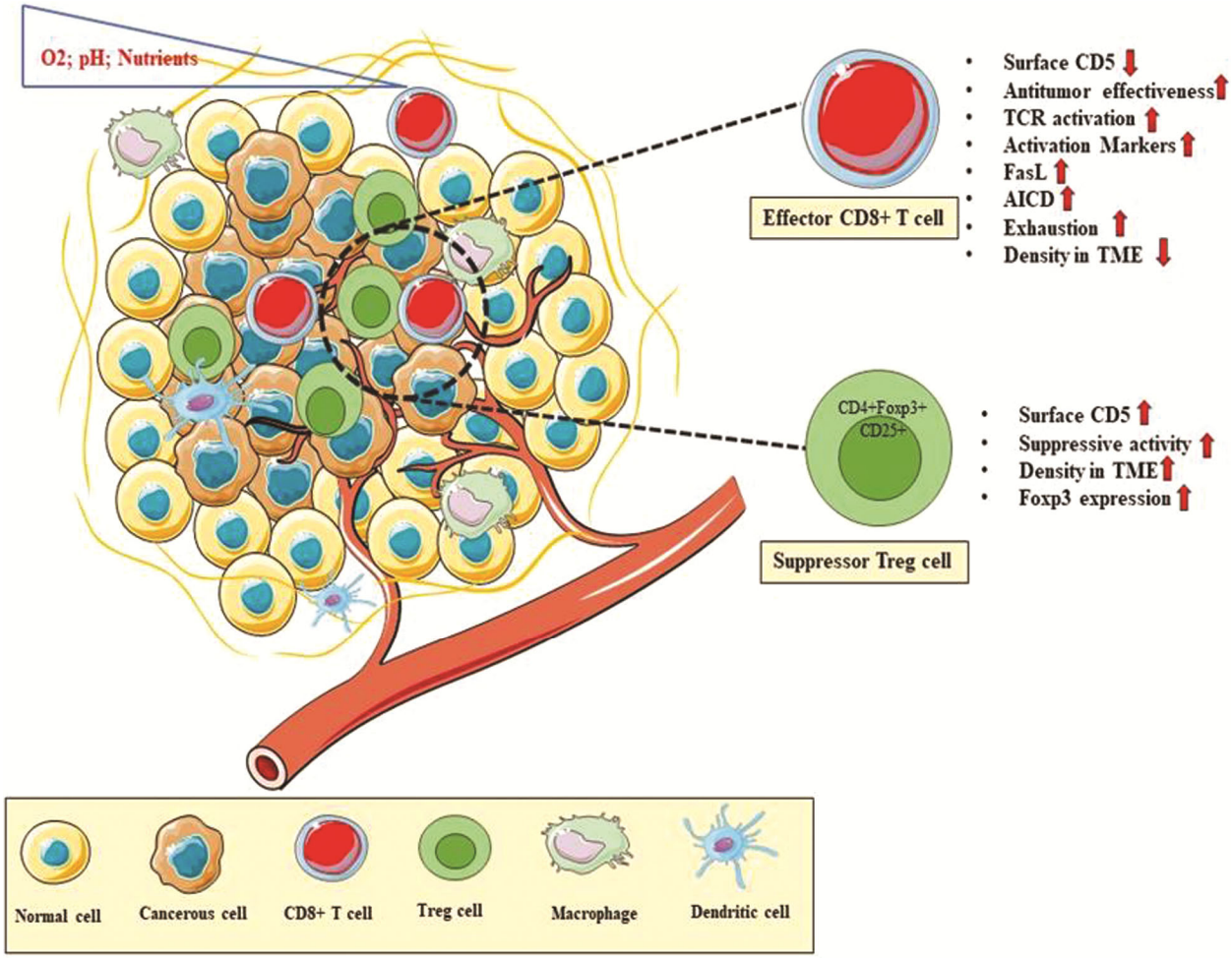

Fig. 2 — Represents some elements and characteristics of TME and their effects on the TILs, particularly effector CD8+ T cells and suppressor Treg cells. Hypoxic conditions deep inside the TME alter the CD5 expression in TILs, which results in the higher activation and antitumor activity of effector cells along with the increased exhaustion and activated induced cell death (AICD), which in turn reduces the density of effector T cells inside the TME. Elevated CD5 expression was linked to increased suppressive activity, Foxp3 expression, and TME density of other TIL, CD4+Foxp3+CD25+ suppressor Treg cells. TME, tumor microenvironment; TILs, tumor infiltrating lymphocytes.

cellular responses to low oxygen tension, i.e., hypoxia-inducible factors (HIFs), have been linked to the transcriptional regulation of CD5 expression, which in turn shapes the functional phenotype of infiltrated T cells, the primary effector cells in TME. Cheng H. et al. reviewed that hypoxia and nutrient restriction induce the CD8+ T cell differentiation towards an exhausted state in TME, ultimately reducing the effector CD8+ T cells[37,38]. Previous reports suggest an inverse relation between CD5 expression with antitumor activity and overall T cell activation. A phenotype of CD5low/- CTL has been reported in solid tumors. The surface expression of CD5 in TILs was much lower than that of its peripheral counterpart. Importantly, these were comparatively better in tumor cell lysis, suggesting an increased overall capability of these TILs[39]. However, we generally fail to find tumor regression and prolonged tumoricidal activity by these CD5- CTLs. According to a study by Tabbekh, M. et al. on CD5 deficient mice, CD5- infiltrated CTLs are more prone to activation-induced cell death (AICD) than the CD5+ T cells in wild-type mice[40]. CD5+ T cells show protection against AICD. In a study on non-small lung carcinoma (NSCLC), Dirician et al. also demonstrated CD5 downregulation, which can be used as an independent prognostic factor for the overall survival of NSCLC patients[41]. Similarly, Alotaibi et al. studies on 4T1 breast tumor-bearing mice showed differential expression of CD5 on CD8+ and CD4+ T cells. In summary, TILs were shown to have a lower degree of CD5 expression than peripheral T cells in peripheral

blood, emphasizing that a lower expression is associated with increased effector functions[42].

Another TIL is regulatory T cells (Treg), a subpopulation of CD4+ T cells that express Foxp3. Tregs suppress the effector T cell activation and are crucial for immune homeostasis and self-tolerance[43]. A Higher level of CD5 is one of the characteristics of Treg cells, suggesting the regulatory role of CD5 in the development and function of these cells[44]. Recent cancer research indicates increased levels of Treg cells within the tumors. It is shown that hypoxia increases the recruitment of Tregs by upregulating the chemotactic factor CCL28 and finding a positive correlation between HIF-1α and CCL28 expressions. The increased recruitment suggests the role of Treg cells in the reduced antitumor response by inhibiting the function of infiltrating T cells[45-47]. Studies have also demonstrated hypoxia upregulates Foxp3 expression in Jurkat T cells and human and murine mononuclear cells through HIF-1α. Consequently, this upregulation promotes the abundance and elicits the potent anti-inflammatory function of Tregs[48,49].

Hypoxia, being dominant in the TME of solid tumors, indicates its significant role in regulating the function of TIL, particularly CTLs. The HIF-1α pathway is upregulated in the state of hypoxia present in the intra-tumoral region and plays a crucial role in carcinogenesis[50]. We propose two important mechanisms. Firstly, HIF-1α reduces the CD5 expression on CTLs, resulting in its susceptibility to AICD[51,52]. S. Kumari et al., showed HIF-1α-driven reduction of surface CD5 (sCD5) expression in TIL under the hypoxic condition, and the same was noted in colorectal cancer. Besides, other studies showed that CD5 promotes T cell survival by preventing T cell overactivation and, thus, AICD by regulating FasL expression and caspase-8 activation. Thus, HIF-1α-driven reduced CD5 expression, as shown by Kumari et al., may also be associated with increased susceptibility to AICD along with the increased antitumor response of TILs[51,52]. Secondly, hypoxia recruits Treg cells preferentially to the tumor and suppresses the infiltrated CTLs[44.45]. The findings and available literature quite well support these two. HIF-1α may also differentiate some TILs towards Treg lineage, contributing to a suppressive atmosphere within TME. However, it requires further concrete validation. Some reports indicate that the HIF-1α function is essential for the effector function of CTLs. Doedens and colleagues demonstrate that elevated HIF supports the cytotoxic function of effector CD8+ T cells[53].

One would wonder at this point that what mechanism results in the decreased CD5 expression on T cells?

The human cd5 gene is located on chromosome no. 11 near the cd6 gene; both belong to the same family (SRCR). The human CD5 gene is approximately 24.5 kb long and has eleven exons[54]. The investigation of mechanisms behind the lower CD5 expression leads to the discovery of the integration of a 5254 bp long human endogenous retrovirus-E (HERV) approximately 8.2 kb upstream from the transcriptional start site of cd5 gene (Fig 3), which begins with exon 1 and ends with exon 11. HERVs are conserved molecular remnants of ancient exogenous retroviruses that infected the human germline millions of years ago. HERV is stably integrated into the human genome, making up around 8.29%[55,56]. The HERVs sequence typically consists of two long terminal repeats (LTRs) flanking the core region, which contains viral genes (gag, pro-pol, and env) encoding essential enzymes and structural components. The LTRs regulate viral gene expression and contain promoters, enhancers, and polyadenylation sites. Being susceptible to mutation, through the host editing system, the accumulation of mutation and epigenetic constraints of LTRs eventually suppressed the expression of viral genes. Therefore, the HERV remains non-productive primarily and does not form virion particles. However, many of them retain their ability to regulate and influence the expression of host genes by acting as alternative promoters and enhancers. The promoter activity of HERV-LTRs has gained significant attention due to their involvement in the pathogenesis of several autoimmune diseases, cancers, and neurological disorders[57,58]. Depending on the direction and transcriptional activation of consensus, LTRs of HERV-E may affect the expression of the candidate genes differently. In the case of CD5 transcription, the HERV element is present in the sense strand and located upstream of the promoter. Thus, LTR can act as an alternate promoter and transcribe a short stretch of its mRNA. During splicing, the alternative exon, i.e., exon E1B of the HERV-E segment, joins with exon 2 of the conventional gene and excises the conventional E1 (referred to as E1A to make a distinction). The non-conventional transcript variant's

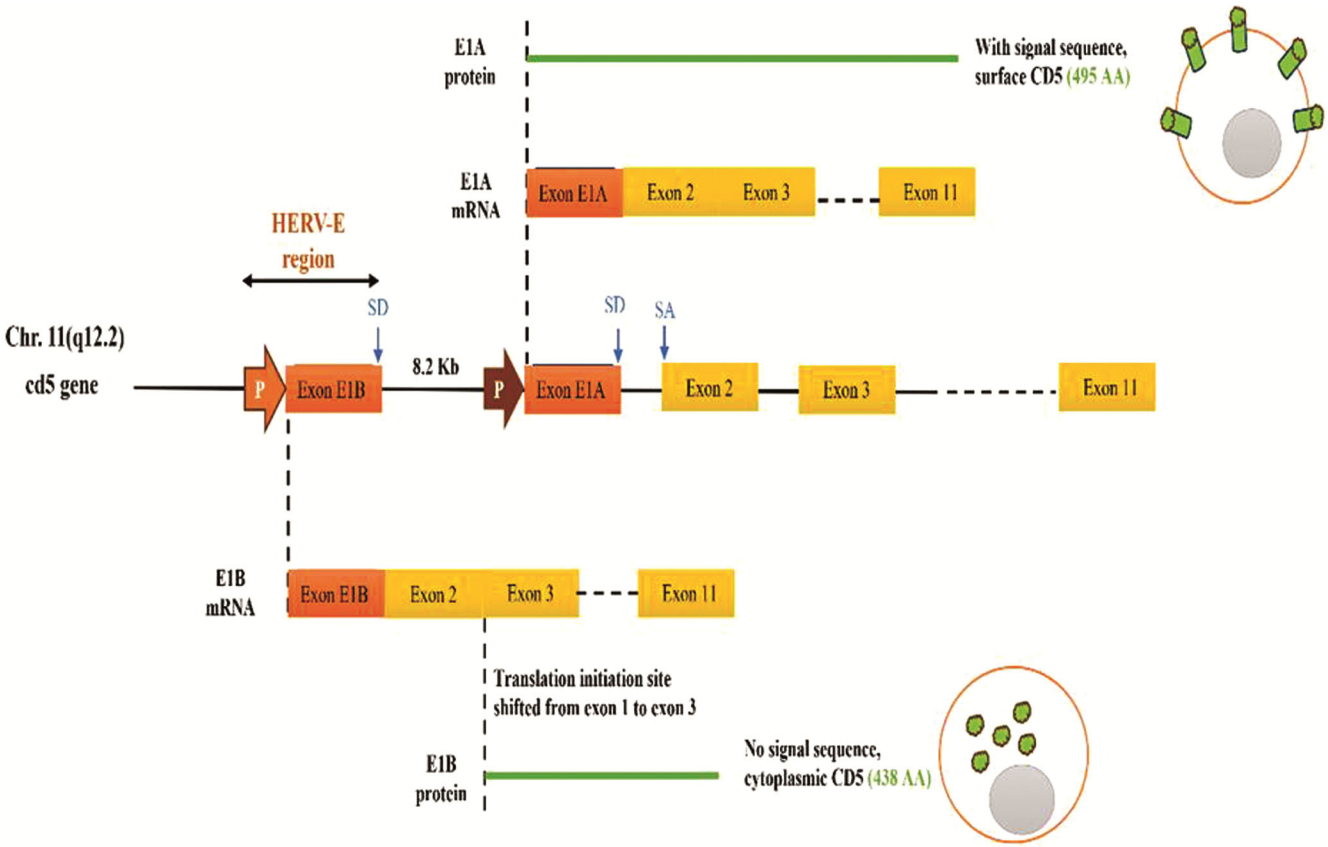

Fig. 3 — Genome organization of CD5 and integrated HERV-E sequence. It depicts the exonal switch mechanism behind the downregulation of surface CD5 expression. (P- promoter; SD-splicing donor site; SA- splicing acceptor site)

protein product lost initial residues containing signal sequences. Therefore, it is accumulated intracellularly and does not go to the surface[59] (Fig 3).

Summarily, two transcript variants have been annotated for the cd5gene, CD5 E1A (conventional form) and CD5 E1B (non-conventional form; of HERV origin), consisting of 11 exons. Variant E1B contains an alternative exon (E1b) in the first position, belongs to integrated HERV origin, and the rest of the exons are identical to the conventional transcript. E1A encodes 495 amino acid long protein, being expressed on the cell surface, whereas the E1B variant contains alternative exon on the first position, which synthesized 438 amino acids long truncated form of CD5 and fails to reach to the surface hence gets accumulated intracellularly[60,61](Fig 3). The expression of E1B is regulated by its promoter, and the upregulated expression of E1B mRNA is expected to decrease the E1A variant expression and, thus, the sCD5 expression. Hence, any transcription factors involved in the transcription of E1B indirectly downregulate the surface expression of CD5. HIF-1α, expressed under hypoxic conditions, decreases the sCD5 expression. Kumari et al. showed the presence of hypoxia response element (HREs) sites in the upstream region of exon E1B and showed HIF-1α binding to this HRE site through ChipQ PCR. This resulted in increased E1B mRNA transcript expression and accumulation of CD5 intracellularly (cCD5)[51].

Rai et al. showed reduced sCD5 and increased cCD5 in leukemic T cells of acute T cell lymphoblastic leukemia cases. This phenotype (sCD5low and cCD5high) is a new hallmark of leukemic T cells. Interestingly, hypoxia, one of the causative factors for leukemogenesis[60], induces a similar phenotype in exposed TILs (sCD5low and cCD5high). Leukemogenesis is a multifactorial phenomenon where exposure to hypoxia results in cCD5 accumulation followed by prolonged survival due to apoptosis resistance[62], AICD[27,34,35], etc. However, the function of cCD5 in leukemic T cells and hypoxia-exposed TIL cells is not yet established. Unraveling its function may offer new avenues to target leukemogenesis and restore the regulated functional capacity with resistance to AICD in TILs.

Conclusion

This mini-review provides a possible explanation for the failed response of TILs in the TME. Firstly, reduced sCD5 expression makes these infiltrating T cells susceptible to AICD, and secondly, skewed TIL/Treg balance may also result in poor TIL response. Not much is known about cCD5 expression in TILs except its increased expression at the expense of sCD5.

Conflict of interest

The authors declare no conflict of interest.

References

1 Lee P, Chandel NS & Simon MC, Cellular adaptation to hypoxia through hypoxia inducible factors and beyond. Nature Reviews, *Mol Cell Biol*, 21(5) (2020) 263. doi:10.1038/s41580-020-0227-y

2 McDonald D. M, & Baluk P, Significance of blood vessel leakiness in cancer. *Cancer Res*, 62 (2002) 5381.

3 Eberhard A, Kahlert S, Goede V, Hemmerlein B, Plate KH & Augustin HG, Heterogeneity of angiogenesis and blood vessel maturation in human tumors: implications for antiangiogenic tumor therapies. *Cancer Res*, 60 (2000) 1388.

4 Chang WH & Lai AG, The hypoxic tumor microenvironment: A safe haven for immunosuppressive cells and a therapeutic barrier to overcome., *Cancer Lett*, 487 (2020) 34.

5 Mamlouk S & Wielockx B, Hypoxia-inducible factors as key regulators of tumor inflammation. *Int J Cancer*, 132 (2013) 2721. Soni S & Padwad YS, HIF-1 in cancer therapy: two-decade long story of a transcription factor, *Acta Oncol*, 56 (2017) 503.

6 Shurin MR & Umansky V, Cross-talk between HIF and PD-1/PD-L1 pathways in carcinogenesis and therapy. *J Clin Invest* 132(2022;):e159473.

7 Bandopadhyay S & Patranabis S, Mechanisms of HIF-driven immunosuppression in tumor microenvironment. *J Egypt Natl Cancer Inst,* 35(2023), 27

8 Cowman SJ & Mei YK, Revisiting the HIF switch in the tumor and its immune microenvironment. *Trends cancer*, 8 (2022) 28.

9 Kumar V & Gabrilovich DI, Hypoxia-inducible factors in regulation of immune responses in tumor microenvironment, *Immunol*, 143 (2014) 512.

10 Ke Q & Costa M, Hypoxia-Inducible Factor-1 (HIF-1), *Mol Pharmacol*, 70 (2006) 1469.

11 Berra E, HIF prolyl-hydroxylase 2 is the key oxygen sensor setting low steady-state levels of HIF-1 in normoxia, *The EMBO Journal*, 22 (2003) 4082.

12 Adams J, Difazio L, Rolandelli R, Luján J, Haskó G, Csóka B, Selmeczy Z & Németh Z, HIF-1: a key mediator in hypoxia (Review), *Acta Physiol Hung*, 96 (2006) 19.

13 Keith B, Johnson RS & Simon MC, HIF1α and HIF2α: sibling rivalry in hypoxic tumor growth and progression, *Nat Reviews Cancer*, 12 (2011) 9.

14 Scholz CC & Taylor CT, Targeting the HIF pathway in inflammation and immunity, *Curr Opin Pharmacol*, 13 (2013), 646.

15 Wang JJ, Lei KF & Han F, Tumor microenvironment: recent advances in various cancer treatments. *Eur Rev Med Pharmacol Sci* , 22 (2018) 3855.

16 Wu T & Dai Y, Tumor microenvironment and therapeutic response. *Cancer Lett*, 387 (2017) 61.

17 Duan Q, Zhang H, Zheng J & Zhang L, Turning cold into hot: firing up the tumor microenvironment, *Trends Cancer*, 6,7 (2020) 605.

18 De Simone M, Arrigoni A, Rossetti G, Gruarin P, Ranzani V, Politano C, Bonnal RJP, Provasi E, Sarnicola ML, Panzeri I, Moro M, Crosti M, Mazzara S, Vaira V, Bosari S, Palleschi A, Santambrogio L, Bovo G, Zucchini N, Totis M & Pagani M, Transcriptional landscape of human tissue lymphocytes unveils uniqueness of tumor-infiltrating T regulatory cells. *Immunity*, 45 (2016) 1135.

19 Plitas G, Konopacki C, Wu K, Bos PD, Morrow M, Putintseva EV, Chudakov DM & Rudensky AY, Regulatory T cells exhibit distinct features in human breast cancer. *Immunity*, 45 (2016) 1122.

20 Lei X, Lei Y, Li JK, Du WX, Li RG, Yang J, Li J, Li F & Tan H-B, Immune cells within the tumor microenvironment: biological functions and roles in cancer immunotherapy. *Cancer Lett*, 470 (2019) 126.

21 Giraldo NA, Peske JD, Sautès-Fridman C & Fridman WH, Integrating histopathology, immune biomarkers, and molecular subgroups in solid cancer: the next step in precision oncology. *Virchows Archiv*, 474 (2022) 463.

22 Whiteside TL, Tumor-infiltrating lymphocytes and their role in solid tumor progression. *Interact Immune Cancer Cells*, 113 (2022) 89.

23 Youinou P, Jamin C & Lydyard PM, CD5 expression in human B-cell populations. *Immunol Today*, 20 (1999) 312.

24 Kodama T, Freeman M, Rohrer L, Zabrecky J, Matsudaira P & Krieger M, Type I macrophage scavenger receptor contains α-helical and collagen-like coiled coils. *Nature*, 343(1990) 531.

25 Vasquez M, Simões I, Consuegra-Fernández M, Aranda F, Lozano F & Berraondo P, Exploiting scavenger receptors in cancer immunotherapy: Lessons from CD5 and SR-B1. *Euro J Immunol*, 47(2017) 1108.

26 Soldevila G, Raman C & Lozano F, The immunomodulatory properties of the CD5 lymphocyte receptor in health and disease. *Curr Opin Immunol*, 23 (2011) 310.

27 Consuegra-Fernandez M, Aranda F, Simoes I, Orta M, Sarukhan A & Lozano F, CD5 as a target for immune-based therapies. *Crit Rev Immunol*, 35 (2015) 85.

28 Mutreja D, Pati HP, Bansal D, Sharma RK & Jain S, Aberrant immunophenotypic expression of CD5 in a case of B acute lymphoblastic leukemia: a case report. *Ind J Hematol Blood Transfusion*, 30 (2014) 212.

29 Tarakhovsky A, Kanner S, Hombach J, Ledbetter J, Muller W, Killeen N & Rajewsky K, A role for CD5 in TCR-mediated signal transduction and thymocyte selection. *Science*, 269 (1995) 535.

30 Azzam HS, Grinberg A, Lui K, Shen H, Shores EW & Love PE, CD5 expression is developmentally regulated by T cell receptor (TCR) signals and TCR avidity. *J Exp Med*, 188 (1998) 2301.

31 Seddon B & Zamoyska R, TCR signals mediated by src family kinases are essential for the survival of naive T cells. *J Immunol*, 169 (2002) 2997.

32 Sestero CM, McGuire DJ, De Sarno P, Brantley EC, Soldevila G, Axtell RC & Raman C, CD5-dependent CK2 activation pathway regulates threshold for T cell anergy. *J Immunol*, 189 (2012) 2918.

33 Freitas CMT, Hamblin GJ, Raymond CM & Weber KS, Naïve helper T cells with high CD5 expression have increased calcium signaling. *PLOS ONE*, 12 (2017) e0178799.

34 Friedlein G, El Hage F, Vergnon I, Richon C, Saulnier P, Lecluse Y, Caignard A, Boumsell L, Bismuth G, Chouaib S, Mami-Chouaib F, Human CD5 protects circulating tumor antigen-specific CTL from tumor-mediated activation-induced cell death, *JImmunol*, 178 (2007) 682.

35 Tabbekh M, Franciszkiewicz K, Haouas H, Lecluse Y, Benihoud K, Raman C & Mami-Chouaib F, Rescue of tumor-infiltrating lymphocytes from activation-induced cell death enhances the antitumor CTL response in CD5-deficient mice. *J Immunol*, 187 (2011) 102.

36 Cheng H, Ma K, Zhang L & Li G, The tumor microenvironment shapes the molecular characteristics of exhausted CD8+ T cells. *Cancer Lett*, 506 (2021) 55.

37 Zheng C, Zheng L, Yoo J-K, Guo H, Zhang Y, Guo X, … Zhang Z, Landscape of infiltrating T cells in liver cancer revealed by single-cell sequencing. *Cell*, 169 (2017) 1342.

38 Dorothee G, Vergnon, El Hage F, Chansac BLM, Ferrand V, Lecluse Y, Opolon P, Chouaib S, Bismuth G, Mami-Chouaib F, *In situ* sensory adaptation of tumor-infiltrating T lymphocytes to peptide-MHC levels elicits strong antitumor reactivity. *J Immunol*, 174 (2005) 6888.

39 Tabbekh M, Franciszkiewicz K, Haouas H, Lecluse Y, Benihoud K, Raman C & Mami-Chouaib F, Rescue of tumor-infiltrating lymphocytes from activation-induced cell death enhances the antitumor CTL response in CD5-deficient mice. *J Immunol*, 187 (2011) 102.

40 Dirican N, Karakaya YA, Gunes S, Daloglu FT & Dirican A, Association of intra-tumoral tumor-infiltrating lymphocytes and neutrophil-to-lymphocyte ratio is an independent prognostic factor in non-small cell lung cancer. *Clin Resp J*, 11 (2015) 789.

41 Alotaibi F, Vincent M, Min W-P & Koropatnick J, , Reduced CD5 on CD8+ T cells in tumors but not lymphoid organs is associated with increased activation and effector function. *Front Immunol*, 11 (2021) 584937.

42 Josefowicz Steven Z, Lu L-F & Alexander Y, Rudensky, Regulatory T cells: mechanisms of differentiation and function. *Ann Rev Immunol*, 30 (2012) 531.

43 Sood A, Lebel M, Dong M, Fournier M, Vobecky SJ, Haddad É, Delisle J-S, Mandl JN, Vrisekoop N, Melichar HJ, CD5 levels define functionally heterogeneous populations of naïve human CD4 + T cells. *Eur J Immunol*, 51 (2021) 1365.

44 Facciabene A, Peng X, Hagemann I. S, Balint K, Barchetti A, Wang L-P, Gimotty PA, Gilks CB, Lal P, Zhang L & Coukos G, Tumor hypoxia promotes tolerance and angiogenesis via CCL28 and Treg cells. *Nature*, 475 (2011) 226.

45 Ren L, Yu Y, Wang L, Zhu Z, Lu R & Yao Z, Hypoxia-induced CCL28 promotes recruitment of regulatory T cells and tumor growth in liver cancer. *Oncotarget*, 7 (2016) 75763.

46 Viguier M, Lemaitre F, Verola O, Cho M-S, Gorochov G, Dubertret L, Bachelez H, Kourilsky P, Ferradini L, Foxp3 expressing CD4+CD25^{high} regulatory T cells are overrepresented in human metastatic melanoma lymph nodes and inhibit the function of infiltrating T cells. *J Immunol*, 173 (2004) 1444.

47 Ben-Shoshan J, Maysel-Auslender S, Mor A, Keren G & George J, Hypoxia controls CD4+CD25+ regulatory T-cell homeostasis via hypoxia-inducible factor-1α. *Euro J Immunol*, 38 (2008) 2412.

48 Clambey ET, McNamee EN, Westrich JA, Glover LE, Campbell EL, Jedlicka P & Eltzschig HK, Hypoxia-inducible factor-1 alpha-dependent induction of FoxP3 drives regulatory T-cell abundance and function during inflammatory hypoxia of the mucosa. *PNAS*, 109 (2012) e2784.

49 Soni S & Padwad YS, HIF-1 in cancer therapy: two-decade long story of a transcription factor, *Acta Oncol*, 56 (2017) 503.

50 Kumari S, Sahu S, Singh B, Gupta S, Kureel AK, Srivastava A, Rikhari D, Srivastava S & Rai AK, HIF-1α regulates the expression of the non-conventional isoform of the cd5 gene in T cells under the hypoxic condition: A potential mechanism for CD5$^{neg/low}$ phenotype of infiltrating cells in solid tumors. *Cellul Immunol*, 391 (2023) 104755.

51 Friedlein G, El Hage F, Vergnon I, Richon C, Saulnier P, Lecluse Y, Caignard A, Boumsell L, Bismuth G, Chouaib S, Mami-Chouaib F, Human CD5 protects circulating tumor antigen-specific CTL from tumor-mediated activation-induced cell death. *J Immunol*, 178 (2007) 6821.

52 Liikanen I, Lauhan C, Quon S, Omilusik K, Phan A. T, Bartroli L. B, Ferry A, Goulding J, Chen J, Scott-Browne JP, Yustein JT, Scharping NE, Witherden DA & Goldrath AW, Hypoxia-inducible factor activity promotes antitumor effector function and tissue residency by CD8+ T cells. *J Clin Invest,* 131 (2021) e143729.

53 Padilla O, Calvo J, Vila JM, Arman M, Gimferrer I, Places L, Arias MT, Pujana MA, Vives J, Lozano F, Genomic organization of the human CD5 gene, *Immunogenetics*, 51 (2000) 993.

54 Wang X, Huang J & Zhu F, human endogenous retroviral envelope protein syncytin-1 and inflammatory abnormalities in neuropsychological diseases. *Front Psych*, 9 (2018) 422.

55 Gao Y, Yu XF & Chen T, Human endogenous retroviruses in cancer: Expression, regulation and function. *Oncol Lett*, 21 (2021) 121.

56 Zhang, M, Liang J. Q & Zheng S, Expressional activation and functional roles of human endogenous retroviruses in cancers. *Rev Med Virol*, 29 (2019) e2025.

57 Tugnet N, Rylance P, Roden D, Trela M & Nelson P, Human endogenous retroviruses (HERVs) and autoimmune rheumatic disease: is there a link? *Open Rheumatol J*, 7 (2013) 13.

58 Le Dantec C, Vallet S, Brooks W & Renaudineau Y, Human endogenous retrovirus group E and its involvement in diseases. *Viruses*, 7 (2015) 1238.

59 Rai AK, Singh A, Saxena A, Seth T, Raina V & Mitra DK, Exonal switch down-regulates the expression of CD5 on blasts of acute T cell leukaemia. *Clin Exp Immunol*, 190 (2017) 340.

60 Renaudineau Y, An alternative exon 1 of the CD5 gene regulates CD5 expression in human B lymphocytes. *Blood*, 106 (2005) 2781.

61 Cioca D & Kitano K, Apoptosis induction by hypercross-linking of the surface antigen CD5 with anti-CD5 monoclonal antibodies in B cell chronic lymphocytic leukemia. *Leuk*, 16 (2002) 335.