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Human Leukocyte Antigen-G as a Novel Target for Switch-Based Chimeric Antigen Receptor Natural Killer Cell Therapy of Solid Cancer

Abstract

Chimeric antigen receptor (CAR) adoptive cell therapy has demonstrated remarkable clinical success in hematological malignancies; however, its application to solid tumors remains limited [1,2]. Major challenges include the absence of a universally expressed tumor-associated antigen across multiple tumor types, tumor antigen heterogeneity, and the highly immunosuppressive tumor microenvironment (TME) [3,4]. Human leukocyte antigen-G (HLA-G), a non-classical major histocompatibility complex class I molecule with potent immunosuppressive properties, is aberrantly expressed in a wide range of solid malignancies and contributes to immune evasion [5,6]. Here, we propose the development of a switch-based anti-HLA-G chimeric antigen receptor natural killer (CAR-NK) cell platform targeting HLA-G1–G7 isoforms. The construct incorporates an inducible caspase-9 (iCasp9) suicide gene to enhance safety and controllability [7]. This strategy aims to overcome antigen heterogeneity and mitigate on-target/off-tumor toxicity while counteracting tumor-mediated immune suppression [8].

Mini Review

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Introduction

CAR-T cell therapy targeting CD19 has revolutionized the treatment of B-cell malignancies, producing durable responses in refractory leukemia and lymphoma [1]. However, clinical trials in solid tumors have shown limited efficacy due to physical barriers, antigen heterogeneity, and immunosuppressive signals within the tumor microenvironment [2,3].

One major limitation is the lack of a tumor-restricted antigen broadly expressed across solid cancers [4]. Targeting lineage antigens often results in damage to normal tissues expressing the same antigen, leading to on-target/off-tumor toxicity [5]. Furthermore, tumor cells can escape immune pressure by downregulating or mutating target antigens [6].

Natural killer (NK) cells represent an attractive alternative platform for CAR engineering. NK cells exhibit intrinsic cytotoxicity independent of antigen priming and show lower incidence of cytokine release syndrome compared to CAR-T cells [9]. Early-phase clinical studies of CAR-NK therapy have demonstrated promising safety profiles and antitumor activity [10].

HLA-G is a non-classical MHC class I molecule physiologically expressed at immune-privileged sites such as the maternal–fetal interface [11]. In cancer, aberrant HLA-G expression has been reported in breast, ovarian, colorectal, lung, melanoma, glioma, and pancreatic cancers [12]. Elevated HLA-G levels correlate with tumor progression, metastasis, and poor patient survival [13].

HLA-G interacts with inhibitory receptors ILT2, ILT4, and KIR2DL4 on immune cells, suppressing NK and T-cell cytotoxic responses [14]. Both membrane-bound and soluble isoforms (HLA-G1–G7) contribute to systemic immune suppression [15]. Because HLA-G expression provides tumors with a survival advantage, it represents a stable and functionally critical immunotherapeutic target [16].

Rationale for Targeting HLA-G

Unlike many tumor-associated antigens that are differentiation markers, HLA-G directly mediates immune escape [14]. Blocking or eliminating HLA-G-expressing tumor cells may simultaneously remove a suppressive signal and restore endogenous immune responses [17].

Studies have demonstrated that high HLA-G expression is associated with resistance to immune checkpoint inhibitors [18]. Thus, targeting HLA-G could complement existing immunotherapies.

Additionally, HLA-G expression is relatively restricted in normal adult tissues, reducing the risk of severe systemic toxicity [11,12]. The presence of multiple isoforms broadens targeting potential and reduces the likelihood of antigen escape variants [15].

Design of Switch-Based Anti-HLA-G CAR-NK Cells

CAR Architecture

The engineered CAR construct consists of an extracellular antigen-binding domain recognizing HLA-G1–G7 isoforms, a hinge and transmembrane region, and intracellular signaling domains such as CD28 or 4-1BB fused to CD3ζ [19]. The addition of costimulatory domains enhances NK cell activation, persistence, and cytotoxicity [20].

An inducible caspase-9 (iCasp9) suicide gene is incorporated to enable pharmacological elimination of CAR-NK cells in case of adverse events [7]. This safety mechanism has been clinically validated in adoptive cell therapy settings [7].

Switch-Based System

The switch-based CAR platform employs a universal receptor that recognizes a tagged adapter molecule rather than directly binding HLA-G. The adapter consists of an HLA-G-specific antibody fragment fused to a peptide tag recognized by the CAR [8].

Advantages include:

- Dose-dependent control of CAR activation [8]
- Reduced cytokine storm risk [9]
- Ability to discontinue therapy by stopping adapter infusion [8]
- Potential to retarget additional antigens using different adapters

Such modular systems have demonstrated improved safety and controllability in preclinical studies [8].

Overcoming Solid Tumor Barriers

Antigen Heterogeneity

Tumor antigen heterogeneity remains a primary cause of therapeutic resistance [4]. Because HLA-G expression is functionally linked to immune evasion, tumors are less likely to completely lose expression without compromising survival advantage [16].

Immunosuppressive Tumor Microenvironment

The TME contains regulatory T cells, myeloid-derived suppressor cells, and inhibitory cytokines such as TGF-β and IL-10 [3]. HLA-G contributes directly to this suppressive network by inhibiting NK cell activation [14].

Elimination of HLA-G-expressing tumor cells may:

- Enhance endogenous immune infiltration
- Reduce inhibitory signaling
- Improve responsiveness to checkpoint blockade [18]

NK Cell Advantages

NK cells recognize stress-induced ligands independently of MHC restriction [9]. Their shorter lifespan may reduce long-term toxicity risks compared to CAR-T cells [10]. Additionally, NK cells produce lower levels of pro-inflammatory cytokines associated with severe cytokine release syndrome [9].

Preclinical Evaluation Strategy

In Vitro Studies

- Flow cytometric validation of HLA-G isoform recognition [15]
- Cytotoxicity assays against HLA-G-positive tumor cell lines [12]
- Cytokine profiling (IFN-γ, TNF-α) [9]
- Assessment of off-target toxicity on normal cells [11]

In Vivo Models

Xenograft mouse models expressing HLA-G will be used to evaluate:

- Tumor regression

- CAR-NK cell persistence
- Adapter dose-response relationships
- Safety of iCasp9 activation [7]

Clinical Translation Potential

CAR-NK therapy offers advantages in scalability and safety [10]. Off-the-shelf NK platforms derived from cord blood or induced pluripotent stem cells may enable broader clinical application [9].

HLA-G targeting may be particularly relevant for:

- Triple-negative breast cancer [12]
- Ovarian carcinoma [13]
- Glioblastoma [12]
- Non-small cell lung cancer [12]
- Pancreatic cancer [12]

Combination strategies with checkpoint inhibitors may further enhance therapeutic efficacy [18].

Conclusion

HLA-G represents a compelling immunotherapeutic target in solid tumors due to its broad expression and central role in immune suppression [5,14]. A switch-based anti-HLA-G CAR-NK platform incorporating inducible caspase-9 offers enhanced safety, controllability, and adaptability [7,8].

This strategy addresses key barriers limiting CAR therapy in solid malignancies, including antigen heterogeneity and the immunosuppressive tumor microenvironment [3,4]. Continued preclinical validation and clinical translation may establish HLA-G–targeted CAR-NK therapy as a next-generation approach for solid cancer treatment.

References

1. Maude, Shannon L., Theodore W. Laetsch, Jochen Buechner, Susana Rives, Michael Boyer, Henrique Bittencourt, Peter Bader et al. “Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia.” New England Journal of Medicine 378, no. 5 (2018): 439-448.
2. Newick, Kheng, Shaun O’Brien, Edmund Moon, and Steven M. Albelda. “CAR T cell therapy for solid tumors.” Annual review of medicine 68 (2017): 139-152.
3. Joyce, Johanna A., and Douglas T. Fearon. “T cell exclusion, immune privilege, and the tumor microenvironment.” Science 348, no. 6230 (2015): 74-80.
4. Majzner, Robbie G., and Crystal L. Mackall. “Tumor antigen escape from CAR T-cell therapy.” Cancer discovery 8, no. 10 (2018): 1219-1226.
5. Carosella, Edgardo D., Benoit Favier, Nathalie Rouas-Freiss, Philippe Moreau, and Joel LeMaoult. “Beyond the increasing complexity of the immunomodulatory HLA-G molecule.” Blood, The Journal of the American Society of Hematology 111, no. 10 (2008): 4862-4870.
6. Rouas-Freiss, Nathalie, Philippe Moreau, Catherine Menier, Joël LeMaoult, and Edgardo D. Carosella. “Expression of tolerogenic HLA-G molecules in cancer prevents antitumor responses.” In Seminars in cancer biology, vol. 17, no. 6, pp. 413-421. Academic Press, 2007.
7. Di Stasi, Antonio, Siok-Keen Tey, Gianpietro Dotti, Yuriko Fujita, Alana Kennedy-Nasser, Caridad Martinez, Karin Straathof et al. “Inducible apoptosis as a safety switch for adoptive cell therapy.” New England Journal of Medicine 365, no. 18 (2011): 1673-1683.
8. Rodgers, David T., Magdalena Mazagova, Eric N. Hampton, Yu Cao, Nitya S. Ramadoss, Ian R. Hardy, Andrew Schulman et al. “Switch-mediated activation and retargeting of CAR-T cells for B-cell malignancies.” Proceedings of the National Academy of Sciences 113, no. 4 (2016): E459-E468.
9. Neal, Bruce, Yangfeng Wu, Xiangxian Feng, Ruijuan Zhang, Yuhong Zhang, Jingpu Shi, Jianxin Zhang et al. “Effect of salt substitution on cardiovascular events and death.” New England Journal of Medicine 385, no. 12 (2021): 1067-1077.
10. Rezvani, Katayoun. “Adoptive cell therapy using engineered natural killer cells.” Bone marrow transplantation 54, no. Suppl 2 (2019): 785-788.
11. Kovats, Susan, Elliott K. Main, Clifford Librach, Marcia Stubblebine, Susan J. Fisher, and Robert DeMars. “A class I antigen, HLA-G, expressed in human trophoblasts.” Science 248, no. 4952 (1990): 220-223.
12. Lin, Aifen, and Wei-Hua Yan. “Human leukocyte antigen-G (HLA-G) expression in cancers: roles in immune evasion, metastasis and target for therapy.” Molecular Medicine 21, no. 1 (2015): 782-791.

13. Amiot, A. “Microbiote et cancer du côlon.” Côlon & rectum 8, no. 3 (2014): 146-152.

14. Colonna, Marco, Francisco Navarro, Teresa Bellón, Manuel Llano, Pilar García, Jacqueline Samaridis, Lena Angman, Marina Cella, and Miguel López-Botet. “A common inhibitory receptor for major histocompatibility complex class I molecules on human lymphoid and myelomonocytic cells.” The Journal of experimental medicine 186, no. 11 (1997): 1809-1818.

15. Paul, Pascale, Franscisco Adrian Cabestre, Sophie Lefebvre, Iman Khalil-Daher, Gilles Vazeux, Rosa Maria Moya Quiles, Fabienne Bermond, Jean Dausset, and Edgardo D. Carosella. “Identification of HLA-G7 as a new splice variant of the HLA-G mRNA and expression of soluble HLA-G5,-G6, and-G7 transcripts in human transfected cells.” Human immunology 61, no. 11 (2000): 1138-1149.

16. Morandi, Fabio, Roberta Rizzo, Enrico Fainardi, Nathalie Rouas-Freiss, and Vito Pistoia. “Recent advances in our understanding of HLA-G biology: lessons from a wide spectrum of human diseases.” Journal of immunology research 2016, no. 1 (2016): 4326495.

17. LeMaoult, Joël, Irene Krawice-Radanne, Jean Dausset, and Edgardo D. Carosella. “HLA-G1-expressing antigen-presenting cells induce immunosuppressive CD4+ T cells.” Proceedings of the National Academy of Sciences 101, no. 18 (2004): 7064-7069.

18. Palucka, A. Karolina, and Lisa M. Coussens. “The basis of oncoimmunology.” Cell 164, no. 6 (2016): 1233-1247.

19. Sadelain, Michel, Isabelle Rivière, and Stanley Riddell. “Therapeutic T cell engineering.” Nature 545, no. 7655 (2017): 423-431.

20. Imai, C. M. I. H. A. R. A., K. Mihara, M. Andreansky, I. C. Nicholson, C. H. Pui, T. L. Geiger, and Dario Campana. “Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia.” Leukemia 18, no. 4 (2004): 676-684.

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