KIR3DL2: A New Therapeutic Target for Cutaneous T-Cell Lymphomas?

Abstract

Cutaneous T-cell lymphomas (CTCL) represent a heterogenous group of diseases primarily involving the skin. Among them, Sézary syndrome (SS) and transformed mycosis fungoides (MF) are aggressive forms of CTCL that currently lack effective therapy. The search for new monitoring and therapeutic targets in this context is in dire need. KIR3DL2 (CD158k) is potentially one of these targets expressed by the tumor cell population when only expressed by few normal T and NK lymphocytes. Recently IPH4102 a humanized monoclonal antibody was developed to selectively bind and deplete KIR3DL2-expressing tumor cells. It acts by recruiting autologous NK cells and macrophages via Fc receptors to target elimination of tumor cells. Moreover, engagement of KIR3DL2 by its recently identified ligand CpG oligodeoxynucleotides induces its internalization and the triggering of a caspase dependent apoptosis of the malignant T cells. These two therapeutic strategies targeting KIR3DL2 are actively pursued toward the development of clinical studies for CTCL.

Keywords: Sézary syndrome; Mycosis fungoides; NK receptors; KIR3DL2; IPH4102; Cutaneous T-cell lymphomas; CTCL; CD7; CD26; CD4+; T-cells; SS; CD8+; T-lymphocytes

Editorial

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Abbreviations: CTCL: Cutaneous T-Cell Lymphomas; MF: Mycosis Fungoides; SS: Sézary Syndrome; TNMB: Tumor-Node-Metastasis-Blood; MAB: Monoclonal Antibody

Introduction

Classification of cutaneous T-cell lymphomas (CTCL), encompass several subtypes that vary considerably in terms of clinical presentation and prognosis [1]. When mycosis fungoides (MF) is a slowly progressing skin invasion by clonally derived malignant CD4+ T-lymphocytes, Sézary syndrome (SS) is a more aggressive form characterized by the presence of clonal T-cell populations in the skin, lymph nodes and blood. Although it is not clearly established whether MF and SS might be seen as variants of the same disease spectrum [2-4].

Their prognosis and treatment strategies are guided by the disease stage according to the revised tumor-node-metastasis-blood (TNMB) classification [5]. While early stage patients have normal life expectancy, patients with more advanced disease do not exceed 25% survival rate at five-year horizon. There is therefore a dire need of new therapeutic approach for these advanced CTCL patients.

Evaluation of the tumor mass is important for the diagnosis and staging of SS. Numerous studies have tried to identify specific markers for unequivocal detection of Sézary cells which are still identified morphologically as small or large cells with atypical cerebriform nucleus. While valuable, flow cytometry analysis of T-cell blood subsets provides a more objective and reproducible means to evaluate blood involvement in CTCL patients. However, antigen expression abnormalities reported so far such as the loss of CD7, CD26, or CD3 expression were not constantly observed for all patients, making the search for more specific markers important for the detection of circulating malignant cells [6-9]. We previously reported that KIR3DL2 represents such a specific cell surface marker of the malignant T-cell clone invading the skin and blood of CTCL patients [10-14].

Evaluation of KIR3DL2+ T-cells compared with quantification by cytomorphology or clonal evaluation by immunoscope gave similar results at initial time points and during the evolution [10]. The specific expression of KIR3DL2 in patient malignant cells prompted us to evaluate its potential use as a therapeutic target in CTCL.

KIR3DL2 receptor in CTCL

The cell surface receptor KIR3DL2 (also named CD158k) belongs to the killer immunoglobulin-like receptor (KIR) family expressed by subsets of circulating NK cells and cytotoxic CD8+ T-lymphocytes. The KIR nomenclature is based on the biochemical structure of the receptors. These receptors may have 2 (2D) or 3 (3D) extracellular immunoglobulin domains associated with a long (L) or short (S) cytoplasmic tail, responsible for an inhibiting or activating signaling activity respectively. KIRs are the main NK cell receptors for MHC-I, encoded in the leukocyte receptor complex (LCR) located on chromosome 19q34. Genetic organization of KIRs is unique. While there are many KIR haplotypes they not only vary by allelic polymorphism but also by their gene content [15]. Thus KIR haplotype may include from 6 to 13 KIR genes. Remarkably, the KIR3DL2 is one of the framework genes with KIR2DL4 and KIR3DL3 (i.e. present in all individuals). The KIR3DL2 is an inhibitory receptor with specificity for HLA-A3 and -A11 [16] and has been reported recently to also recognize CpG oligodeoxynucleotides [17].

In healthy individuals, The KIRs display a clonally distributed expression in human NK cells and while KIR3DL2 expression was reported to be restricted to a few NK and T cells [16], we recently found it at the surface of cutaneous CD4+ T cells [18]. This occasional expression of KIR3DL2 on rare CD4+ T-cells from healthy individuals makes it a valuable positive marker of malignant T-cell clone invading the skin and blood stream in CTCL, even when present at low levels, and also offers a unique opportunity to develop a tumor-targeted therapy.

IPH4102 mAb for KIR3DL2 targeted therapy

IPH4102 is a humanized IgG1 monoclonal antibody (mAb) selected to bind and deplete KIR3DL2-expressing tumor cells [19,20]. In vitro, IPH4102 has shown compelling efficacy in recruiting, via Fc receptors, autologous NK cells to kill patient's KIR3DL2+ tumor cells. In this antibody dependent cell cytotoxicity (ADCC) assay, despite a very low spontaneous anti-tumor activity, patient's NK cells remained fully functional as revealed by their activation by the IPH4102 mAb. Of note, this activation did not promote NK cell death and therefore preserve from immunosuppression. In KIR3DL2+ xenograft mouse models, IPH4102 treatment significantly delayed tumor growth and improved the overall survival of the animals in a dose-dependent fashion. Taken together these preclinical data fully support the relevance of KIR3DL2 as a therapeutic target in CTCL. IPH4102 has recently demonstrated a favorable preclinical safety evaluation in non-human primates, a step toward the conduct of a phase I clinical trial.

CpG ODN for KIR3DL2 targeted therapy

On NK and CD8+ T cells, KIR3DL2, as the other KIR-L proteins, deliver negative signals through the phosphorylation of their intracellular immunoreceptor tyrosine-based motif and their subsequent interaction with SH2-domain containing phosphatase 1 (SHIP-1) [21]. In terms of ligands, KIR3DL2 has specificity for HLA-A3 and -A11 through a peptide-specific interaction, and to HLA-B27 through peptide-independent recognition [22,23]. More recently, CpG oligodeoxynucleotides (ODN) were also identified as KIR3DL2 ligands. On NK cells, CpG ODN promotes KIR3DL2 cell surface down-modulation and cell activation [17].

On Sézary cells, CpG ODN also induce KIR3DL2 internalization but contrary to what is observed in NK cells, they lead to a caspase-dependent apoptosis of malignant CD4+ T-cells [24]. This discrepancy with NK cells may be related to the lack of TRL9 expression in Sézary cells when KIR3DL2 can be viewed as a carrier protein that brings CpG ODN to its receptor TLR9 in the endosomal compartment, resulting in NK cell activation [17]. Phase I/II trials using CpG ODN injected subcutaneously in CTCL patients led to a clinical response rate of 32 to 36% with no major cytotoxic side effects [25,26]. Altogether these data suggest that CpG ODN might initiate a direct anti-tumor effect on Sézary cells by binding to KIR3DL2.

In conclusion, KIR3DL2 is not only a useful marker to identify the tumor population in CTCL; it also constitutes a very promising therapeutic target to improve patient clinical support. This could be achieved by promoting NK or macrophage recruitment as well as complement to eliminate tumor cells through the use of specifically design IPH4102 anti-KIR3DL2 mAb or through the use of TLR9 agonist CpG ODN that bind to KIR3DL2 surface receptor and induce caspase-dependent tumor cell apoptosis. Future will tell how successful these strategies are.

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