Original Article

Interleukin 13 participates in terminal differentiation of esophageal squamous cell carcinoma cells

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Background: In China, esophageal squamous cell carcinoma (ESCC) accounts for more than 90% of all esophageal cancer cases. Interleukin 13 (IL-13) was widely reported to play a key role in tumor progression. Our previous study reported that IL-13 was a favorable predictive marker for the overall survival of esophageal squamous cell carcinoma (ESCC) patients, but how IL-13 contributes to ESCC progression remains unknown. This study aims to explore the role of IL-13 and its underlying downstream molecular mechanisms in ESCC progression.

Methods: Tissue microarrays including 262 primary ESCC tumor tissues were collected and analyzed. The expression of IL-13 in ESCC tumor tissue was detected with immunohistochemistry staining (IHC). Quantitative real-time polymerase chain reaction (qRT-PCR) was performed to qualify the expressions of *KRT13*, *KRT4* and 15-lipoxygenase-1 (*15-LOX-1*) in cultured ESCC cell lines with recombinant IL-13 treatment.

Results: IL-13 was expressed in the esophageal epithelium cells and ESCC tumor cells. High IL-13 expression in ESCC tumor cells predicted a good prognosis for patients. Recombinant human IL-13 raised *KRT13* and *15-LOX-1* mRNA levels, but lowered *KRT4* mRNA level 15-LOX-1 in ESCC cells *in vitro*.

Conclusions: In summary, our study suggests that IL-13 might improve the prognosis of ESCC by promoting the terminal differentiation of ESCC cells. This may offer potential new therapeutic target for early treatment of ESCC.

Keywords: 15-LOX-1; terminal differentiation; esophageal squamous cell carcinoma (ESCC); interleukin 13 (IL-13); prognosis

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Introduction

Esophageal cancer is a fatal disease with the characteristic of rapid progression and poor prognosis (1). As the main histological sub-type of esophageal cancer, esophageal squamous cell carcinoma (ESCC) has the feature of squamous cell differentiation and is highly prevalent in Asia (2,3). In China, ESCC accounts for more than 90% of all esophageal cancer cases (4). Smoking and drinking, diet lack of fresh fruit and vegetables, hot beverage and pickled vegetables, micronutrient deficiency, infections, family history of esophageal cancer, as well as genetic changes are related to the occurrence of ESCC (4,5). More comprehension of the molecular mechanism of ESCC occurrence and development are believed to has great value for ESCC diagnosis and therapy.

Interleukin 13 (IL-13) is a cytokine of chemokine family and mainly secreted by T helper 2 cell (Th2) (6). In generally, IL-13 takes part in the inflammatory response via multiple pathways, including promoting monocyte differentiation, inducing B lymphocyte proliferation and stimulating NK cells to produce interferon (IFN) (7). It is widely reported that IL-13 play a key role in various inflammation-related diseases, such as asthma, atopic dermatitis, systemic sclerosis and allergic inflammation (8-11). The relationship between inflammation and cancer is very complex (12). There are a large number of immune cells in the tumor microenvironment (TME), including T cells, monocytes and macrophages. Earlier literature reported that IL-13 could promote the polarization of macrophages toward M2 phenotype, which showed more phagocytic activity and carcinogenesis function (13). For ESCC, Rothe *et al.* (14) and Dalessandri *et al.* (15) revealed that IL-13 inhibited the incidence of epithelial-derived tumors in mice. Lu *et al.* (16) discovered that IL-13 could induce epithelial gene and protein expression changes at the sites of inflammation. Zhou *et al.* (17) found that IL-13 expression was up-regulated in the basal cell hyperplasia and early cancer stages of ESCC. More importantly, our earlier research reported that IL-13 expression in tumor stroma was positively correlated with the overall survival of ESCC patients after operation, which could be serve as a prospective immune marker for ESCC prognosis prediction (18). However, how IL-13 contributes to ESCC progression remains unknown.

In this research, we continued to study the detailed regulatory mechanism of IL-13 in the progression of ESCC. As far as we know, it is the first study concerning the regulatory role of IL-13 in ESCC progression. The finding of our research will provide new experimental evidence for further understanding the key role of IL-13 in ESCC development. We present the following article in accordance with the MDAR reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-559/rc).

Methods

Specimens and cell lines

A total of 262 pairs of primary ESCC tumor tissues and adjacent non-tumor tissues were collected from the Sun Yat-sen Memorial Hospital of Sun Yat-sen University (Guangzhou, China) and Cancer Hospital of Linzhou (Henan, China) to constitute tissue microarrays (TMA) as reported in the references (18). The samples collected in this study were carried out under approval of Ethics Committee of Sun Yat-sen Memorial Hospital affiliated to Sun Yat-sen University (No. 2018-198). The Cancer Hospital of Linzhou is informed and agreed with this study. Informed consent was obtained from participants before the experiment. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013). The ESCC cell lines, KYSE30 and KYSE510, were gifts from Professor Srivastava (University of Hong Kong, Department of Pathology). Both cell lines were cultured in Roswell Park Memorial Institute (RPMI)1640 supplemented with 10% fetal bovine serum.

Immunohistochemistry (IHC) staining

IHC staining of the TMA was performed as described previously (18). Briefly, paraffin-embedded, formalin-fixed tissues and TMA sections were deparaffinized. Non-specific bindings were blocked with 5% bovine serum albumin (BSA) in phosphate buffered saline (PBS) for 30 min. The tissues were then incubated with primary antibody against human IL-13 (Boster, China) at 4 ℃ overnight, and subsequently incubated with horseradish peroxidase (HRP)-conjugated second antibody (Dako, Denmark) for 2 hours at room temperature. Diaminobenzidine tetrahydrochloride (DAB) was used as the visualization substrate followed by

Table 1 Primers list for qPCR

ID	Sequences (5'-3')
15-LOX-1 forward primer	TCCCTGTGGATGAGCGATT
15-LOX-1 reverse primer	TGACCACACCAGAAAATCCG
KRT4 forward primer	CGAATGCTGCGTGAGTACC
KRT4 reverse primer	CACTTCCTAATCCTCCGCT
KRT13 forward primer	GACCGCCACCATTGAAAACAA
KRT13 reverse primer	TCCAGGTCAGTCTTAGACAGAG
GAPDH forward primer	AACGGATTTGGTCGTATTGGG
GAPDH reverse primer	TTGATTTTGGAGGGATCTCGC

qPCR, quantitative polymerase chain reaction.

counterstaining with hematoxylin. The IL-13 expression level in tumor cells was scored as strong, moderate, weak, and negative using InForm™ 2.1 software (Leica, Germany) under microscopy (Leica, Germany). The negative and weak expression cases were subsequently grouped as the low IL-13 expression group and the remaining cases as the high IL-13 expression group.

Quantitative real-time PCR (qPCR)

The KYSE30 and KYSE510 cell lines were treated with 20 ng/mL recombinant human IL-13 (rhIL-13) (PeproTech, Rocky Hill, NJ) or a buffer control for 48 hours. Total RNA of differently treated cells was isolated with TRIzol Reagent (Invitrogen, Carlsbad, CA). The BeyoRT™ II cDNA Kit (Beyotime, China) was used to reverse transcript isolated total mRNA. Finally, cDNA was amplified with primers (*Table 1*) and GAPDH was used as the internal control. qPCR was performed in an ABI 7900 real-time PCR system. The relative expressions of *KRT13*, *KRT4* and 15-lipoxygenase-1 (*15-LOX-1*) genes was calculated using the $2^{-\Delta\Delta Ct}$ method with GAPDH as endogenous control (19).

Statistical analysis

GraphPad Prism 8 was used to conduct statistical analyses. The long-rank test and Kaplan-Meier method were performed to estimate overall survival. *In vitro* cell experiments were repeated three times, different expressions between groups were analyzed using the two-tailed Student's *t*-test.

Results

IL-13 was expressed in the normal esophageal epithelium and ESCC tumor cells

IL-13 is an immune cell-secreted cytokine that can be secreted by numerous immune cells. Surprisingly, we found that IL-13 was expressed not only in immune cells (18) but also in tumor cells and the esophageal epithelium (*Figure 1*). In adjacent non-tumor tissue, IL-13 was mainly expressed in the suprabasal layers of stratified squamous esophageal epithelium, but not in the basal cells, which indicated that the expression of IL-13 in the esophageal epithelium might be correlated with its specific differentiation status.

Low IL-13 expression in ESCC tumor cells predicted a poor prognosis

We have reported previously that total IL-13 expression in the ESCC tumor area was correlated with patients' prognosis (18). In this study, we aimed to further explore whether the IL-13 expression level in tumor cells could also predict the prognosis. We divided the patients into two groups according to their IL-13 expression level in ESCC tumor cells. The results demonstrated that patients expressing higher levels of IL-13 in tumor cells had a relatively longer overall survival time than patients whose tumor cells expressed lower levels of IL-13 (*Figure 2*, $P<0.0001$).

ESCC patients with a well-differentiated histological grade expressed relatively higher levels of IL-13 in tumor cells

The loss of normal differentiation is one of the basic features of ESCC cells. As we observed that the stratified squamous esophageal epithelium expressed significantly higher levels of IL-13 than that in basal and tumor cells, we also investigated the expression of IL-13 in ESCC cells with different histological differentiation statuses. We found that tumor cells with higher IL-13 expression were more common in well-differentiated ESCC patients compared to poorly differentiated patients (*Figure 3*).

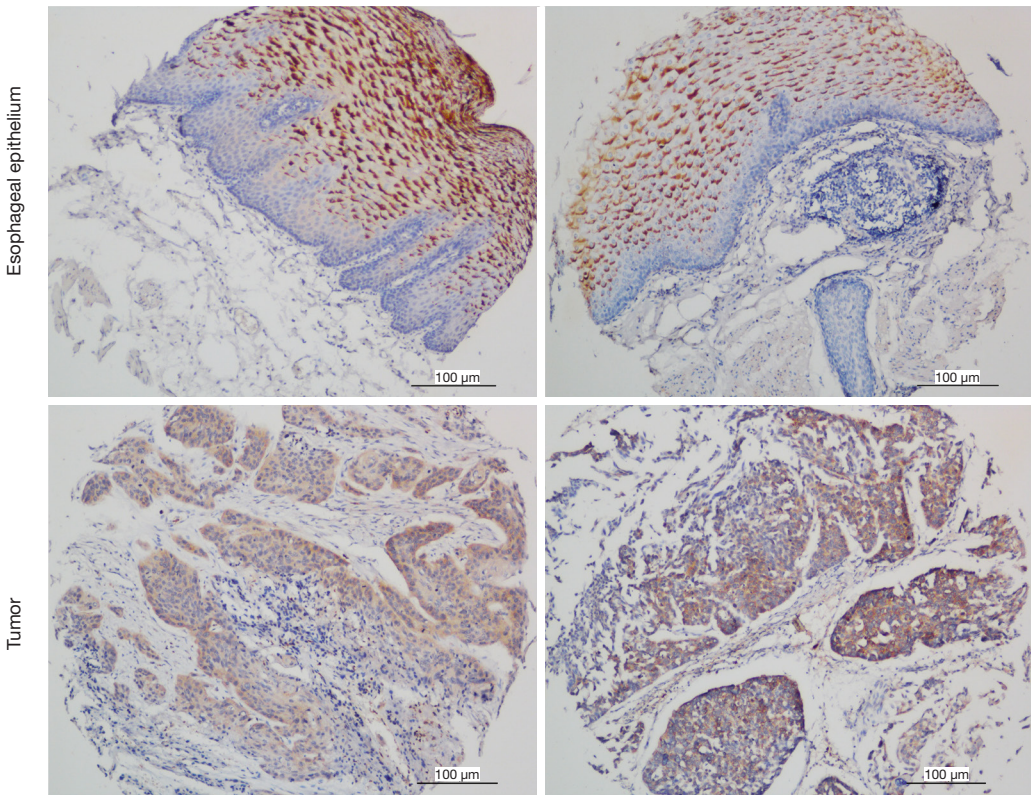

Figure 1 IHC results of IL-13 expression in the esophageal epithelium and ESCC tumor cells. Expression of IL-13 in the esophageal epithelium and ESCC tumor cells were detected with IHC staining in the TMA (brown indicated a positive signal). IHC, immunohistochemistry; IL-13, interleukin 13; ESCC, esophageal squamous cell carcinoma; TMA, constitute tissue microarrays.

IL-13 promoted 15-LOX-1 mRNA expression in ESCC cell lines

The observation above suggested that the expression of IL-13 in ESCC tumor cells might be related to their differentiation status. To verify whether IL-13 could promote the differentiation of ESCC, we treated ESCC cell lines, KYSE30 and KYSE510, with 20 ng/mL rhIL-13 and detected the expression of epithelial differentiation-related molecular markers (*Table 1*). The results demonstrated that rhIL-13 could increase the expression of *KRT13* in KYSE510 and decrease the expression of *KRT4* in KYSE30 (*Figure 4A*,*4B*), which were reported to be differently expressed in the non-cornified suprabasal layers and stratified squamous epithelium (20). Furthermore, rhIL-13 could also improve the expression of 15-LOX-1 in both KYSE30 and KYSE510 (*Figure 4C*), which was reported to be a terminal differentiation promoting molecule in most cells (21,22).

Discussion

ESCC is an epithelium-derived cancer; the loss of normal differentiation is a characteristic feature of most epithelium-originated cancers (23). The induction of normal differentiation is an important clinical therapy strategy for these cancers. IL-13 is a multifunctional cytokine that has been found to contribute to the differentiation and function of some immune cells, including macrophages, B lymphocytes and Th2 cells (6). Recent years, some studies found that IL-13 could induce differentiation of non-immune cells. For example, Kanoh *et al.* and Kondo *et al.* (24,25) revealed that IL-13 promoted mucin MUC5AC

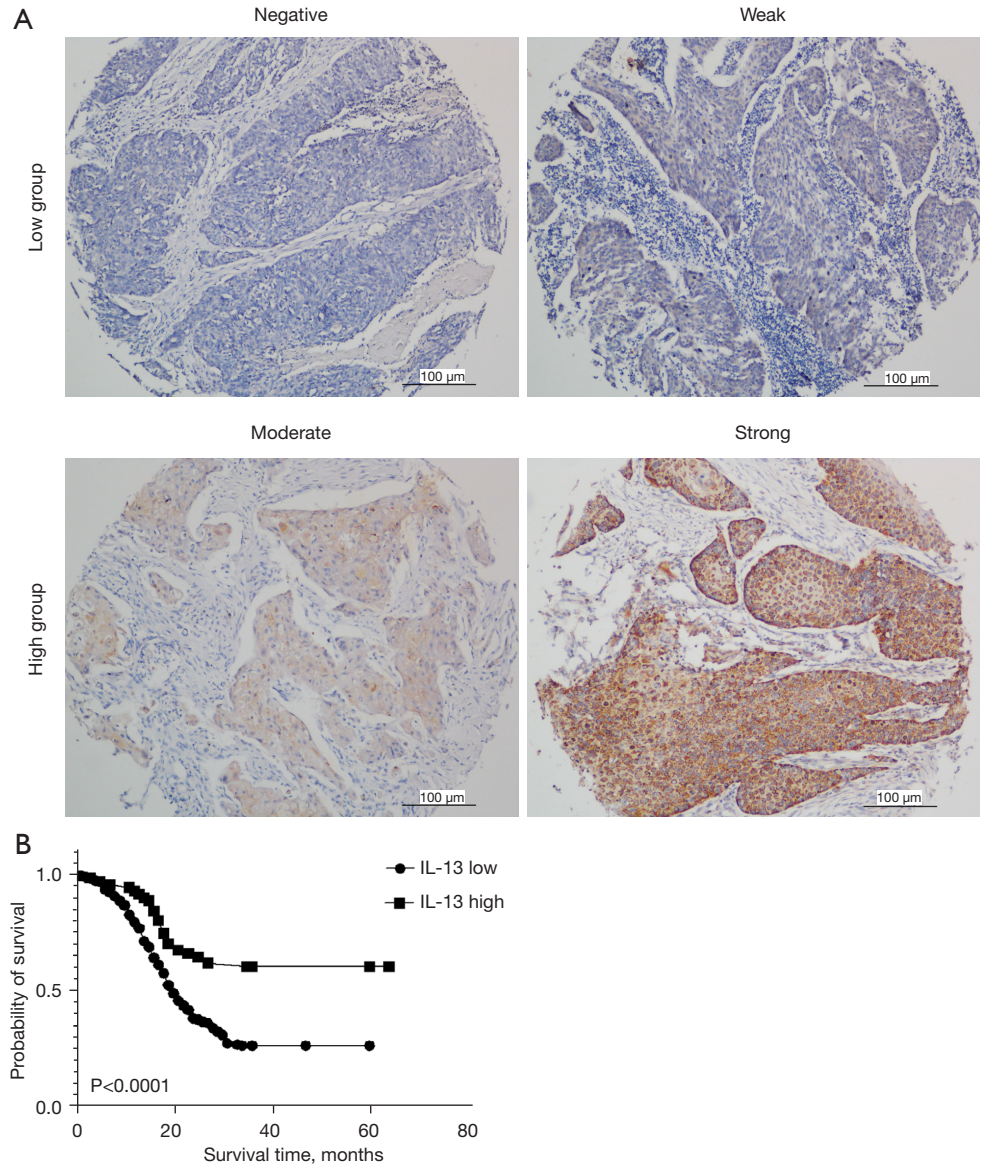

Figure 2 ESCC patients with higher IL-13-expressing tumor cells had a longer overall survival time. (A) IL-13 expression in ESCC tumor cells demonstrated by IHC staining; (B) overall survival function analysis of IL-13 expression in ESCC tumor cells. ESCC, esophageal squamous cell carcinoma; IHC, immunohistochemistry; IL-13, interleukin 13.

production and goblet cell differentiation in human airway cells. Laoukili *et al.* (26) discovered that IL-13 took part in the modulation of mucociliary differentiation in human respiratory epithelial cells.

In this study, we observed that IL-13 was highly expressed in the stratified squamous esophageal epithelium and the expression of IL-13 in ESCC tumor cells seemed to be correlated with the differentiation status. Furthermore, we also found that IL-13 could increase *KRT13* expression and decrease the expression of *KRT4* in ESCC cells *in vitro*. The upregulated expression of KRT13 was previously reported to be an important marker for ESCC tumor cell differentiation (27). Moreover, a switch from a $KRT13^{low}$ and $KRT14^{high}$ to a $KRT13^{high}$ and $KRT14^{low}$

phenotype has been reported to accompany the transition of cell morphology during the progression of urothelium differentiation (28). Esophageal epithelium-secreted IL-13 might also serve to promote its own differentiation through this switch, although the detailed mechanism requires further exploration.

15-LOX-1 is a member of the lipoxygenase family and has been reported to promote cell differentiation, especially in the process of terminal differentiation (21,22,29). According to the report of Moussalli *et al.* (22), 15-LOX-1's expression level in tumor cells is lower than that in the corresponding normally differentiated cell. Enhancing the expression of 15-LOX-1 in tumor cell lines can promote their terminal differentiation and significantly reduce their tumorigenic capacity. Shureiqi *et al.* (30) reported that low 15-LOX-1 expression in ESCC tumor tissue predicted a poor prognosis for patients. They also found that increasing the expression of 15-LOX-1 or its function in ESCC cells could promote the differentiation and apoptosis of ESCC cells. Earlier research reported that IL-13 could activate 15-LOX-1, enhanced the 15-LOX-1 mRNA and protein synthesis (31,32). Herein, we found that IL-13 could promote the expression of 15-LOX-1 in ESCC cells, which implied that IL-13 could exert anti-ESCC role via inducing the terminal differentiation of ESCC cells. It was reported that the promoter and enhancer regions of the *15-LOX-1* gene contain binding sites for SP-1, STAT6 and STAT2. STAT6 is one of the strongest stimulation signals for 15-LOX-1 expression. Phosphorylated STAT6 could induce the rapid transcription of 15-LOX-1 by binding to STAT6 response elements in the *15-LOX-1* gene enhancer region. IL-13 can promote the rapid phosphorylation of STAT6 after it binds with IL-4R/IL-13R1 receptor, followed by activation of the Jak2/Tyk2-STAT6 pathway in various cells (6,33). Therefore, IL-13 might promote 15-LOX-1 expression by activating STAT6 in ESCC cells, resulting in a favorable prognosis in ESCC patients. Our study indicates that IL-13 signaling pathway could be a new target for ESCC immunotherapy, in spite of further preclinical and clinical study are still needed. In the future, we will continue study the regulatory effect of IL-13 on differentiation of ESCC cells.

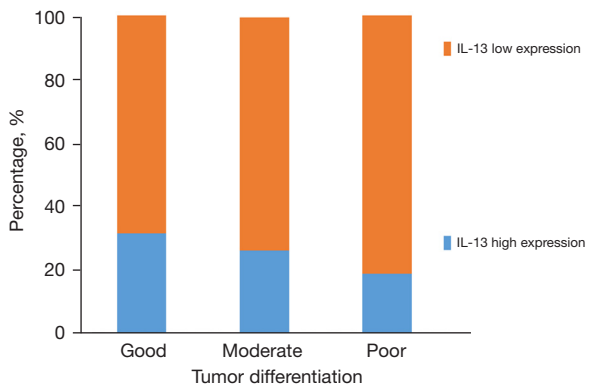

Figure 3 Relationship between IL-13 expression in ECSS tumor cells and tumor differentiation status. The frequencies of low or high tumor IL-13 expression ESCC patients in different histological differentiation statuses. IL-13, interleukin 13; ESCC, esophageal squamous cell carcinoma.

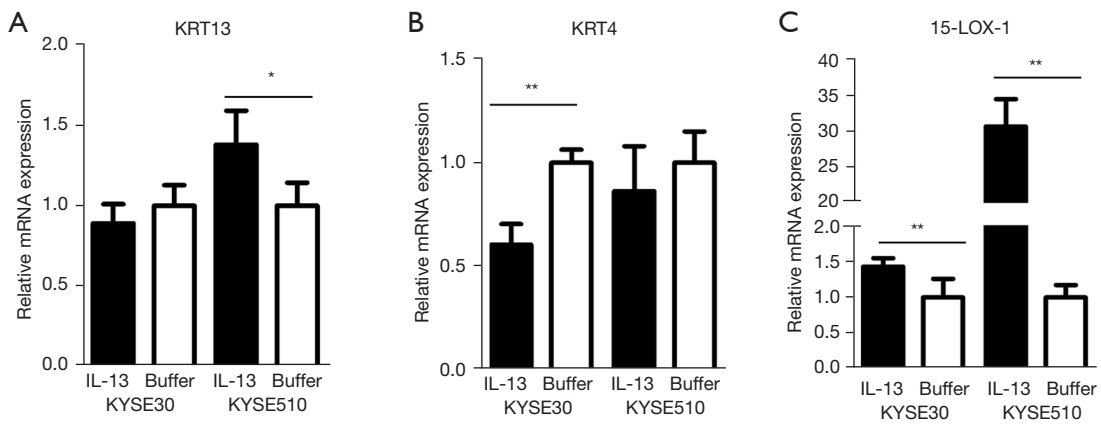

Figure 4 Relative mRNA expression of different molecules in ESCC cells lines after rhIL-13 treatment. (A-C) Relative mRNA expression level of indicated molecule in KYSE30 and KYSE510 cell lines after treatment with 20 ng/mL rhIL-13 or a buffer control for 48 hours (*, P<0.05; **, P<0.01). ESCC, esophageal squamous cell carcinoma; IL-13, interleukin 13.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-559/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-559/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-559/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The samples collected in this study were carried out under approval of Ethics Committee of Sun Yat-sen Memorial Hospital affiliated to Sun Yat-sen University (No. 2018-198). The Cancer Hospital of Linzhou is informed and agreed with this study. Informed consent was obtained from participants before the experiment. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013).

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