Ruskinn 低氧工作站应用案例——肿瘤免疫治疗

Hypoxia Induced Impairment of NK Cell Cytotoxicity against Multiple Myeloma Can Be Overcome by IL-2 Activation of the NK Cells

NK 细胞 IL-2 活化可克服缺氧性 NK 细胞对多发性骨髓瘤的杀伤作用

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工作站使用情况：In Vivo$_2$ 1000

BACKGROUND:Multiple Myeloma (MM) is an incurable plasma cell malignancy residing within the bone marrow (BM). We aim to develop allogeneic Natural Killer (NK) cell immunotherapy for MM. As the BM contains hypoxic regions and the tumor environment can be immunosuppressive, we hypothesized that hypoxia inhibits NK cell anti-MM responses.

METHODS:NK cells were isolated from healthy donors by negative selection and NK cell function and phenotype were examined at oxygen levels representative of hypoxic BM using flowcytometry. Additionally, NK cells were activated with IL-2 to enhance NK cell cytotoxicity under hypoxia.

RESULTS: Hypoxia reduced NK cell killing of MM cell lines in an oxygen dependent manner. Under hypoxia, NK cells maintained their ability to degranulate in response to target cells, though, the percentage of degranulating NK cells was slightly reduced. Adaptation of NK- or MM cells to hypoxia was not required, hence, the oxygen level during the killing process was critical. Hypoxia did not alter surface expression of NK cell ligands (HLA-ABC, -E, MICA/B and ULBP1-2) and receptors (KIR, NKG2A/C, DNAM-1, NCRs and 2B4). It did, however, decrease expression of the activating NKG2D receptor and of intracellular perforin and granzyme B. Pre-activation of NK cells by IL-2 abrogated the detrimental effects of hypoxia and increased NKG2D expression. This emphasized that activated NK cells can mediate anti-MM effects, even under hypoxic conditions.

CONCLUSIONS: Hypoxia abolishes the killing potential of NK cells against multiple myeloma, which can be restored by IL-2 activation. Our study shows that for the design of NK cell-based immunotherapy it is necessary to study biological interactions between NK- and tumor cells also under hypoxic conditions.

主要内容：缺氧是大多数肿瘤组织的特征，可以改变不同免疫细胞的功能，研究发现缺氧可消除 NK 细胞对多发性骨髓瘤的杀伤作用，故为了设计基于 NK 细胞的免疫治疗，也有必要研究 NK 细胞与肿瘤细胞在低氧条件下的相互作用。

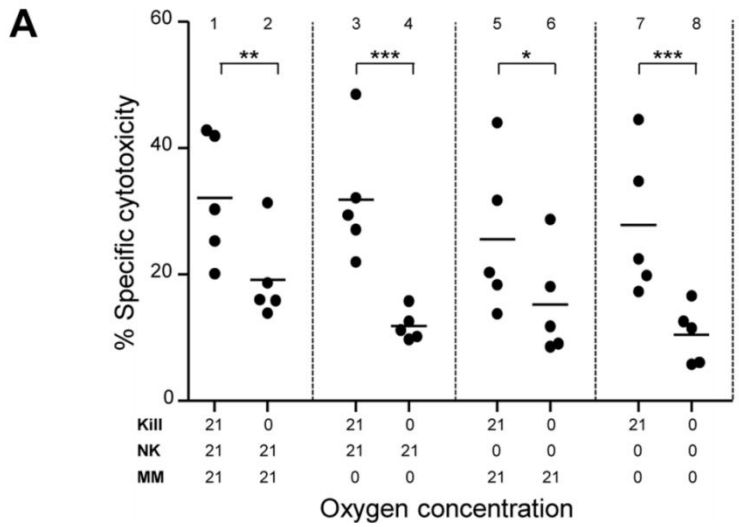

Figure 4. Oxygen concentration during NK cell killing is the key regulating parameter determining the cytotoxic potential. (A) Preincubation (16 hours) of MM- and NK cells followed by 4.5 hour assessment of cytotoxicity were performed at the O2 concentration depicted on the x-axis. Each dot represents mean of triplicate cultures of individual donors. Statistics were performed with one-way repeated measures ANOVA with Bonferroni correction * p,0.05, ** p,0.01, *** p,0.001.

将 NK 细胞、MM 细胞或两者都预先孵育在 21%或 0%的 O_2 中，并将它们组合在 21%或 0% O_2 中进行细胞毒性评估。在 0% O_2 中预孵育的 NK 细胞不影响其杀伤活性(图中第 3 组和第 5 组)。相反，在 0% O_2 条件下进行细胞毒试验(第 2、4、6 和 8 组)，与在 21% O_2(第 1、3、5 和 7 组)中进行细胞毒试验相比，均显示 NK 细胞的细胞毒性降低。