Migration of Natural Killer Cells

Matrix interaction, locomotion and regulation of matrix metalloproteinases (MMPs) by IL-2 and chemokines

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ABSTRACT

Activated natural killer (NK) cells are effective anti-tumour cells. In order to reach target cells in a tumour mass they need to migrate in the extravascular space. The process of tumour localisation begins when the NK cell is attracted in the blood stream, and utilisation of matrix-degrading enzymes is crucial for passing of the basal membrane (BM) and for locomotion outside the vascular bed. NK cells express several members of the family of matrix-degrading enzymes, matrix metalloproteinases (MMPs). The aim of this study was to gain more knowledge on the regulation of NK cell migration that affects infiltration of the extracellular matrix (ECM) equivalent Matrigel. In specific; morphologically study NK cell locomotion in a matrix environment; identify the repertoire of MMPs expressed by freshly isolated human NK cells and the human NK cell lines YT and NK-92; explore the role of MMPs in NK cell migration and investigate the effect of IL-2 and chemokine stimulation as well as matrix (Matrigel) contact on NK cells' migratory ability and MMP expression.

IL-2-activated mouse A-NK cells cultured in Matrigel revealed two different patterns of matrix disintegration depending on their time in culture, and similar differences were found between two human NK cell lines. Younger ($\leq$ 5 days) mouse A-NK and NK-92 cells gave rise to a general widespread matrix reorganisation, interpreted to be due to direct release of soluble matrix-degrading enzymes. Older ($\geq$ 6 days) mouse A-NK and YT cells instead produced large excavations in the Matrigel. These cavities could be explained by a release of proteoglycan-rich material with matrix-dilating properties, combined with associated matrix-degrading proteases. The IL-2-independent NK cell line YT and freshly isolated human NK cells was used to investigate the effects of IL-2 stimulation on NK cell migration and MMP expression and production. IL-2 stimulation of the YT cell line demonstrated opposing effects related to the duration of stimulation. A rapid stimulatory response at about 2-4h on MMP production, and a later negative effect on MMP expression and MMP-9 production was seen after prolonged stimulation ($\geq$ 24h). Both responses correspondingly affected the migratory ability. In freshly isolated NK cells, migration increased MMP-dependently in response to IL-2 and MT6-MMP expression increased. MMP-13, MT3- and MT6-MMP, previously not described in NK cells, was found to be expressed by freshly isolated human NK cells. While matrix (Matrigel) contact did not affect MMP expression in either the NK-92 or YT cell line, the chemokine CX3CL1 was found to increase NK-92 cells' MMP-9 production significantly, but had no effect on their migration.

These findings increase our understanding of how NK cell migration is regulated and provide one further step in the development of strategies to achieve greater number of tumour infiltrating NK cells.

Keywords: NK cell, MMP, Matrigel, migration, IL-2

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I Albertsson P, Basse PH, **Edsparr K**, Kim MH, Goldfarb RH. Kitson RP, Lennernäs B, Nannmark U, Johansson BR
Differential locomotion of long- and short-term IL-2-activated murine natural killer cells in a model matrix environment
Scand J Immunol 2007 Oct; 66(4):402-9

II **Edsparr K**, Johansson BR, Goldfarb RH, Basse PH, Nannmark U, Speetjens FM, Kuppen PJK, Lennernäs B and Albertsson P
Human NK cell lines migrate differentially *in vitro* related to matrix interaction and MMP expression
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III **Edsparr K**, Speetjens FM, Mulder-Stapel A, Goldfarb RH, Basse PH, Lennernäs B, Kuppen PJK and Albertsson P
Effects of IL-2 on MMP expression in freshly isolated human NK cells and the IL-2 independent NK cell line YT
Manuscript, submitted

IV **Edsparr K**, Cullin F, Barth H, Goldfarb RH, Basse PH, Lennernäs B, Kuppen PJK and Albertsson P
The Fractalkine (CX3CL1) chemokine stimulates NK-92 natural killer cell production of MMP-9
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