Immune escape in chronic leukemia

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs universitet kommer att officiellt försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg,
torsdagen den 22 oktober 2015 kl. 09.00

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Avhandlingen baseras på följande delarbeten:


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ABSTRACT

Reactive oxygen species (ROS) are produced by myeloid cells as a mechanism of defense against infection, but also to resolve inflammation, as ROS can induce cell death in T cells and NK cells. ROS production may also be deployed as a mechanism by which myeloid cells suppress anti-leukemic lymphocytes to promote malignant progression. The aim of this thesis was to define the role of myeloid cell-derived ROS in chronic leukemias as a putative target of immunotherapy. In paper I, the transductional pathways leading to ROS-induced lymphocyte death were investigated and found to involve the ERK1/2 mitogen-activated protein kinase (MAPK). These results challenge the view of ROS-induced cell death being a direct consequence of ROS-inflicted DNA damage. Papers II and III demonstrate that anti-CD20 monoclonal antibodies (mAbs) triggered ROS production by monocytes and neutrophils, which translated into reduced NK cell-mediated antibody-dependent cytotoxicity (ADCC) towards autologous leukemic cells derived from patients with chronic lymphocytic leukemia (CLL). The anti-oxidative agent histamine dihydrochloride (HDC) was found to restore ADCC by preventing ROS formation from adjacent monocytes, suggesting that anti-oxidative therapy might increase the efficacy of therapeutic mAbs. In paper IV, monocytic leukemic cells obtained from patients with chronic myelomonocytic leukemia (CMML) were shown to suppress T cells and NK cells by producing ROS. HDC counter-acted the suppression of lymphocytes by preventing ROS formation, and augmented the anti-leukemic activity of NK cells. Collectively, these results suggest that myeloid cell-derived ROS may be operational in CLL and in CMML as a mechanism of immune escape and that immunotherapy by anti-oxidative intervention should be further investigated in these forms of chronic leukemia.

Keywords Immune escape, immunotherapy, reactive oxygen species, chronic lymphocytic leukemia, chronic myelomonocytic leukemia, MAPK