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Sphingosine-kinase and sphingosine-1-phosphate regulate migration of immature dendritic cells

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Introduction

Currently, dendritic cells (DC) are tested as vectors for cancer immunotherapy. However, little is known about the mechanisms regulating DC migration. Sphingosine-kinase (SphK) and its catalytic product Sphingosine-1-phosphate (S1P) play a central role in processes such as cellular differentiation, survival and migration, which are often disregulated in cancer. Here, we examined the role of SphK and S1P in migration of DC.

Methods

DC were generated in the presence of GM-CSF and IL-4 for 5 days, then matured with PGE_2, TNF-α and IL1-β for 2 days. Expression of SphK and S1P-receptors was examined by RT-PCR. In transwell assays migration of immature (i) and mature (m) DC towards SDF-1, MiP-1a, MCP, 6Ckine, MiP-3β [100 ng/ml] and S1P [10^{-5} M] was tested for being dependent on SphK using the SphK inhibitor Dihydrosphingosine [DHS, 10^{-6} M]. The role of $S1P_3$ receptor in S1P-induced migration was tested using the $S1P_3$-inhibitor Suramin [10^{-6} M]. In parallel, Ca^{2+}-flux was assessed by FACS with Fura Red.

Results

SphK expression was declining from iDC to mDC to antigen-loaded mDC. Expression levels of S1P receptors were $S1P_1 > S1P_2 = S1P_3$, unrelated to maturation stage or antigen uptake. IDC migrated on SDF-1, MIP-1α, MCP and S1P, whereby S1P combined with a chemokine acted synergistic. MDC migrated on 6Ckine and MIP-3β, but not on S1P. Pre-treatment with DHS inhibited migration of iDC but not mDC, showing that SphK is required for iDC migration. Pre-treatment with Suramin inhibited iDC migration in response to S1P, demonstrating a mediation via $S1P_3$. Chemokine induced Ca^{2+}-flux was inhibited by DHS, indicating that SphK-mediated migration might be Ca^{2+}-dependent.

Conclusion

Our results suggest a role for SphK/S1P in accumulation of peripheral iDC at sites of antigen invasion. These findings could provide a new approach to optimise DC-based cancer immunotherapy by therapeutic modulation of SphK/S1P and have to be verified in an animal model in the next step.

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