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The extracellular matrix in stem cell commitment: Biphasic role of chondroitin sulfate in cardiac differentiation of embryonic stem cells through inhibition of Wnt/beta-catenin signaling

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The glycosaminoglycan chondroitin sulfate is a critical component of proteoglycans on the cell surface and in the extracellular matrix. As such, chondroitin sulfate side chains and the sulfation balance of chondroitin play important roles in the control of signaling pathways, and have a functional importance in human disease. In contrast, very little is known about the roles of chondroitin sulfate molecules and sulfation patterns during mammalian development and cell lineage specification. Here, we report a novel biphasic role of chondroitin sulfate in the specification of the cardiac cell lineage during embryonic stem cell differentiation through modulation of Wnt/beta-catenin signaling. Lineage marker analysis demonstrates that enzymatic elimination of endogenous chondroitin sulfates leads to defects specifically in cardiac differentiation. This is accompanied by a reduction in the number of beating cardiac foci. Mechanistically, we show that endogenous chondroitin sulfate controls cardiac differentiation in a temporal biphasic manner through inhibition of the Wnt/beta-catenin pathway, a known regulatory pathway for the cardiac lineage. Treatment with a specific exogenous chondroitin sulfate, CS-E, could mimic these biphasic effects on cardiac differentiation and Wnt/beta-catenin signaling. These results establish chondroitin sulfate and its sulfation balance as important regulators of cardiac cell lineage decisions through control of the Wnt/beta- catenin pathway. Our work suggests that targeting the chondroitin biosynthesis and sulfation machinery is a novel promising avenue in regenerative strategies after heart injury.

Biography

Michael Kluppel received a Master's degree from the University of Heidelberg, Germany, and a PhD from the University of Toronto, Canada. After Postdoctoral studies at The Hospital for Sick Children and Mount Sinai Hospital in Toronto, he currently holds an Assistant Professor position at the Feinberg School of Medicine of Northwestern University in Chicago. He has published more than 30 peer-reviewed papers in reputed journals, and serves as an Editorial Board Member for several international journals.

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