Desmoglein-2: getting to the heart of adhesion

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Desmogleins (DSG) are a family of cadherin adhesion proteins that were first identified in desmosomes and provide cardiomyocytes and epithelial cells with the junctional stability to tolerate mechanical stress. However, one member of this family, DSG2, is emerging as a protein with additional biological functions on a broader range of cells. Here we reveal that DSG2 is expressed by non-desmosome forming human endothelial progenitor cells (EPCs) as well as their mature counterparts (endothelial cells (ECs)) in human tissue from healthy individuals and cancer patients. Analysis of normal blood and bone marrow showed that DSG2 is also expressed by $CD34^{+}CD45^{dim}$ hematopoietic progenitor cells. An inability to detect other desmosomal components *i.e.* DSG1, DSG3 and desmocollin (DSC)2/3 on these cells supports a solitary role for DSG2 outside of desmosomes. Functionally, we show that $CD34^{+}CD45^{dim}DSG2^{+}$ progenitor cells are multipotent and pro-angiogenic *in vitro*. Using a 'knock-out first' approach we generated a *Dsg2* loss-of-function strain of mice ($Dsg2^{lo/lo}$) which exhibited a phenotype of arrhythmogenic right ventricular cardiomyopathy (ARVC) which is also prominent in humans with mutated *DSG2*. Interestingly, in response to reduced levels of *Dsg2* we also observed (i) $CD31^{+}$ ECs exhibit an altered and hypertrophic morphology, (ii) bone marrow-derived endothelial colony formation is impaired, (iii) *ex vivo* vascular sprouting from aortic rings is reduced and (iv) vessel formation *in vitro* and *in vivo* is attenuated. Finally, knock-down of *DSG2* in a human bone marrow EC line reveal a reduction in an *in vitro* angiogenesis assay as well as relocalisation of actin and VE-cadherin away from the cell junctions, reduced cell:cell adhesion and increased invasive properties by these cells. In summary, we have identified DSG2 expression in distinct progenitor cell sub-populations and show that, independent from its classical function as a component of desmosomes, this cadherin also plays a critical role in the vasculature.