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Title: Contribution of stem-like cells to angioproliferative pulmonary arterial hypertension in the SU5416/chronic hypoxia model

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Body: Severe pulmonary arterial hypertension (PAH) is a disease with high mortality and no curative treatment. The goal of our study was to investigate the potential contribution of stem-like cells to the angioobliteration in the SU5416/chronic hypoxia (SuHx) model of severe PAH. Animals were treated according to the SuHx protocol and underwent sequential labeling with two halogenated thymidine analogues to investigate asymmetrical cell division, and treatment with the CXCR4 inhibitor AMD3100 (day 1-21) or recombinant human G-CSF (day 14-21). After three weeks, we identified by immunofluorescence/confocal microscopy in the angioproliferative lesions of the SuHx rat model of severe PAH cells expressing markers of pluripotent stem cells and multipotent differentiation. We also showed that lesion cell division in SuHx animals was asymmetrical. The CXCR4 inhibitor AMD3100 reduced pulmonary artery muscularization and obliteration of medium size vessels in the animal model without greatly impacting PAH. This was associated with a reduction in the numbers of c-kit+ cells in the vessel. We further show that G-CSF-induced cell mobilization from the bone marrow did not affect the PAH, but caused enhanced pulmonary artery muscularization together with pulmonary neovascularization instead, associated with an augmented accumulation of c-kit+ cells in and around the vessels. In conclusion, our data indicate that putative stem-like cells, which express pluri- and multipotency markers, contribute to the pulmonary angioproliferation. Successful treatment of severe angioobliterative PAH will likely require a better knowledge of the role of such cells in the pathobiology of PAH.