Signalling and endocytic trafficking in endothelial cells: Basic mechanisms and perspectives in stem cells biology and differentiation

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ABSTRACT

Endocytic trafficking plays a key role in the regulation of growth factor signaling. The endocytic pathway is the portal of entry into the cell and following ligand/receptor binding, the endocytic route of the ligand/receptor complex determines where, and for how long, the signals are emitted depending on the localisation of signalling effectors and inhibitors along the various endocytic pathways. Should different internalisation routes and trafficking pathways exist for a receptor/ligand complex, then the internalisation route followed may dramatically alter the overall downstream responses. The presence or absence of endocytic pathways in a particular cell type may also affect the overall response to ligand/receptor activation. But what happens during development and differentiation? Do pluripotent stem cells possess the full endocytic complexity of differentiated cells, or do they appear as the cells differentiate? We have addressed these issues using Activin A, a member of the TGFβ superfamily, characterised by its developmental effects maintaining pluripotency or inducing mesendoderm differentiation of human embryonic stem cells (hESCs) in a concentration dependent manner by regulating gene transcription including pluripotency genes such as NANOG. In differentiated cells Activin A has multiple biological activities ranging from effects in the reproductive system, inflammation, development, tumorigenesis and angiogenesis. Our results indicate that Activin A traffics through clathrin-mediated and macropinocytic pathways in differentiated cells while in stem cells signalling is mainly from the plasma membrane with a contribution from the clathrin pathway. In addition we show that macropinocytosis is absent from stem cells and is induced upon differentiation. Our findings have wider implications, it may well be that as cells differentiate endocytic pathways emerge and this may control the differentiation process itself.