Shed vesicles are involved in the release of some leaderless proteins.

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Most proteins destined for secretion in the extracellular matrix are characterized by the presence of N-terminal signal peptides which direct their translocation into the endoplasmic reticulum, they are subsequently transferred to the Golgi apparatus and then secreted in the extracellular space.
A growing number of secreted proteins, are being identified which, however, lack signal peptides allowing their entrance into the endoplasmic reticulum. They include the inflammatory cytokine interleukin 1β, galactins, macrophage migration inhibitory factor (MIF), acid and basic fibroblast growth factors (FGF-1, FGF-2) and Sphingosine kinase1(SphK-1). These proteins are secreted from the cell by unconventional processes which are the subject of numerous studies.
Several types of normal and tumor cells can release in the extracellular medium microvesicles, called esovesicles, which result from budding of their plasma membranes. The vesicle diameter ranges between 100nm and 1000nm, the vesicle composition and function depends on the kind of the cell from which they have been produced. We already reported that FGF-2, a secreted lectin that transmits proangiogenic signals, and which is recognized as a potential oncoprotein able to modulate tumour growth and malignancy (Sorensen et al 2006), is released from SkHep1 cells, and from transfected NIH 3T3 cells through vesicle shedding (Taverna et al.2003).
Now we are trying to elucidate the intracellular route followed by the growth factor from the site of synthesis to vesicles budding from the cell membrane. Actin filaments appear to be a binary for this intracellular trafficking. After 6h of treatment with cytocalasine, a drug that interferes with actin polymerization, the amount of vesicles was in fact decreased and FGF-2 clustering in granules localized near the cell surface was avoided. On the contrary no effects were observed when cells were treated with drugs which interfere with microtubule polymerization or de-polymerization. We also observed that FGF-2 granules are not included in lipid-coated vesicles.
We are also analyzing the possibility that esovesicles are involved in the secretion of another leader-less signalling protein: Sphingosine kinase1 (SphK1). SphK1 has been shown to regulate a wide variety of cellular processes, including promotion of cell proliferation, survival and motility (Spiegel et al. 2003). SphK1 is primarily localized in the cytosol; when a signal induces the phosphorylation of Ser 225 of SphK1 through the activation of MAPK and ERK1/2, the molecule is translocated in plasma membranes and the involvement of actin filaments in its targeting has been reported (Pitson et. al. 2003). Three SphK1 isoforms having a different number of amino acids (384, 398 and 470) have been identified, we found that extracellular vesicles are enriched in the 47kDa isoform. SphK assays with TLC confirm that the enzyme is present in shed vesicles and that it has enzymatic activity. The substrate Sphingosine is also present in esovesicles therefore shed vesicles are likely to be a site of Sphingosine 1 Phosphate production.

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