

# Exosomes in developmental signalling

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## ABSTRACT

In order to achieve coordinated growth and patterning during development, cells must communicate with one another, sending and receiving signals that regulate their activities. Such developmental signals can be soluble, bound to the extracellular matrix, or tethered to the surface of adjacent cells. Cells can also signal by releasing exosomes – extracellular vesicles containing bioactive molecules such as RNA, DNA and enzymes. Recent work has suggested that exosomes can also carry signalling proteins, including ligands of the Notch receptor and secreted proteins of the Hedgehog and WNT families. Here, we describe the various types of exosomes and their biogenesis. We then survey the experimental strategies used so far to interfere with exosome formation and critically assess the role of exosomes in developmental signalling.

## Introduction

M. c. f. e ce - ce c. ca . a cc. d.  
de e' e' ed a ed b. c a. c. a d- ece . e ac .  
I. a ca e \$, e a d a \$e eed . e . E a. e c de  
e be \$f \$e WNT, Hed e \$ (HH) a d b. e . e e c  
e (BMP) fa e . L a d ca a. be a s e b a e  
e , a s e ca e f N c. a d. A s e eed  
a d\$ ca s ead a s e ce b dff . , e e \$ a  
ea a. a s ace a s e ce (EV) a c s b. e .  
e ea e a d. ead f. e e ca s ca a d a d/ . ed a e  
a s fe f a e f b s ca ac e s ec. e f . e ce  
a s e. S. c. e ce , ac a ed . e , cec a cd a d  
d, a e deed f. d a s e ace . a e . T e  
a e be ee 30 a d 1000 s da ee, a d a e ca f ed  
acc d . e , . ca . e e a d f. c . (G . d  
a d Ra . , 2013). E s a e, EV f s ed b . e . a d  
b. dd s f. e a a e b a e a e . a c s e ce  
ec . e (B. 1), . e ea EV . a f s . e e d . a  
s s e a e e ed e s e (C. c. cc a d Med e . , 2015). He e,  
s s e f c s . e s e s a d . e f a . a d f. c .  
de e .







ed a s fe s e e c e ; e ee, e ~ e ace f  
 ee e s a a s e d a a a a, ~ e  
 e ba s e a a e c effec A ~ e s , ~ e  
 a ee s c b e e f c ~ e Rab-GAP,  
 TBC1D10 (H e e a., 2010). T e s a g e GTPase  
 ac f RAB27 (I a d F u da, 2006), ce a a  
 RAB27 s e e e c e . TBC1D10 add a ac a e  
 RAB35, ~ c s a a bee ~ c b e e s e  
 ece (H e e a., 2010). Ye a e Rab fa ~ e be  
 caed s e e d c RAB11 (Bec e e a., 2013;  
 K e e a., 2012; Sa a e a., 2002). I a , ~ e s ffce  
 f a e d d a Rab fa e be ~ ffce  
 c ee b c e e e c e , e a s beca e f  
 ed d a c . A e a e , ~ be a e a c f ~ e Rab  
 c d e e e c e fa b e f e .  
 SNARE s e edae ~ f s f e c e ~ e a e  
 e b a e c a e a d a e s e e f e ~ c b e  
 e e a e f ILV a e . Ve ce SNARES ( SNARE )  
 caed s e MVB ec s e a e SNARES ( SNARE )  
 caed a ~ e a a e b a e d e f . f ~ e  
 e b a e (Ca e a., 2007). T e s a c a c e e ed f  
 MVB a a e b a e f ~ a bee f ~ e c da ed . T e  
 SNARE s e VAMP7 a bee ~ e ed ~ e da e e ~ e  
 ece , a ~ ~ a bee ~ d ~ ed (Fad e a., 2009;  
 P -G a de a s e a., 2007). T e Drosophila SNARE YKT6  
 a d S a 1A a e bee ~ e ed ~ e a e s e  
 e da ed e c e ~ f W e s (G e e a., 2012; K e e a.,  
 2012). H e e , ~ e s d ffce ~ e a a e beca e  
 e e SNARE s s c b e f ~ a a e ~ e  
 ece a ad e d c a a a (Ja a d Sc e e., 2006). T e  
 s ~ a fa SNARE s e ~ be e c f a  
 s ~ ed s e e e a e .

## The role of exosomes in developmental signalling

G e e a ed ca e, a d e e e a fe f  
b ec e ( ee B+ 1), e e a e bee e a ed a

e a ed a f a d de e e , a c a  
ec e f WNT ad HH a . T e WNT ad HH  
a a a e ae a ad a e d  
se b c de e s e (Pe , 1994; Pe e a., 2012;  
a A e e a d N e, 2009), a e a e ce - be  
e e a e c a a s e f e ad s e e (Cee e a.,  
2014). U e s e ace s a a s e , HH ad  
WNT a e d fed b e add f a d d d e  
b e i s e . T a e e s e b s e e because d  
e i s e affc a b s e add ff f e s e  
s a e e e e ace a ace. T e e e e f  
- a e a s b WNT ad HH a bee e be  
debae (A a d e e a., 2014; Fa e a., 2016; Se a b a d  
Ma ce e, 2014). Ne e e e , b e e a bee ac  
e e e a ce da ee (Ne , 2010; Pe e a., 2012;  
S a d C e , 1997; Zecca e a., 1996). H d d fed,  
a d e e ce b e , e ca ac e e - a e ac  
a a a ce a d de e a b . O se  
b s a WNT ad HH a eed d ff e de  
ac a a s a e. I deed, a bee e ed a s e e  
c d e a e e ed a e a ed a f d a ca ed  
c e e , a c e ed d a s e (B c ff e a., 2013;  
H e a., 2005; Ra e -Webe a d K be , 1999;  
Sa a e a d Sc , 2016). H e e , e e a e  
ec fc ea f e e c e e f a , s ec d a  
d ec e f s de. O e a e a e c e e s a  
e a c e c a e e ed d a s e  
c c a , a c a e e f WNT ad HH. S ec fc a ,  
e d add c d d e e a c e e d  
a e a a d d e d c e (Pa a a e a., 2005).  
A e de s a a e d add c f WNT HH c d b  
e ded b a e ace a d b d c a e e a SWIM  
(Sec ed W e I e ac M ec e), a e be f e  
ca fa (M a e a., 2012). Ye a e b ,  
e ed f HH , a e d add c c d be e ded  
ce e (G e e a., 2006; Ze e a., 2001), a de s a



~ a e , ac , ~ ed b , a d ac fW ss (Bec e  
e a ., 2013). T s ed s e a s f 7.4( ed)

Complex targeted	RNAi or DN used*	References	Effect	Caveats/other effects
Small GTPase	RAB11	Koles et al., 2012  Beckett et al., 2013  Gross et al., 2012 Gradilla et al., 2014	Reduced release of WLS-containing vesicles from S2 cells; reduced postsynaptic WLS at neuromuscular junction  Reduced exosome release by S2 cells; no effect on Wingless gradient in imaginal discs  Lethal Reduced HH secretion and/or target gene expression imaginal disc	RAB11 regulates endocytic recycling; regulates membrane delivery during cytokinesis; participates in epithelial cell polarisation; regulates transcytosis of certain cargo; may be redundant with other Rabs
	RAB35	Beckett et al., 2013	No effect on exosome release from S2 cells	RAB35 regulates endocytic recycling; regulates endosomal trafficking of synaptic vesicles; may be redundant with other Rabs
	RAB27	Koles et al., 2012  Gross et al., 2012 Parchure et al., 2015 Koles et al., 2012  Parchure et al., 2015	Reduced release of WLS-containing vesicles from S2 cells  No effect on wing patterning Reduced HH secretion in S2 cells Reduced release of WLS-containing vesicles from S2 cells Reduced HH secretion in S2 cells	RAB27 is specific to exosome secretion; may be redundant with other Rabs
	RAB10, RAB14, RAB6, RAB8			

d<sub>s</sub> c c s a d ac i e s . U f - ae , s

$\hat{s}_{2014}$ ). . . e . a e HH $\hat{s}$  ec e . . a d $\hat{s}$  . . a . . (G ad a e a.,

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