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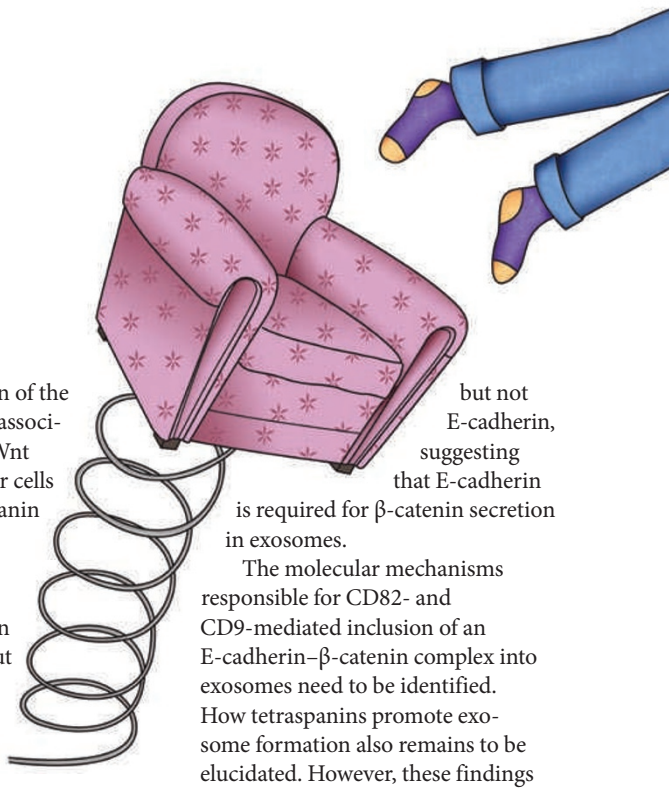

TUMOUR SUPPRESSION

Ejector seat

Exosomes are small vesicles that are secreted by various cells under certain conditions. They have recently gained prominence in cancer research owing to their capacity to carry mRNAs, microRNAs, and pro-oncogenic and pro-angiogenic proteins and deliver them to surrounding cells. Tetraspanin transmembrane proteins have been implicated in the formation and secretion of exosomes, as well as in the suppression of tumour development. A paper published in the *Journal of Cell Biology* now implicates both tetraspanins and exosomes in the inhibition of the Wnt–β-catenin pathway.

β-catenin is a crucial downstream regulator of the canonical Wnt pathway. Its levels in the nucleus are carefully controlled through phosphorylation, ubiquitylation and proteasomal degradation. However, β-catenin also resides at the cell membrane where it binds with cadherins to form adherens junctions that are involved in cell adhesion. Arthit Chairoungdua and colleagues noted from the literature that increased expression of the tetraspanin CD9 is associated with reduced Wnt signalling in tumour cells and that the tetraspanin CD82 is a known tumour suppressor. They showed that increased expression of CD9 or CD82, but not the tetraspanin CD63, reduced the Wnt-mediated activation of a β-catenin–luciferase reporter gene. Both CD9 and CD82 expression reduced the protein levels of β-catenin in cells, but this did not occur through the proteasomal or lysosomal degradation of β-catenin. Instead, expression of CD9 or CD82 in HEK 293T cells promoted the formation and secretion of exosomes that contained β-catenin. Further experiments showed that E-cadherin, β-catenin and CD82 could be co-immunoprecipitated from cells, and that β-catenin secretion in exosomes was reduced in cells expressing CD82 but not E-cadherin, suggesting that E-cadherin is required for β-catenin secretion in exosomes.

The molecular mechanisms responsible for CD82- and CD9-mediated inclusion of an E-cadherin–β-catenin complex into exosomes need to be identified. How tetraspanins promote exosome formation also remains to be elucidated. However, these findings clearly indicate that exosomes are an alternative pathway for regulating levels of β-catenin and canonical Wnt signalling and provide a biological explanation for the association of increased CD9 or CD82 expression with the reduced expression of Wnt target genes, and the correlation of reduced CD9 or CD82 expression with tumour progression.

Nicola McCarthy

> “exosomes are an alternative pathway for regulating levels of β-catenin and canonical Wnt signalling”

ORIGINAL RESEARCH PAPER Chairoungdua, A. *et al.* Exosome release of β-catenin: a novel mechanism that antagonizes Wnt signaling. *J. Cell Biol.* **190**, 1079–1091 (2010)