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The effect of exosomes in transferring TET signaling alterations

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Abstract: Ten eleven translocation (TET) enzymes are composed of three representatives: TET1/2/3 which are involved in the hydroxymethylation of methylated cytosines. Because of the wide array of processes that are governed by these epigenetic marks, there have been a wide range of clinical effects associated with TET alterations. Even though many research groups have focused on analyzing the effect of TET alterations within certain cells, few have taken into consideration the effect of TET in the context of intercellular communication. One important entity through which intercellular communication occurs is represented by exosomes. Thus, in the current viewpoint we discussed the direct transfer of TET by exosomes, its alterations in the cell targeted by exosomes and the effect of TET alterations on exosome secretion.

Introduction

Ten eleven translocation (TET) enzymes are composed of three representatives: TET1/2/3 which are involved in the hydroxymethylation of methylated cytosines. This not only initiates the process of demethylation, but also determines the generation of another epigenetic mark, 5-hydroxymethylcytosine (Kohli and Zhang, 2013; Wu and Zhang, 2017). Because of the wide array of processes that are governed by these epigenetic marks, there have been a wide range of clinical effects associated with TET alterations. The most common fields in which these alterations have an impact are represented by the fields of oncology (Aslanyan *et al*., 2014) and immunity, including autoimmunity and atherosclerosis (Tanaka *et al*., 2020; Oh *et al*., 2020; Pasca *et al*., 2021). Even though many research groups have focused on analyzing the effect of TET alterations within certain cells, few have taken into consideration the effect of TET in the context of intercellular communication (Kohli and Zhang, 2013; Wu and Zhang, 2017). One important entity through which intercellular communication occurs is represented by exosomes. These are nanoscale vesicles that transfer a variety of molecular species between different cell types or between different cells of the same type (Jurj *et al*., 2020). Because of this variety, it is with no doubt possible for them to also transfer TET enzymes or factors implicated in the alteration of TET in the target cell. Added to this, because of the multitude of effects that TET enzymes have, it is also possible for it to influence exosome loading and secretion.

Thus, we will further discuss the direct transfer of TET by exosomes, its alterations in target cells and the effect of TET alterations on exosome secretion (Fig. 1).

TET direct transfer

One manner through which exosomes can alter the target cell is through the direct transfer of proteins and increase in their level within the target cell. In this context, it has been shown that CD137 activation reduces the loading of TET2 within exosomes secreted by endothelial cells, thus reducing the TET2 that would normally be transferred to smooth muscle cells. Normally, the physiological transfer of TET2 from endothelial cells protects smooth muscle cells from phenotype switch, inducing an anti atherosclerotic effect. The reduction of TET2 transfer is associated with an increased phenotype switch in smooth muscle cells and atherosclerosis promotion (Li *et al*., 2020).

TET alteration within the target cell

Current studies have shown that TET activity in the target cell can be altered either through the influence of microRNAs or through certain metabolites shuttled via exosomes. Nonetheless, because of the small number of studies currently present in the literature, there might also be other manners through which TET enzymes within the target cell might be affected by exosomes.

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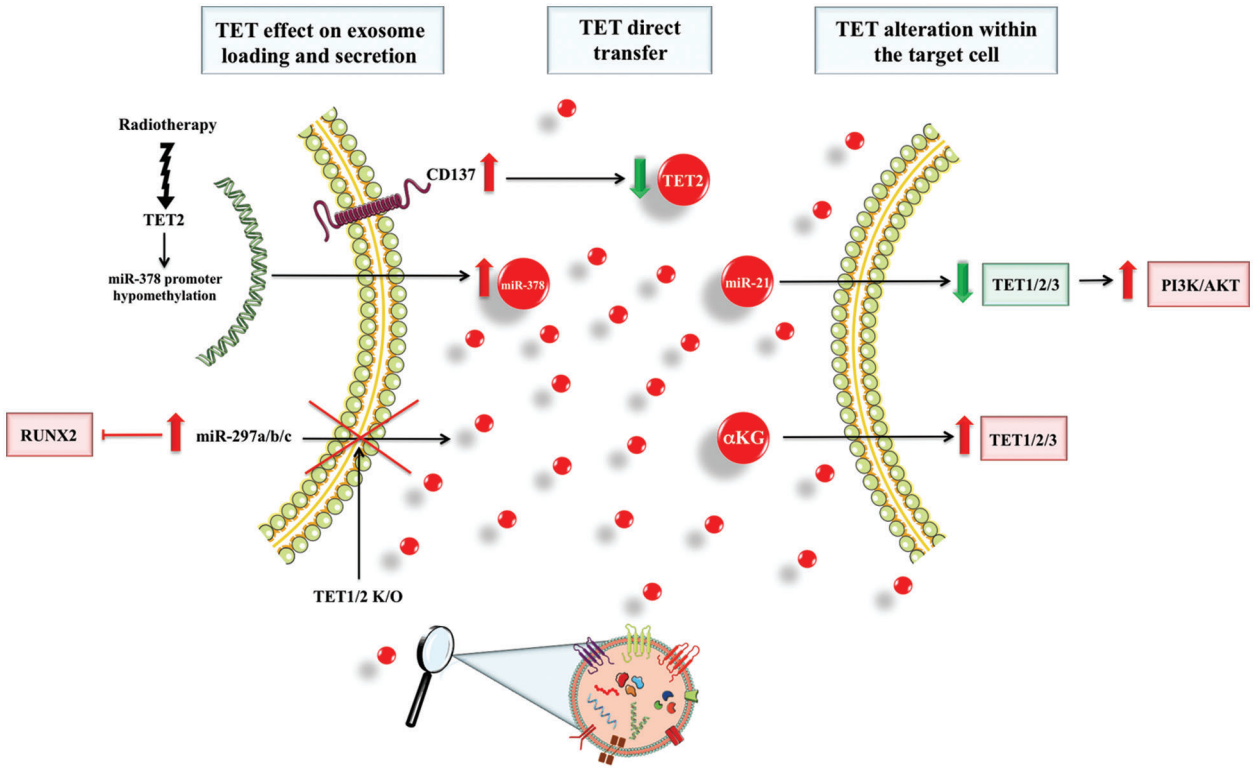

FIGURE 1. Representation of exosome-mediated pathways through which TET1/2/3 are altered in the target cell. Added to this, we also represented the effects that TET1/2 have on exosome loading and secretion within the secreting cell. K/O = knock out.

In the case of hepatocellular carcinoma, exosomes secreted from the malignant clone were shown to have a higher miR-21 content, which can alter the level of TET1/2/3 in the target cell. This, indirectly activates the PI3K/AKT pathway *via* the TET-mediated alteration in *PTENp1* methylation pattern (Cao *et al.*, 2019).

Added to this, certain metabolites that influence the activity of TET in the target cell can be transferred *via* exosomes. One important example in this direction is represented by the transfer of α-keto-glutarate to macrophages, which leads to the skewing of these cells towards an M2 (anti-inflammatory) phenotype, in a TET-mediated manner (Liu *et al.*, 2018). This is important as TET enzymes and, especially TET2, are known to have importance in affecting macrophage polarization and, thus, the inflammatory effects of these cells (Liu *et al.*, 2021).

TET alteration within the secreting cell

Alteration of TET enzymes activity can also affect both exosome loading and secretion. TET1/2 knock-out experiments in bone marrow mesenchymal stem cells showed that exosome secretion is reduced, which further leads to the intracellular accumulation of miR-297a/b/c. This is important as these reduce the activity of RUNX2, thus inhibiting the role of bone marrow mesenchymal stem cells in bone formation, and further explaining the osteopenic phenotype a TET1/2 knock-out mice model presents (Yang *et al.*, 2018). Added to this, irradiation of tumors was shown to decrease the methylation of miR-378 promoter in a TET2-mediated manner, leading to its overexpression and increased loading into exosomes. In this context, the transfer of miR-378 to NK-cells leads to the decrease of granzyme-B, thus reducing the immune activity of these cells and offering a biological cue to the acquisition of resistance to radiotherapy (Briand *et al.*, 2020).

Perspectives

In the future it is possible that more studies showing the interdependence between exosomes and TET signaling will be made. Considering the wide range of processes in which TET signaling is a key component of (Tanaka *et al.*, 2020; Oh *et al.*, 2020; Pasca *et al.*, 2021), it is possible that the current studies only scratched the surface of the interplay between TET signaling and exosomes. Thus, it is possible not only that further studies will deepen the understanding of how TET or its alterations can be transferred *via* exosomes, but also, given its role in immunity, it is possible that these pathways could be targeted in the future in the fields on oncology, autoimmunity and atherosclerosis.

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