cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Mutant KRAS Exosomes Influence the Metabolic State of the Colon Microenvironment

KRAS is mutated in approximately 30% to 40% of colorectal cancers (CRC) and *KRAS* mutations lead to an adaptive metabolic shift in cancer cells with increased aerobic glycolysis (Warburg effect) in part owing to higher uptake of glucose. In mutant KRAS CRC cells, overexpression of the glucose transporter (GLUT-1) (*SLC2A1*) is observed and contributes to increased glucose uptake, leading to acquisition of this metabolic change. However, the ability of KRAS to reach beyond the cancer cell and alter the metabolic state within the tumor microenvironment is not entirely clear.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Zhang et al[1] tested the hypothesis that KRAS can alter the metabolic state of the tumor microenvironment in a cell-nonautonomous fashion through secretion of exosomes. Exosomes are small (50–150 nm) membrane-bound extracellular vesicles that are released by almost all types of cells and carry specific protein and RNA cargos that are present in the releasing cell. These exosomes can modulate a variety of physiological and pathologic functions in adjacent or remote cells by transferring its contents to recipient cells, allowing them to be mediators of cell-to-cell communication. Prior work from this group has shown that mutant KRAS influences the cargo present in CRC exosomes, including proteins and enzymes involved in metabolism and glycolysis, and these exosomes can transfer their contents and enhance the growth of wild-type KRAS cells.[2]

By using exosomes purified from DLD-1 colon cancer cells (1 wild-type and 1 mutant *KRAS* allele) and isogenic cell variants that express only the wild-type *KRAS* allele or only the mutant *KRAS* allele, Zhang et al[1] showed that exosomes derived from mutant KRAS-expressing cells caused increased cellular glucose uptake in recipient cells. This impacted the balance between glycolysis and oxidative phosphorylation, and promoted enhanced growth of recipient cells. These findings were extended in vivo using the $Apc^{Min/+}$ mouse model of intestinal tumorigenesis. Treatment of these mice with mutant KRAS exosomes led to increased aerobic glycolysis in recipient tumor cells assessed by a change in the tumor redox ratio and positron emission tomography imaging. These metabolic changes were attributed to the increased presence of functional GLUT-1 in the mutant KRAS exosomes, whereas other glucose transporters (GLUT-2, GLUT-3, and GLUT-4) were not detected in these exosomes. Further demonstration of the role of exosomal GLUT-1 was shown using exosomes secreted from GLUT-1 knockout cells, in which these exosomes show decreased glucose uptake and significantly reduced lactate and glutamate secretion from recipient cells.

Several studies have shown roles for exosomes contributing to the pathophysiology of diseases including cancer, metabolic disorders, cardiovascular disease, and immune diseases.[3–5] The findings presented here describe a novel mechanism linking a common oncogenic mutation in CRC to a Warburg-like effect on the tumor microenvironment through exosomes. Further research in this area will determine the contribution of other proneoplastic proteins and RNAs present in CRC cell-derived exosomes on tumor progression. The translational implications of identifying GLUT-1 in mutant KRAS exosomes are significant. Because exosomes are readily detected in circulation, the possibility of detecting active GLUT-1 in plasma exosomes indicates its potential as a biomarker of disease progression. Furthermore, evaluation of these findings using human exosomes derived from CRC patients in whom their *KRAS* mutational status is known will further define the role of exosomal GLUT-1 in defining the metabolic state of CRC tumors.

RANJAN PREET, PhD
DAN A. DIXON, PhD
Department of Molecular Biosciences
University of Kansas
Lawrence, Kansas
University of Kansas Cancer Center
Kansas City, Kansas

References

1. Zhang Q, Jeppesen DK, Higginbotham JN, Demory Beckler M, Poulin EJ, Walsh AJ, Skala MC, McKinley ET, Manning HC, Hight MR, Schulte ML, Watt KR, Ayers GD, Wolf MM, Andrejeva G, Rathmell JC, Franklin JL, Coffey RJ. Mutant KRAS exosomes alter the metabolic state of recipient colonic epithelial cells. Cell Mol Gastroenterol Hepatol 2018;5:627–629.
2. Demory Beckler M, Higginbotham JN, Franklin JL, Ham AJ, Halvey PJ, Imasuen IE, Whitwell C, Li M, Liebler DC, Coffey RJ. Proteomic analysis of exosomes from mutant KRAS colon cancer cells identifies intercellular transfer of mutant KRAS. Mol Cell Proteomics 2013;12:343–355.
3. De Toro J, Herschlik L, Waldner C, Mongini C. Emerging roles of exosomes in normal and pathological conditions: new insights for diagnosis and therapeutic applications. Front Immunol 2015;6:203.
4. Kalluri R. The biology and function of exosomes in cancer. J Clin Invest 2016;126:1208–1215.

5. Lawson C, Vicencio JM, Yellon DM, Davidson SM. Microvesicles and exosomes: new players in metabolic and cardiovascular disease. J Endocrinol 2016; 228:57–71.

Correspondence
Address correspondence to: Dan A. Dixon, PhD, Department of Molecular Biosciences, The University of Kansas, 1200 Sunnyside Avenue, 2034 Haworth Hall, Lawrence, Kansas 66045. e-mail: dan_dixon@ku.edu.

Conflicts of interest
The authors disclose no conflicts.

Funding
Supported by the National Institutes of Health/National Cancer Institute Cancer Center Support grant P30 CA168524 (D.D.) and the Prevent Cancer Foundation (R.P.).

Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2018.01.021