Nearly three decades after the identification of the first drug transporter P-glycoprotein (P-gp) [1], cancer multidrug resistance (MDR) continues to challenge researchers trying to untangle its molecular basis, and to thwart oncologists attempting to cure cancer patients [2]. One of the important insights gained over the years is that in addition to overexpression of MDR transporters, MDR often involves additional mechanisms, prominent among which is the regulation of cellular apoptosis and survival pathways. In a previous issue, Kwong and co-workers reported that expression of P-gp, product of the MDR1 gene, and of caveolin-1, a putative pro-survival protein, in leukemic cells are highly correlated [3]. This report raises the intriguing possibility that the emergence of different MDR mechanisms may be coordinately regulated.

Caveolin-1 is an essential protein constituent of plasma membrane caveolae, which are non-clathrin-coated, flask-shaped invaginations of the plasma membrane [4]. Caveolin-1 is a principal component of the caveolar coat and a regulator of caveolae-dependent signaling and endocytosis. In addition, caveolin-1 exhibits an unusual ability to interact with and modulate multiple signaling pathways. The interaction of caveolin-1 with other proteins occurs via a 'scaffolding' domain that binds short sequence motifs, such as xxxxxxxx (where x is an aromatic amino acid) [5]. The ability of caveolin-1 to modulate signal transduction indicated that its expression is likely to profoundly affect cell function and cell fate. Indeed, the expression of caveolin-1 with other proteins occurs via a 'scaffolding' domain that binds short sequence motifs, such as xxxxxxxx (where x is an aromatic amino acid) [5]. The ability of caveolin-1 to modulate signal transduction indicated that its expression is likely to profoundly affect cell function and cell fate. Indeed, the expression of caveolin-1 is tightly controlled: it is upregulated in terminally differentiated epithelial cells and, conversely, is downregulated upon oncogenic transformation. These and other results led to the suggestion that caveolin-1 is a tumor-suppressor protein [6]. However, this idea was inconsistent with the fact that caveolin-1 is highly expressed in some cancer cells, including mouse metastatic prostate cancer [7] and human multidrug resistant colon cancer cells [8]. In fact, a large body of data that has since accumulated reveals that there are major, divergent changes in caveolin-1 expression in human cancer cell lines and tumor specimens, that depend on the type of cancer and on the tumor cell grade and progression stage [9]. In some forms of cancer caveolin-1 expression is downregulated, but in many other cancers caveolin-1 levels are high. The expression of caveolin-1 is positively correlated with the tumor's cell grade and its progression stage and, in some cases, the expression of caveolin-1 was shown to be an independent predictor of poor disease prognosis.

The relationship of caveolin-1 with MDR is multifaceted. As mentioned above, caveolin-1 is upregulated in numerous human MDR cancer cells [8,10–12]. P-gp, the prototypical MDR transporter, is often overexpressed in multidrug resistant cells, usually accompanied by other changes that affect drug metabolism and/or drug response [2]. P-gp is partially co-localized with caveolin-1 in lipid rafts as shown by sucrose gradient fractionation [8,13,14]. P-gp can also be co-immunoprecipitated with caveolin-1 in drug-resistant cancer cells as well as in bovine brain capillary endothelial cells co-cultured with astrocytes, representing a model of blood brain barrier [13,15]. Together, the data suggest a physical interaction between these two proteins that may be mediated by a caveolin-1-binding motif in the N-terminal portion of P-gp (37-FSMFRYSNW-45). On the basis of these data, Kwong and co-workers hypothesized that caveolin-1 and MDR1 genes may be functionally related and therefore could be coordinately regulated [3]. Their retrospective study documents caveolin-1 and MDR1 gene expression in normal and acute myeloid leukemia (AML) bone marrow at diagnosis, at relapse and during regeneration, by means of quantitative real time polymerase chain reaction. A highly significant positive correlation was found between caveolin-1 and MDR1 mRNA levels in all tissue samples, indirectly supporting the idea that the two proteins are functionally related. In addition, the authors proposed that the observed correlation may explain the poor prognosis associated with up regulation of caveolin-1 in tumor samples [3]. The data of Kwong and co-workers highlight a more general question: Why is a putative tumor-suppressor protein like caveolin-1 expressed in so many cancer cells? Overexpression and gene-specific suppression studies leave little doubt that caveolin-1 has anti-proliferative actions in normal...
cells. Furthermore, genetic knockout of caveolin-1 results in tissue-specific hyperplasia and increased sensitivity to carcinogenic stimuli (although there is no evidence of spontaneous tumorigenesis) [16,17]. However, this begs the question of caveolin-1 function(s) in advanced stage/high grade, metastatic and multidrug resistant cancer cells, in which its expression is maintained or is up regulated. One possibility is that in such cells caveolin-1 promotes cancer cell survival and this hypothesis is consistent with some recent work [18–20]. However, the mechanisms whereby caveolin-1 affects cancer cell survival are still quite poorly understood.

Be that as it may, the ability of caveolin-1 to effect both growth-inhibitory and survival-promoting actions may explain its divergent expression in human cancers. It may be hypothesized that, at early stages of cancer progression, expression of caveolin-1 is down regulated to suppress its growth inhibitory actions. Conversely, at later stages of the disease when the metastatic and drug resistant phenotypes are prevalent, expression of caveolin-1 is up regulated, reflecting its pro-survival actions. Clearly, much remains to be done to achieve a better understanding of the impact of caveolin-1 on human cancer cell phenotype, the mechanisms involved and its possible link to progression of the disease.

References


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