Defining D-Arabinose Metabolism in Leishmania major and Crithidia fasciculata

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The metabolism of D-Arabinose (D-Ara) in eukaryotes is poorly understood. Arabinose (Ara) is one of the "rare" aldopentose sugars distributed in Nature principally as a component of cell wall structures in plants and bacteria. Arabinose exists naturally in both pyranose and furanose conformations and D- and L- configurations. The most abundant form of arabinose is L-arabinose which is present in the arabinogalactans of plants. D-arabinofuranose (D-Araf) is found mainly in the arabinomannans, arabinogalactans, lipoarabinomannans and mycolylarabinogalactan-peptidogalactans of mycobacterial cell walls. However, D-arabinopyranose (D-Ara*p*) is found, uniquely, in cell surface glycoconjugate structures of certain trypanosomatid parasites: *Leishmania major* lipophosphoglycan (LPG) *Crithidia fasciculata* lipoarabinogalactan (LAG) and *Endotrypanum schaudinni* glycoinositol phospholipids (GIPLs). The activated donor molecule of D-Ara*p* has been identified in *L. major* as GDP-α-D-Ara*p* . However, the source of the GDP-Ara*p* is not fully understood. So far it is known that both *L. major* and *C. fasciculata* have a salvage pathway allowing the parasites to internalize D-Ara from the extracellular medium or the lumen of the insect guts and convert it to GDP-α-D-Ara*p* via an arabinose-1-kinase/pyrophosphorylase. A *de novo* pathway, whereby D-Glucose (D-Glc) is converted to D-Ara*p* via loss of the Glc C-1 carbon atom has been postulated but many details are missing. Many gram-negative bacteria have an Arabinose-5-phosphate isomerase (APIs) enzyme. In bacteria API enzymes catalyse the interconversion of D-ribulose-5-phosphate (Ru5P), the product of the oxidative phase of the pentose phosphate pathway, and D-arabinose-5-phosphate (A5P). A5P is a precursor to 3-deoxy-D-manno-octulosonic acid (KDO) that is a component of the bacterial capsular polysaccharides and lipopolysaccharides (LPS). KDO is an essential component of the cell envelope of gram-

negative bacteria. We speculate that trypanosomatids may also convert D-Glc to D-Ara*p* via Ru5P and its isomerisation to A5P followed by dephosphorylation to D-Ara*p*. Apart from cell surface incorporation by *L. major* and *C. fasciculata,* it is possible that D-Ara*p* may be used by all the kinetoplastids to make D-erythroascorbate, a C5 ascorbate analogue similar in structure and physicochemical properties to ascorbate (Vitamin C). In animals and plants, L-ascorbate is involved in cellular defence against oxidative stress. The D-erythroascorbate analogue of ascorbate appears in yeast and other fungi, but this antioxidant role is not well understood. The biosynthesis of D-erythroascorbic acid starts from D-Ara*p*, which is oxidized by $NAD(P)^+$ specific dehydrogenases to D-arabino-1,4-lactone, which is further oxidized to D-erythroascorbic acid by D-arabino-1,4-lactone oxidase. The source of the original D-Ara*p* in yeast and fungi is, however, unknown. In summary, central to the problem of eukaryotic D-Ara*p* metabolism is the bioconversion from D-Glc to D-Ara*p*.