Arabidopsis Homologues to the LRAT a Possible Substrate for New Plant-Based Anti-Cancer Drug Development

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ABSTRACT
This article describes how an NC gene family has been identified in the genome of the Arabidopsis thaliana (Arabidopsis) by homology to the human Lecithin Retinal Acyl Transferase (LRAT) and the picornavirus 2A protein. The Arabidopsis proteins contain two motifs identified in a vast variety of organisms, an H-Box and an NC. Among related proteins are the C. elegans EGL-26, a regulator protein of cell morphogenesis in the vulva region, and human proteins that might be related to cell proliferation or development. Human homologues include HRAS-like tumour suppressors, the Tazarotene-induced gene 3 (TIG3), and a deSumoylating Isopeptidase (PNAS-4) that induces apoptosis in lung cancer cells. Preservation of the two motifs observed in the Arabidopsis proteins in homology to tumour suppressors, and the conservation of residues important for the function of the LRAT amongst the Arabidopsis homologues can be indicative not only of the importance of these domains for the function of the plant proteins but can also reveal a new candidate group for the design of plant-based tumour-targeting drug development.

KEYWORDS
Arabidopsis Thaliana, EGL-26, HRAS-Like Tumour Suppressor, Lecithin Retinal Acyl Transferase, NC Motif, PNAS-4, Tazarotene-Induced Gene 3

INTRODUCTION
The H-Box/NC proteins were subsequently suggested to belong to a larger group of proteins, termed the NIpC/P60 superfamily. The NIpC/P60 superfamily was divided into four families according to their amino acid sequence similarities and motifs. The P60-like family, the ACMB/LytN-like divergent family, the lecithin retinal acyl transferase-like (LRAT-like) family and the YaeF/poxvirus G6R type family (Anantharaman & Aravind, 2003). The NIpC/P60 proteins are predicted to have a thiol-protease fold. This is made up of a β-strand region containing a conserved histidine, an orientating polar residue (part of a conserved GD [glucine-aspartic acid] motif) and a α-helix domain containing a conserved cysteine. Some members of the NIpC/P60 superfamily proteins (including the LRAT-like ones) exhibit circular permutation. In the thiol-protease fold area, variable sized inserts are often seen
in the region between the strand containing the histidine and the strand bearing the orienting polar residue (Anantharaman & Aravind, 2003).

The LRAT-like family is made up of eukaryotic and animal virus sequences. Studies on the picornavirus non-structural proteins (2A, 2B, 2C, 3A, 3B, 3C and 3D) showed that the 2A protein of some genera is related to two identified cellular proteins, possibly involved in the control of cell proliferation (Hughes & Stanway, 2000). These cellular proteins, Hrev107; one of several proteins able to revert the transformed phenotype of cells containing HRAS (Akiyama et al., 1999) and TIG3, a Tazarotene-induced protein (Sturniolo et al., 2003) are closely related to one another but distantly related to the 2A protein (Hughes & Stanway, 2000). However, all three proteins contain two motifs, an H-Box and an NC region, also present in the viral 2A protein. Homology searching revealed the presence of the same motifs in the lecithin retinal acyl transferase (LRAT) (Hughes & Stanway, 2000), an enzyme closely related to the nematode C.elegans EGL-26 protein. The LRAT is involved in the processing and mobilization of vitamin A in tissues including retinal pigment epithelium, the liver and the intestine (Mondal, Ruiz, Bok, & Rando, 2000; Mondal, Ruiz, Hu, Bok, & Rando, 2001) and has shown to catalyse the palmitoylation (a process at which fatty acids covalently attached to the cysteine residues of membrane proteins) of the retinal pigment epithelial protein RPE65 (Estes, Kalameghan, & Hanna-Rose, 2007). It also catalyses the transfer of the acyl group in phosphatidylcholine, a phospholipid and major component of the lecithin, resulting in the formation of retinyl esters, an intracellular storage form of vitamin A (Uyama, Morishita, et al., 2009). Similarly to H-rev107 and TIG3, LRAT has been found to be down-regulated in carcinoma cell lines from different human tissues and it has been suggested that human carcinoma cell lines are retinoid-deficient relative to normal epithelial cells (Guo et al., 2002; Guo, Ruiz, Rando, Bok, & Gudas, 2000). In the nematode C.elegans the Egl-26 protein, also containing an H-Box and an NC motif, is believed to have a role as a developmental regulator as it mediates vulval cell morphogenesis (Hanna-Rose & Han, 2002). It has been suggested that may be acting as an acyltransferase (like LRAT) to facilitate the morphogenesis of the vulF cells (retinyl esters as a secreted differentiation signal) (Estes et al., 2007). In humans, H-rev107 is a tumour suppressor protein that negatively regulates the HRAS oncogene (a plasma membrane-associated GTPase) in carcinoma cell lines. The protein is absent or very low in tumours while the gene is ubiquitously expressed in normal tissues (Sers et al., 1997). Also, there is evidence of H-rev107 phospholipase activity like LRAT. Analysis of H-rev107 truncated proteins indicated a possible relevance of catalytic and anti-proliferating activity. The TIG3, also known as retinoic-acid receptor responder 3 (RARRES) or retinoid-inducible gene 1 (RIG1) again could be an inhibitor of cell proliferation, especially as its expression reduced in tumour cells (DiSerio et al., 1998; Sturniolo et al., 2003) and it exhibits tumour suppressing activities (Uyama, Jin, Tsuboi, Tonai, & Ueda, 2009).

It is a regulatory protein that is expressed in the epidermis and regulates the viability, differentiation and proliferation of keratinocytes. Over-expression of TIG3 reduced the cell proliferation/survival in association with a 10-fold increase in accumulation of structures resembling cornified envelopes (Sturniolo et al., 2003). In tumours and in skin cancer cell lines, its level is reduced signifying that loss of expression may be required for cancer cell survival (Scharadin, Jiang, Jans, Ronke, & Eckert, 2011). TIG3 regulates the expression of the type I transglutaminase (TG1) in the epidermis (Eckert et al., 2009), an important enzyme for the human epidermis as its activity is essential for the assembly of the cornified envelope, the maintenance of the skin barrier function. Abnormalities in the function of the TG1 results in the serious disease of lamellar ichthyosis in with the patient experience thickened scaled epidermis (Jans, Sturniolo, & Eckert, 2008). TIG3 has been identified as the suppressor of the RAS activation gene, like the H-rev107 and has been found to localise in the endoplasmic reticulum and the Golgi apparatus, with the TIG3 Golgi form to be related to the anti-RAS and the pro-apoptotic activity of the TIG3 (Tsai, Shyu, & Jiang, 2007). Induction of the TIG3 has also been suggested to be associated with the function of the tumour suppressor p53 protein in cell proliferation and the Wnt/β-catenin signalling pathway by acylation of Wnt proteins, resulting in the suppression of epithelial-mesenchymal transition and cancer stem cell properties (Hsu et al., 2015).
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