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Tumor-suppressing 15-Lipoxygenase-2: Time for prime time?

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Lipoxygenases (LOX) comprise a family of non-heme-iron-containing proteins that catalyze the dioxygenation of polyunsaturated fatty acids to form bioactive lipids. Metabolism of arachidonic acid by LOXs leads to the formation of regioisomeric cis/trans-conjugated hydroxyeicosatetraenoic acids (HETEs), leukotrienes, lipoxins, and hepoxilins. Dependent on the predominant position of the incorporation of hydroperoxy group, LOXs are classified as 3-, 5-, 8-, 12(S)-, 12(R)-, and 15-LOwXs, whose main products are 3(S)-, 5(S)-, 8(S)-, 12(S), 12(R)-, and 15(S)-HETE, respectively. There are two 15-LOX: 15-LOX1 (gene: *ALOX15*) and 15-LOX2 (gene: *ALOX15B*). 15-LOX1, whose murine ortholog is leukocyte-type 12-LOX, prefers linoleic acid as the substrate to form 13(S)-HODE, although it can convert arachidonic acid to 15(S)-HETE and, to a lesser extent, 12(S)-HETE. On the other hand, 15-LOX2 mainly uses arachidonic acid to form 15(S)-HETE.[1] The involvement of LOXs in carcinogenesis is complex, since both tumor-promoting and -suppressing activities are reported for the various members of LOX family.

A number of studies suggest 15-LOX2 as a functional tumor suppressor, particularly in the prostate. Its expression or activity is frequently suppressed during carcinogenesis of prostate, lung, esophageal, and sebaceous gland. Restoration of 15-LOX2 expression in prostate cancer cells inhibited DNA replication, caused G_0/G_1 arrest, reduced tumor growth and even tumor development.[2,3] Interestingly, when 15-LOX2 is expressed in mouse prostate, the transgenic mice presented indications of prostate hyperplasia,[4] suggesting the complex function of 15-LOX2 in disrupting tissue homeostasis in the mouse prostate.

Suraneni et al.[5] in this issue presented experimental evidence unequivocally establishing the tumor-suppressing activities of 15-LOX2. By crossing 15-LOX2 transgenic mice with a Hi-Myc mouse model for prostate cancer, they found that the presence of 15-LOX2 inhibited Myc-induced tumor development in the prostate of double transgenic mice. Given the frequent amplification of Myc in human prostate cancer, it is reasonable to extrapolate that the loss of 15-LOX2 can contribute to Myc-induced prostate carcinogenesis. However, whether Myc suppresses 15-LOX2 expression remains to be elucidated.

A common biological effect of 15-LOX2 is cell senescence. Suraneni et al. observed an increased cell senescence in the mouse prostate with expression of human 15-LOX2, possibly through induction of RB1CC1 expression.[4] In this issue, Suraneni extended this observation.[5] They found an upregulation of RB1CC1 in the prostates of double transgenic Myc;LOX mice when compared with the Hi-Myc prostates. Paradoxically, RB1CC1 is found upregulated, instead of being suppressed as 15-LOX2, in human prostate cancers, suggesting that the link between 15-LOX2 and RB1CC1 can be compounded by many other extraneous factors uniquely present in the human prostate.

An important question is how to harness the tumor-suppressive activities of 15-LOX2 as possible prevention and treatment of prostate cancer. Reactivation of 15-LOX2 expression in human prostate cancer cells, while conceptually plausible, requires detailed understanding how 15-LOX2 is suppressed during carcinogenesis and identification of druggable targets. Another approach is to utilize the arachidonate product of 15-LOX2, 15(S)-HETE, to suppress prostate cancer. A limitation for this approach is the uncertainty whether 15(S)-HETE can recapitulate the tumor-suppressive activities of 15-LOX2. 15(S)-HETE treatment has been shown to suppress prostate cancer cell growth and induce RB1CC1, as 15-LOX2 did.[3,5] However, the enzymatic activity of 15-LOX2 seems dispensable for its tumor-suppressing activities. PC-3 cells transfected with a splice variant of 15-LOX2, 15-LOX2sv-b, which did not have the capacity of synthesizing 15(S)-HETE, also had reduced tumor development.[3] This evidence suggests that 15(S)-HETE may not fully recapitulate the tumor-suppressing activities of 15-LOX2.

Further studies are needed to resolve the complex roles of lipoxygenases in cancers. From a gene evolution perspective, all *ALOX* genes come from one ancestral gene that has duplicated several times (**Fig. 1**). Comparisons of the orthologous genes between mouse and human *ALOX5* or *ALOX12R* demonstrate that those genes have more than 85% amino acid identities. On the other hand, comparisons of paraologous ALOX genes, such as *ALOX15* vs *ALOX15B* or *ALOX12* vs *ALOX15B*, reveal only 40% amino acids identities. However, the amino acid identity between human *ALOX15B* and mouse *ALOX8* is as high as 78%. In this sense, the murine *ALOX8* is the ortholog of human *ALOX15B*, although their metabolic products can be different. Studies show that 8-LOX possesses anti-proliferation and anti-tumorigenic activities, as does 15-LOX2.[6,7] Although 8-LOX expression is not detected in the prostate of 3- or 6-mo-old mice (human equivalent ages of 8 or 16 y), it is unknown whether 8-LOX is expressed in more senescent or diseased mouse prostate. Given the remarkably similar organization of murine *ALOX8* and human *ALOX15B* in their respective genome (**Fig. 1**), further studies are needed to determine whether deletion of *ALOX8* can lead to increased carcinogenesis, particularly in the prostate.

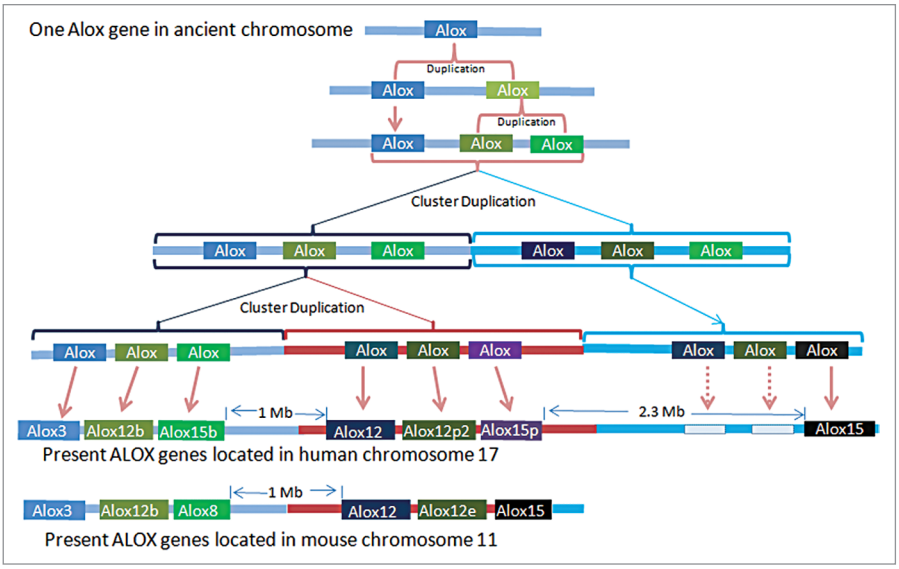

Figure 1. Evolution of *ALOX* genes. Based on the arrangements and sequence homology, it is deduced all *ALOX* genes are derived from one ancient *ALOX* gene through duplications and evolutions. Note the remarkable similarity in genomic localization of murine *ALOX8* and human *ALOX15B* and the lack of a 2.3 million base pair (Mb) segment between *ALOX12E* and *ALOX15* in mouse genome.

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