Curcumin Functions as a Positive Regulator of miRNA Processing & a Negative Regulator of Cancer Stem Cell Proliferation

L.Boominathan,

M.Sc.,(Med. Bio., JIPMER), M.Sc., (Life Sci.,(Cancer bio.) Wizemann Inst., Israel), Ph.D. (NUS, Singapore),

Past Post-doc. (NEITPI, Boston; MDACC, Houston)

49 Nattar main street,

Murungapakkam,
Modilarpet,

Puducherry- 605 004.

Email: lakshmanan.boominathan@gmail.com

Introduction

Identifying agents that inhibit the proliferation of stem cells is of great importance in regenerative medicine. In addition, identifying agents that increase the expression of miRNAs to inhibit cancer stem cell (CSC) proliferation is of great importance in cancer biology.

Curcumin has been shown to function as an anti-cancer agent. However, its mechanism of action remains elusive.

Hypothesis

Curcumin has been shown to function as an anti-cancer/inflammatory/diabetic agent (Figure 1). However, it is not known whether it inhibits cancer stem cell (CSCs) proliferation to inhibit caner proliferation. Here, I propose for the **first time that Curcumin: a) inhibits CSCs proliferation**; and b) **increases miRNA processing**. Thereby, it **increases** the expression of a number of **miRNAs to control the proliferation of CSCs**.

Results-1

The tumor suppressors that appear to be induced in response to curcumin treatment are **p53 and TA-p73**. A recent study suggests that curcumin increases the expression of miRNAs, such as **miR-22, miR-181a, b, c, miR-15/16a, miR-34, miR-103, and miR-21**(Figure 2).

Intriguingly, miR-34, 181-b, c, miR-103, miR-21, miR-15/16a, and miR-24 have been identified as transcriptional targets of the tumor suppressor p53. This data suggests a possibility that curcumin, by inducing the expression of **p53/p73**, it **could increase the expression of these microRNAs** (Figure 2).

A number of groups have shown that **c-Myc, Sox-2, Klf-4, Oct-4, Sox-2, Nanog, and Lin28** are required for **reprogramming** of differentiated cells into pluripotent stem cells and for cancer stem cell proliferation. Interestingly, **miR-21** has recently been shown to **represses stem cell factors such as Oct4, Nanog, sox2, and c-Myc**,

indicating that **curcumin by increasing the expression of miR-21, it could inhibit cancer stem cell proliferation**.

Results-2

In addition, curcumin induced **p53/TA-p73** may result in increased expression of its **target, miR-145**. Interestingly, it has recently been shown that **miR-145 suppresses** the expression of **c-myc, klf-4, Oct-4, and Sox-2** in human embryonic stem cells (hESCs) and thereby promotes the differentiation of hESC.

This data suggests that **p53/p73-dependent miR-145** expression will result in **down regulation of Oct-4, Klf-4, Sox-2, Nanog, and c-myc** and **inhibition of stem cell proliferation (Figure 3).**

Further, **curcumin induced miR-22** appears to **inhibit the expression of estrogen receptor α.** Remarkably, it has recently been shown that **estrogen receptor α inhibits the processing of several**

microRNAs, including the tumor suppressor miR-145(Figure 3). In addition, Curcumin- a) induced miR-15/16a appears to inhibit the expression of the negative regulator of INK4a/ARF, BMI (figure 4); and b) inhibited NFKB activity appears to inhibit the expression of lin-28 and thereby induce the tumor suppressor let-7 expression (figure 4).

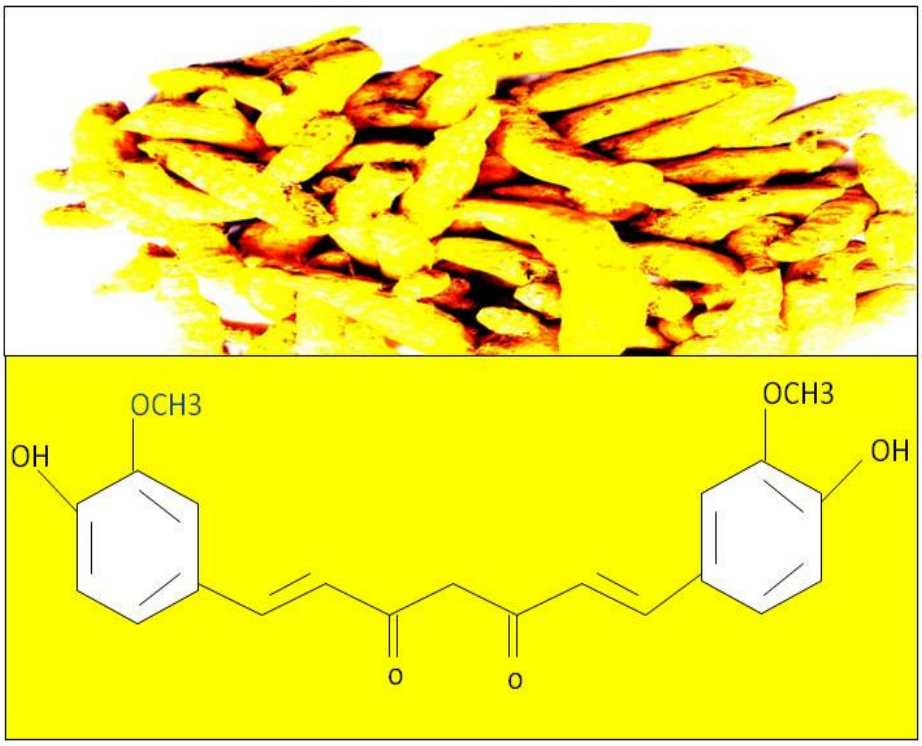

Figure 1 Structure of Diferuloylmethane (Curcumin)

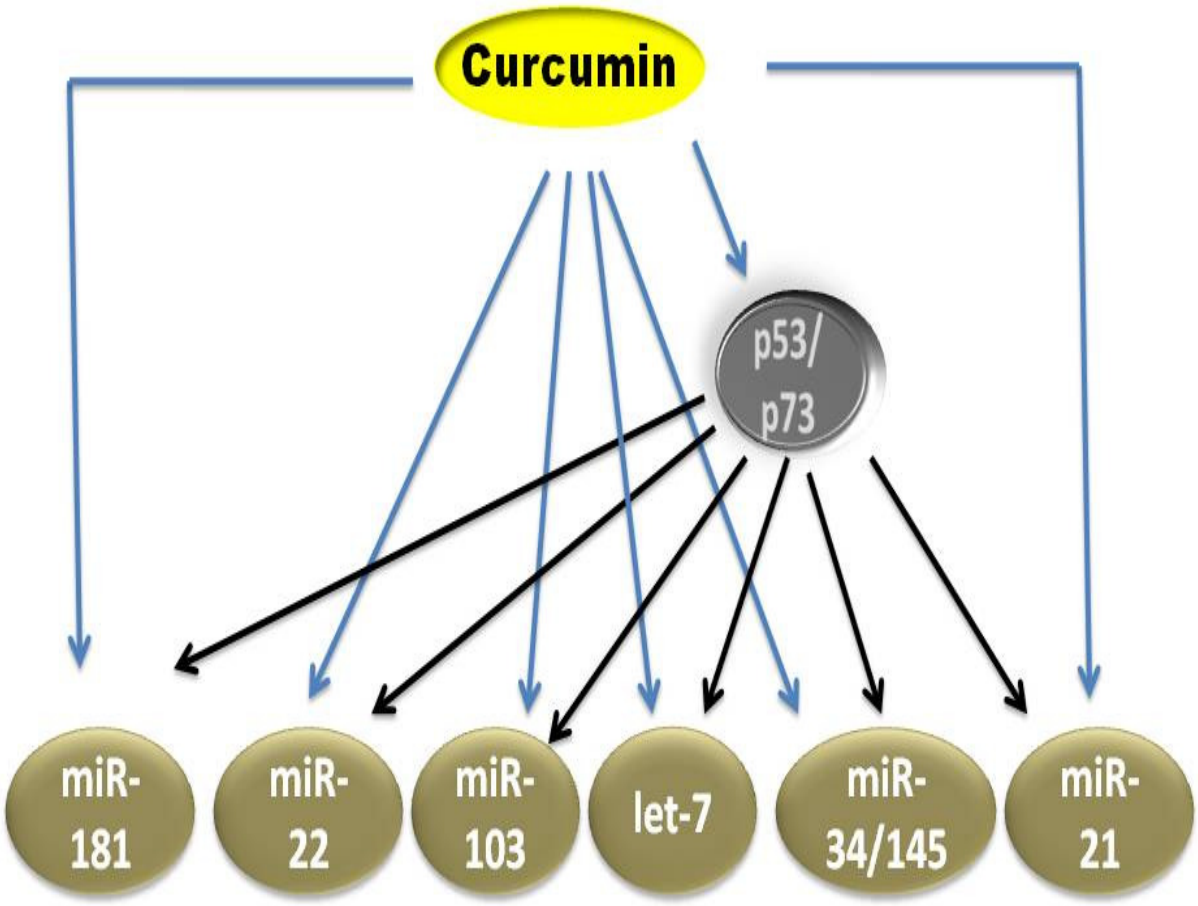

Figure 2 Molecular targets of Curcumin

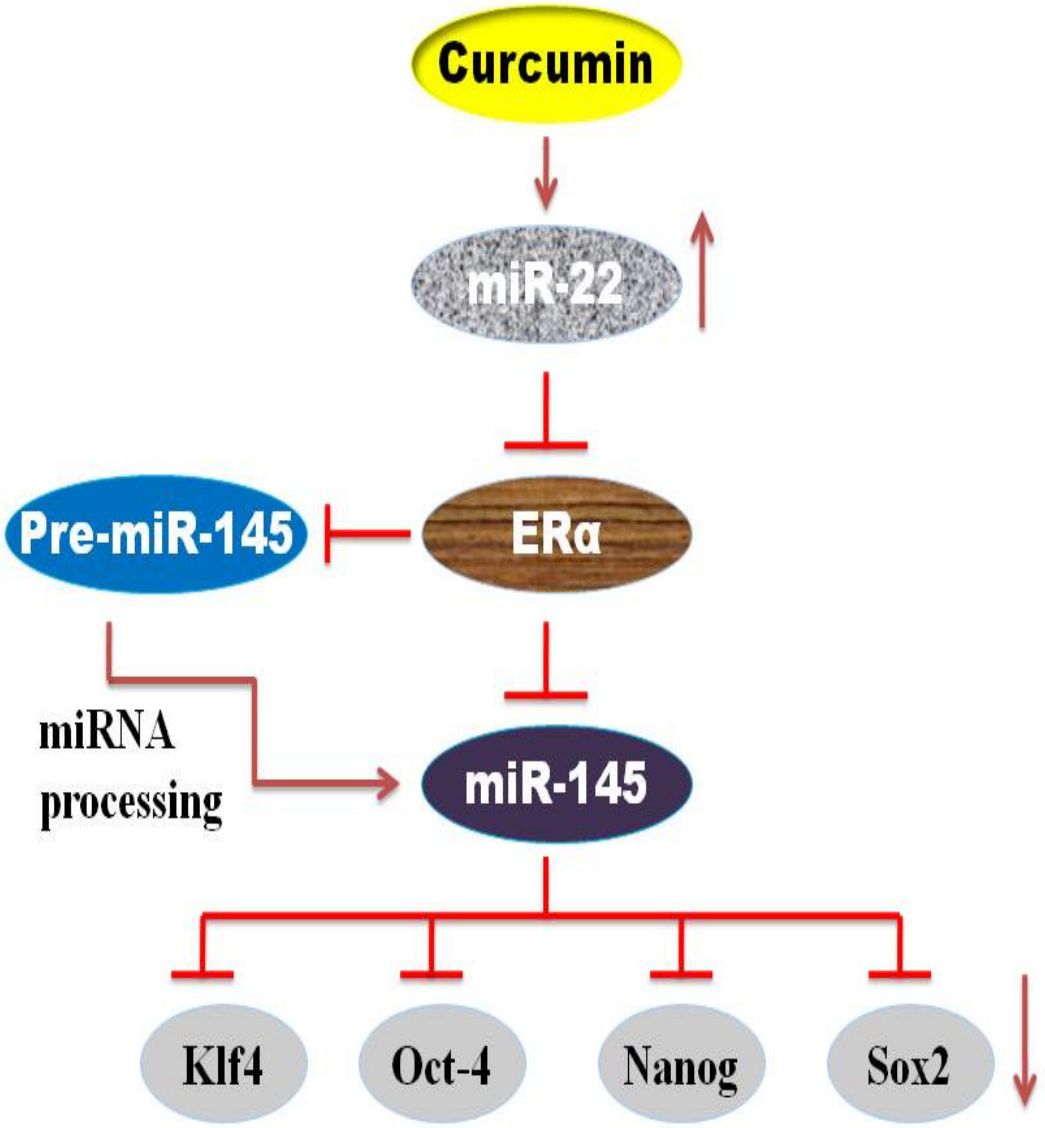

Figure 3 Curcumin functions as a positive regulator of miRNA processing and a negative regulator of Stem cell proliferation

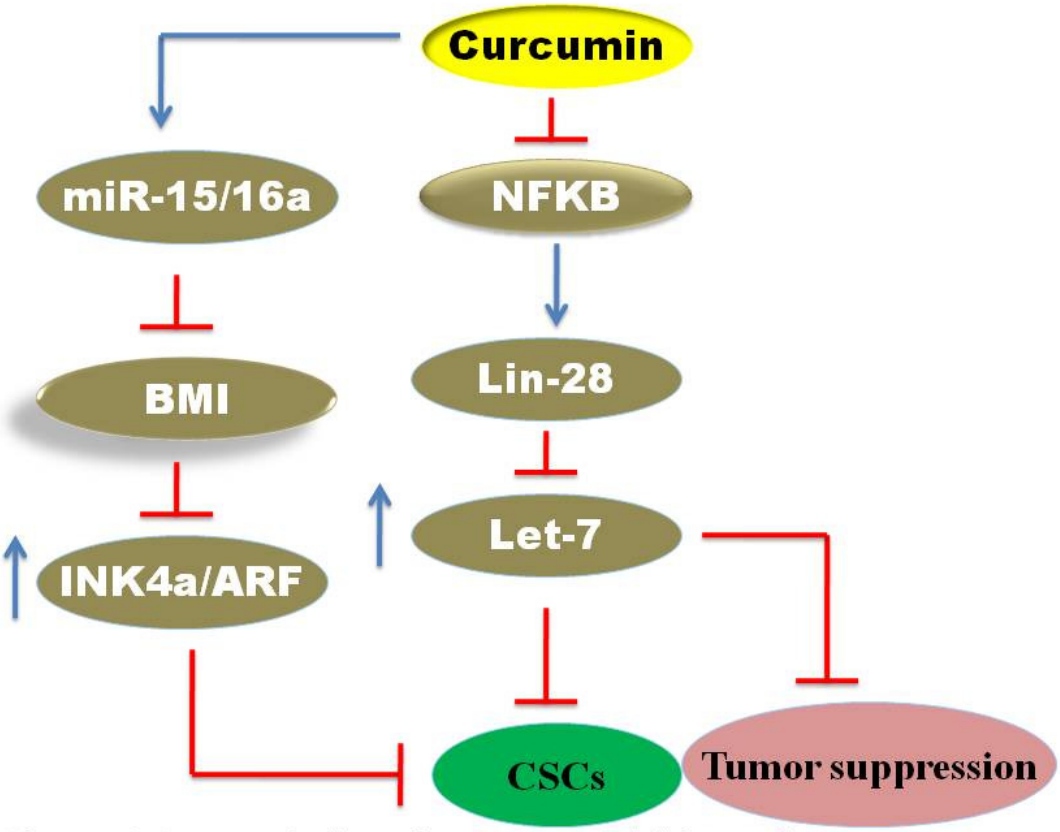

Figure 4 Curcumin functions as an inhibitor of cancer stem cell Proliferation and tumor growth.

Conclusion

This data suggests that curcumin, by inhibiting the expression of estrogen receptor α through its target miR-22, it could increase the processing of miR-145 and down regulate the expression of its target genes (Oct-4, Klf-4, Sox-2, Nanog, and c-myc). In addition, it may increase the processing of let-7 by inhibiting the NFKB-dependent lin-28 expression. Thereby, curcumin could function as a positive

regulator of miRNA processing and a negative regulator of cancer stem cell proliferation.