

Natural (tryptophan) metabolites – mediated activation of aryl hydrocarbon receptor inhibits cancer stem cell signaling: what does it mean to prevent cancer recurrence?

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Introduction

Environmental pollutants and toxicants have long been believed as the drivers for cancer initiation and progression. The aryl hydrocarbon receptor (AhR) is one of the master regulators of the metabolism of the environmental toxicants in the cells. The AhR ligands which act as agonist have been identified in a broad range such as air pollutants of Dioxin (also called TCDD) in mist, Polycyclic aromatic hydrocarbon found in soil and particulate matter suspended in air, benzo(a)pyrene found in atmospheric wood burning, indigo dye and dietary carotenoids (1). Ligand bound AhR can be released from HSP90-AhR complex and enter into the nucleus. As a transcription factor with basic helix-loop-helix/Per-Arnt-Sim (bHLH-PAS) domains, AhR nuclear translocation can promote transcription of several genes whose encoding proteins catalyze the metabolism and conjugation of xenobiotics or carcinogens such as CYP1A1 in which gene promoter embeds dioxin response elements (DREs) (1).

The oncogenic roles of ligand dependent AhR have been well studied in carcinogenesis. Un-liganded AhR retains in cytosol but it may also involve in tumor formation through crosstalk with kinase signaling networks. Without exogenous ligand, constitutive active form of AhR constructed by deletion of ligand-binding domain, shows oncogenic activation of stomach (2) and liver tumors (3) formation.

Alternatively, endogenous ligands of AhR have been identified such as tryptophan metabolite kynurenine (4) and they may contribute to the constitutive activation of AhR. AhR antagonism studies may reveal the function of AhR activated by endogenous ligands. For instance, a study using antagonist CH-223191 showed that endogenous active AhR promotes clonogenic survival and invasion in glioma (5). In addition, AhR can be activated by exogenous ligand TCDD which can activate transcription of Nedd9/Hef1/Cas-L to promote changes in cell morphology for migration (6).

A few studies suggest that AhR may act as a tumor suppressor in some types of cancers. Cancer initiation usually is driven by cancer stem cells, a subpopulation that are resistant to chemo-drugs and induces metastasis and recurrence. Here we discuss the topic on the effect of ligands of AhR, including environmental toxins and diet-derivatives on cancer stem cells.

Ligand activated AhR in nucleus inhibits cancer stem cell properties

Recently, a few studies suggest that certain AhR activation by ligand such as tranilast or the tryptophan metabolite, 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) does not activate but inhibit AhR mediated cancer stemness. The earlier report showed

that AhR activation can inhibit breast cancer stem traits such as mammosphere forming, repopulation of aldehyde dehydrogenase 1 active cells through Wnt and Notch signaling pathways (7). Moreover, ITE as an endogenous AhR ligand which can also be found in protein rich food, enhances differentiation of cancer stem-like cells detected by the decrease of sphere formation and proliferation from glioblastoma cells U87 (8). Mechanically, ITE bound AhR inhibits transcription of OCT4, an inducer of pluripotent stem cells, through direct binding to OCT4 promoter (8). As a consequence, ITE treatment significantly represses the tumor formation in xenograft model using injection of U87 cells (8). The similar result has been found in leukemia HL60 cells, breast cancer and liver cells. For example, retinoic acid which is used for induction of differentiation of leukemia stem cells, can promote AhR transcriptional activity through ligand-dependent complex formation of AhR with RAR/RXR nuclear receptor. Ligand activated AhR then enhances differentiation of leukemia stem cells (9). Surprisingly, OCT4 is also found as a target of endogenous liganded AhR in this study using leukemia stem cells (9). Moreover, in breast cancer cells, AhR ligand tranilast inhibits cancer stemness and drug resistant cells mediated metastasis in a xenograft model (10). Thus AhR activation by a subset of exogenous or endogenous ligand may also inhibit cancer stemness.

AhR antagonist promotes expansion of stem cells

To further investigate the function of constitutive active AhR and role of endogenous ligand of AhR in stem cells, AhR antagonist should be applied. Given that AhR ligand can inhibit cancer stem cell property, the small molecular of antagonism of AhR ligand will in turn promote stemness. This is confirmed in human hematopoietic stem cells. A purine derivative named StemRegenin 1 is a selective antagonism of AhR which competes with ligand TCDD to increase the number of cultured CD34+, CD133+, and CD90+ hematopoietic stem and progenitor cell populations and engrafted repopulation cells which represent hematopoietic stem cells (11).

Environmental toxins or natural non-toxic AhR ligand: not bad for prevention of cancer initiation and metastasis?

Without exogenous ligand, namely, free state of AhR can function as a tumor suppressor protein based on the findings in liver cancer through dysregulated cell division and proliferation (12). Moreover, numerous studies in breast cancer further confirmed that liganded AhR is a suppressor of

cancer stem cells self-renewal and invasiveness (10,13). Thus AhR ligand of environmental toxins or natural non-toxins might also not be so bad for prevention of stem cell initiated oncogenesis and metastasis. Of course, the hypothesis is limited to certain conditions such as low dose exposure of cancer patients to AhR ligand such as TCDD which is found in air pollutants or non-toxic diet. However, large dose of exposure of AhR ligand may cause physiological damage in multiple organs including immune system (1).

Dietary ligand: good for treatment of AhR driven recurrent cancer?

Given that diet derivatives can act as AhR ligands, it is possible to use them as nutrition supplements to treat recurrent cancers via inhibition of cancer stem cell expansion and self-renewal by targeting AhR pathway. Thus AhR driven cancer relapses might be abrogated through inhibition of AhR mediated cancer stemness as shown by a recent study (8). While these diet drugs may have much less side effects for cancer treatment, diet derived AhR ligand might have the greatest potential to be applied for treatment of AhR induced cancer recurrence in precision medicine.

Conclusions

Recently a few studies in stem or cancer stem cells have shown that a subtype of exogenous ligand or endogenous ligand mediated activation or constitutive activation of AhR inhibits cancer stem cell properties through repressing OCT4. In addition, multiple mechanisms may contribute to the AhR mediated inhibition of cancer stem cells. First, the balance between stem cell differentiation and “proliferation” is essential to maintain the cancer stem cell self-renewal and cancer cell differentiation followed by cancer cell proliferation. Inhibiting differentiation pathway may therefore activate or inhibit its crosstalk pathways through multiple networks (*Figure 1*). Moreover, immune system may also involve in the bidirectional function of AhR in cancer. Using knockout mouse model, AhR has been found to constitutively inhibit inflammation (1) but in breast cancer cells, AhR activates IL8 production (14) which may promote cancer stemness and metastasis by crosstalk with growth factor pathways. In addition, AhR activation with increased production of TReg suggests the oncogenic role of TCDD as indicated by a review (1). Thus microenvironment in different cell or tissue types expressing multiple signaling pathways may regulate AhR or complex with AhR in stemness. As we showed before that microenvironment may switch an oncogene to be a

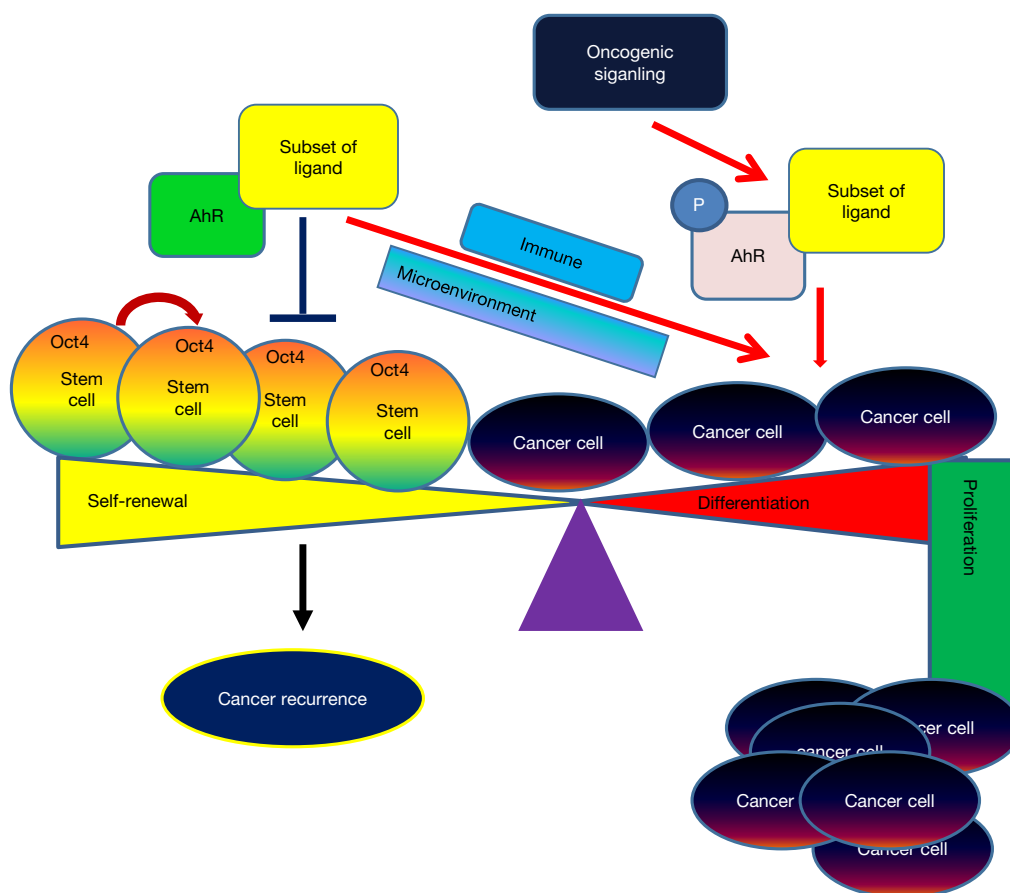


Figure 1 The role of AhR in cancer stem cells. In addition to the canonical AhR pathways for cancer progression through transcription of target genes such as CYP1A1, AhR can also inhibit cancer stem cell self-renewal through downregulation of OCT4 by a subset of ligand. This unique inhibition may promote differentiation and cancer cell growth through multiple pathways including immune response, kinase signaling and microenvironment. Targeting AhR by a subset of ligand may prevent cancer recurrence. P, phosphorylation; AhR, aryl hydrocarbon receptor.

tumor suppressor (15) involving in multiple signaling such as PTEN/AKT pathway (16-19). Moreover, in future further evidence need to be provided to clarify the ligand and tissue specify for AhR mediated inhibition in cancer stem cells. Finally, gene profiling of AhR knock out mice identified that AhR activates differential genes related to a verities of cellular process activated by AhR such as invasion pathways of MMP8 and MMP9 but they may be inhibited by AhR mediated cell cycle arrest to prevent the exhaustion of cancer stem cell self-renewal by p16 or p21 (15,17).

In summary, AhR ligand or antagonist ligand can be used for preventing AhR driven cancer initiation by targeting stem cells. While the environmental air pollutes contain AhR agonist/ligand, low dose exposure to environmental dioxin might not be bad for prevention of

cancer recurrence as we thought before. Most importantly, natural (tryptophan) metabolites, other types of AhR ligand, or antagonist of AhR suppressor (20), have provided the greatest potential for treatment of recurrent or metastatic cancer induced by cancer stem cells (8,13).

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