NF-κB, macrophage migration inhibitory factor and cyclooxygenase-inhibitions as likely mechanisms behind the acetaminophen- and NSAID-prevention of the ovarian cancer

Minireview

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Recent epidemiological studies indicated risk reductions in ovarian cancer with consumption of acetaminophen or non-steroid anti-inflammatory drugs. Until now, there is not a systematic analysis, why these agents may reduce risk of ovarian cancer, as it has been performed to explain aspirin-reduction of colon cancer risk. This review tries to explain molecular mechanisms pertinent to acetaminophen- and NSAID-reduction of ovarian cancer. It is proposed that the major mechanism by these anti-inflammatory agents is a shared pathway dependent on the suppression of NF-kappaB activity, which may subsequently decrease transcription of growth factors, chemokines and proteases such as COX-2, VEGF, IL-8/CXCL8, MCP-1/CCL-2, MIP1alpha/CCL-3, tPA and uPA, which are shown to be elevated in ovarian carcinoma, and which play diverse roles such as inducing angiogenesis, invasion, autocrine growth loops and resistance to apoptosis. Besides these, specific mechanisms of action can be attributed to acetaminophen-reduction of ovarian cancer risk via I. Induction of specific reproductive atrophy due its sex-steroid resembling phenolic ring; II. Reduction of glutathione pools due to its NAPQI metabolite, which may play an important role for sterilizing pre-malignant ovarian lesions, since they are shown to lack proper levels of glutathione; III. Inhibition of tautomerization activity of MIF (macrophage migration inhibitory factor), which is shown to be released from ovarian cancer, and which is necessary for proper ovulation; IV. Inhibition of cytokine-induced and endothelia-origined cyclooxygenases. Except the chemosensitization studies, acetaminophen and NSAIDs should be investigated in animal models to test likely benefits in ovarian cancer, since most of their activity may origin from intervening with the cancer growth-stimulating inflammatory stimuli, rather than with the direct cellular toxicity.

Key words: acetaminophen, NSAID, Nf-kappaB, macrophage migration inhibitory factor – MIF, cyclooxygenase, ovarian cancer, prevention

Ovarian carcinoma has the highest mortality rate among gynecological-malignancies [43]. Patients with tumors at stage III have a 5-year survival rate of only 28% and, 60% of patients are diagnosed with already advanced disease [43]. Due to the limited success of the current therapy, non-toxic modulators of ovarian cancer growth should be developed. With the discovery that aspirin reduces risk of human colon cancer [6], non-steroidal anti-inflammatory drugs (NSAIDs) have been intensively studied as modulators of tumor growth and drug sensitivity. Recent studies also showed a potential for acetaminophen and other NSAIDs in prevention of ovarian cancer [3, 23, 37, 40, 68, 84, 85, 95, 101, 103]. It has been long accepted that suppression of prostaglandin synthesis was the main mechanism behind the action of NSAIDs [106]. Nonetheless, current studies illuminated many different pathways modulated by NSAIDs, which could explain their anti-tumor potency. Among those suppression of the NF-κB appeared one of

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the dominant targets by NSAIDs both in their anti-tumor and anti-inflammatory actions [1, 7]. NF-κB suppression is also a mechanism of classical steroid-type anti-inflammatory agents [9, 30]; and some data also favor their potential for ovarian cancer. To elucidate, whether non-steroid anti-inflammatory agents play a role for the ovarian cancer, the role of inflammation in ovarian carcinogenesis is discussed.

Ovarian cancer and inflammation

Until now, two major hypotheses for ovarian carcinogenesis have been put forward: Ovulation and gonadotropin hypotheses. According to the first hypothesis, cyclic ovulation periods induce repeated rupture of the ovarian surface epithelium, which necessitates ongoing requirement of epithelial mitosis. This repair of the 'ovulation wound' may enhance the chance of mutations and may act like a promoter for carcinogenesis [38]. This hypothesis is parallel to gonadotropin hypothesis, which proposed that ovarian cancers arose from the ovarian surface epithelium, and specially from the inclusion cysts, which form via parenchyma entrapment of surface epithelium after ovulation and which get exposed to high levels of estrogens and gonadotropins (FSH and LH) [25]. Hence, factors which will increase LH-levels should increase ovarian carcinogenesis, and factors which will decrease LH-levels should decrease ovarian carcinogenesis. Indeed, the factors that induce greatest overall risk reduction for ovarian cancer are parity, oral contraceptive use and prolonged-breast feeding [74]. During pregnancy, high levels of estrogen and progesterone suppress levels of LH and follicle-stimulating hormone (FSH) and disallow ovulation [74]. During oral contraceptive use, stable levels of estrogens and progestins inhibit the gonadotropins and their ability to stimulate ovulation; and during breast-feeding, low levels of estrogen and LH suppress ovulation [74]. Nonetheless, Ness counter-argues that two prospective cohort studies have failed to find a link between gonadotropin levels and ovarian cancer occurrence, and she proposes inflammation as a major component of ovarian cancer etiology [74]. She underlines that among major etiological factors of ovarian carcinogenesis, many inflammatory conditions occupy a big portion including endometriosis, pelvic inflammatory disease, asbestos and talc exposure [74]. Moreover, both tubal ligation and hysterectomy without oophorectomy provide long-term reductions of the ovarian cancer risk. This is presumably by cutting off the pathway between the lower and upper genital tract and thereby disallowing environmental inflammatory agents from reaching the ovarian epithelium [74]. QUIRK et al also proposed inflammation as an etiological basis of ovarian cancer [82]. They claimed that long-lasting and silent infection-induced inflammations may be causal for ovarian carcinogenesis [82].

The ovulation theory is partly complementary to the inflammation theory to explain ovarian carcinogenesis, since ovulation itself involves inflammation by rising levels of pro-inflammatory cytokines such as TNFα, and IL-1, and also via boosting cell proliferation, prostaglandins, leukotrienes, and oxidative stress [73]. Moreover, epithelial ovarian cancers bear elevated mRNAs for above described cytokines [73], and even TNFα has been shown to propagate solid tumor nodule formation, when acted on the ovarian carcinoma ascites [61].

The interplay between the inflammation- and ovulation-inhibiting roles of NSAIDs

Indomethacine is a widely used NSAID to inhibit ovulation in vertebrates, and the ovulation inhibiting roles of NSAIDs are well known [70]. Until recently, prostaglandin suppression has been attributed as the sole mechanism behind the NSAID-blockage of ovulation, however, a series of studies by MURDOCH et al showed that NSAIDs inhibit ovulation via blocking apoptosis of ovarian surface epithelium [70], and that the ovulation induces DNA damage (rise of 8-oxoguanine levels) among ovarian surface epithelial cells juxtaposed the ovulation site, which can be prevented by indomethacine application [71]. On the other hand, if NSAIDs prevent apoptosis of the ovarian epithelium, someone would argue that it would be possible that they may also suppress apoptosis of pre-malignant clones in the ovarian epithelium. Nonetheless, this proposed risk does not exist. ACKERMAN and MURDOCH report no induction of apoptosis in OVCAR-3 cell up to 5 ng/μl PgE_2, despite the same dosages induced 40% apoptosis in healthy ovarian epithelia [2]. Moreover, MUNKARAH et al have found that PgE_2 both stimulates proliferation and reduce apoptosis in COX-2 expressing MDAH-2774 and SKOV3 human ovarian cancer cells by modulating bcl-2/bax ratio [69]. Thus, there is a signal shift in ovarian cancer cells, in which prostaglandins act anti- rather pro-apoptotic in opposite to benign ovarian epithelia. Hence, NSAIDs may act anti-apoptotic for the benign, but pro-apoptotic for the malignant ovarian cells. (There are some prostaglandins, which can induce apoptosis in ovarian cancer cells with anti-inflammatory nature, which are called cyclopentenone-prostaglandins [88].) Direct cellular toxicity and induction of atrophy on ovaries may be also performed by some NSAIDs, including acetaminophen. For instance HANEY et al monitored female reproductive toxicity of NSAIDs and acetaminophen in a cell culture model [45]. They have found that only acetaminophen, fenoprofen and sulindac suppressed the granulosa function out of the 13 NSAIDs tested, which included butazolidin, ibuprofen, indomethacine, meclomen, mefenamic acid, naproxen, salicylate, tandearil, tolmetin and zomepirac [45]. Thus, a particular

atrophic effect of certain NSAIDs and acetaminophen may have mediated ovarian cancer reducing-action. Such a toxicity on reproductive organs has a biochemical basis pertinent to the phenol ring of acetaminophen (N-acetyl-*p*-aminophenol), which resembles to the sex steroids. Indeed, feeding with 3000 ppm of acetaminophen suppresses ovarian cysts, whereas feeding with 25000 ppm of acetaminophen induces rodent uterine, ovrian and testicular atrophy [72]. Parallel to animal data, CRAMER et al showed reduced basal levels of gonadotropins and especially of LH among infertile women who use acetaminophen for menstrual pain, but not among those who use aspirin or other NSAIDs [24]. NF-κB as a shared target of acetaminophen and NSAIDs in ovarian cancer.

Ovarian cancers are among tumors, where profound misuse of inflammatory mechanisms contributes to the tumor progression. In addition to the above-mentioned release of cytokines and eicosanoids, ovarian cancers have been also found to release IL-6 [109]. IL-6 secretion occurs even at a constitutive manner as shown in human ovarian cancer cell lines (CAOV-3, OVCAR-3, SKOV-3) [109]. Ovarian cancers also release the endothelial growth factor VEGF [47] simultaneously with the cytokine/chemokine IL-8/CXCL8 [47, 90], and the chemokines CCL18/PARC, MCP-1/CCL-2, MIP-1α/CCL-3 [90]. Interestingly, an important transcription factor NF-κB has been shown to be responsible of constitutive expression of IL-1α, IL-6, IL-8 and GM-CSF in head and neck cancers [32]. NF-κB also mediates induction of IL-6 by PgE_1- [29], TNFα- [55] and radiation [15]. NF-κB is responsible of basal transcription- [99], TNFκ- [111], IL-1β- and Platelet activating factor- [59] induction of COX-2. Furthermore, NF-κB mediates bacterial superantigen- [102], taxol- [4], IFNγ- and lipopolysaccharide- [22] induction of TNFα. NF-κB is also responsible of constitutive expression of IL-8 and VEGF in ovarian cancer [47]. Moreover, NF-κB also provides IL-1β- [50], VEGF- [62], lipopolysaccharide- [104] and TNFα- [105] induction of MCP-1/CCL2. At last NF-κB is also mediating endotoxin- [44] stimulation of MIP1α/CCL-3, and production of uPA in human ovarian cancer cells [83]. Thus, it would not be illogical to assume that almost all pro-inflammatory cytokines released by human ovarian cancer cells may be dependent on the activation of the NF-κB transcripton factor. There are not many studies on the activation status of NF-κB in ovarian cancer yet, it is responsible of VEGF, IL-8 and uPA synthesis in SKOV3 and OV-MZ-6 human ovarian cancer cells, respectively [47, 83]. Inhibition of the NF-κB induced dramatic regression of carcinomatous peritonitis-growth of SKOV3 in nude mice [47] with decreased peritoneal vascularization. Another human ovarian cancer cell line OVCAR-3 also bear constitutively active NF-κB [11]. This information is interesting, when considering that OVCAR-3 is the cell line, in which DRAKE and BECKER found approximately 70% growth inhibition with 5 mM aspirin [33] and SAUNDERS et al found c-myc oncogene suppression and growth inhibition with dexamethasone [87]. GUPTA etal showed a correlation between COX-1 expression and the expressions of HIF1α and the VEGF in ovarian cancer [42]. Ibuprofen, a widely used NSAID, is shown to strongly inhibit NF-κB, HIF1α and VEGF levels in human prostate cancer cells at a clinically achievable 2 mM concentration [78, 79, 80]. It is very striking that sodium ibuprofen at a dose of 7 mg/kg/day could strongly inhibit (more than 70%) the *in vivo* growth in a 33% of human primary ovarian adenocarcinomas in a subrenal xenograft implantation model [98]. Suppression of NF-κB has been shown for clinical concentrations of aspirin and salicylate and their major anti-inflammatory mechanism has been attributed to this effect [52]. Recently, acetaminophen has been also shown to suppress LPS and IFNγ-stimulated NF-κB activity in macrophages [86]. Thus, NF-κB might be a common target by acetaminophen and NSAIDs to suppress inflammation and subsequently the growth of ovarian cancer, which is dependent on the presence of a pro-inflammatory micro-milieu. Further studies are necessary to take benefit from these drugs as easily applicable NF-κB-suppressors in ovarian cancer.

Glutathione depletion by acetaminophen as a mechanism of ovarian carcinogenesis-suppression: Where the pro-oxidants change their roles for carcinogenesis

Acetaminophen is converted to NAPQI (N-acetyl-*p*-benzoquinone imine) by the P450 system, which is detoxified by conjugation with reduced glutathione (GSH) leading to severe depletion of this essential thiol reagent in cells [53]. Once GSH is depleted, NAPQI will further react with thiol groups of essential cellular proteins, leading to membrane Ca^{2+}ATPase depletion, nuclear Ca^{2+} accumulation, mitochondrial oxidant stress and caspase-3 independent DNA fragmentation associated with necrotic type of cell death [53].

Among the p450 components, microsomal CYP2D6 catalyzes cysteine conjugation of acetaminophen [112], and interestingly CYP2D6 resides at 22q, where loss of heterozygosity was detected in 53% of 123 analyzed ovarian carcinoma [16]. Despite that the known polymorphic variants of CYP2D6 are not associated with this disease [16], it is possible that some variants of CYP2D6 metabolizes acetaminophen at accelerated rates to NAPQI, which may mediate self destruction and early elimination of pre-malignant ovarian cancer cells with the continuous acetaminophen exposure.

This possibility makes especially sense, when remembering that the oxidative metabolism of acetaminophen is increased in liver carcinoma [54] and that the liver carcinoma cells can be eliminated *in vitro* by exposure to acetamino-

phen even with the presence of N-acetylcysteine rescue to protect benign hepatocytes [110].

We should admit that it seems paradoxical at the first glance to propose that a pro-oxidant effect may mediate anti-carcinogenic action of acetaminophen for ovarian cancer, when considering the overwhelmingly dominant abundance of the views that anti-oxidants are anti-, and pro-oxidants are pro-carcinogenic. Yet there are a number of evidences that the antioxidants fail to prevent cancer, even promote it, while some pro-oxidants are anti-carcinogenic [49, 63, 65, 81, 89, 96]. It may be possible that pre-malignant lesions demand for glutathione, which make them particularly vulnerable to pro-oxidant actions of certain compounds at non-toxic exposures. For instance, it is known that low grade astrocytomas [58] and soft tissue sarcomas [46] are having lower amounts of glutathione than the corresponding high-grade tumors. Concomitant with these findings, total levels of glutathione in ovarian cancer tissues have been found to be less in low FIGO-grade tumors than the high FIGO-grade ones [100]. A similar and well-known finding is that chemosensitive ovarian cancers bear less glutathione than their sensitive subtype [57]. SPREM et al [97], found that benign ovarian cancers have lost approximately 40% of their glutathione content in comparison to normal ovaries. Thus, a continuous pro-oxidant environment in the vicinity of pre-malignant ovarian lesions may induce their necrosis.

Acetaminophen as specific inhibitor of Macrophage migration inhibitory factor: A good link between inhibition of ovulation, inflammation and ovarian cancer

Macrophage migration inhibitory factor (MIF) was defined originally as an activity responsible for the inhibition of random macrophage migration during the delayed-type hypersensitivity response [10, 27, 92]. MIF is released by the anterior pituitary gland during systemic stress response [8, 17], and it is expressed in macrophages [18] and T cells [5, 10, 27] after immune and inflammatory stimuli. During trauma [51] and septic shock [8], MIF level in circulation is considerably high, and it has an augmenting role on the pro-inflammatory and lethal responses against LPS [19] and enterotoxin [14] in the systemic inflammatory response syndrome models.

Although glucocorticoids inhibit the production of inflammatory molecules, they induce secretion of MIF from macrophages [17] and T cells [5]. In turn, MIF counter-regulates the glucocorticoid activity by suppressing the glucocorticoid-inhibition of pro-inflammatory signal [17]. As outlined above, glucocorticoids are antagonising NF-κB activity; and they do so via increasing the transcription of IκBα, a natural cytoplasmic antagonist of NF-κBα [26]. Since MIF is inhibiting transcription of IκBα, and increasing the transcription of NF-κB in opposite to glucocorticoids [26], this would be a mechanism whereby MIF counter-regulates glucocorticoid-activity. Parallel to its activity to increase pro-inflammatory NF-κB levels; MIF is increasing TNFα and IL-8 secretion from alveolar cells during adult respiratory stress syndrome [31]. When remembering the strong-angiogenic character of these cytokines, it is not surprising to learn that MIF is a significant stimulator for lymphoma- [21] and colon cancer- [75] vascularization. Besides these tumors, MIF is over-expressed in prostate cancer [28], melanoma [93], and glial brain tumors [60]. Moreover, MIF is a transriptional inhibitor of the wild-type p53 [48], indicating a likely strong role of MIF in maintaining malignant behavior of these tumors.

A very interesting knowledge is that the MIF production in the human ovarian carcinoma ascites is so high, such that it can be used to purify MIF at quantities large enough to create anti-MIF monoclonal antibodies [34, 35, 36]. MIF is expressed in the murrhine ovary, fallopian tubes, and the uterus during the pre-implantation period and all stages of estrus cycle [107]. Recent studies also revealed the MIF-presence in human ovaries, which is up-regulated via HCG [108]. The most noteworthy fact is that the MIF-inhibition in mice models is leading to suppression of follicular growth and ovulation [64]. Thus, MIF is a cytokine, which directly involves in ovulation, which induces a strong pro-inflammatory milieu, and which is high in ovarian cancer, indicating a very likely role to link ovulation and inflammation hypotheses for ovarian cancer. More importantly, MIF is very recently found to be a specific target for acetaminophen [92]. Unlike other cytokines, MIF shares peculiar similarities with microbial enzymes and it is found to catalyse reactions on non-physiological substrates such as L-dopachrome [56, 92]. This tautomerization-based catalytic function of MIF is necessary to induce metalloproteases MMP-1 and MMP-3 from synovial-fibroblasts [76]. Based on the similarity of the non-physiological substrates of MIF to acetaminophen, SENTER et al have assessed, whether acetaminophen or acetaminophen metabolites are capable to block MIF activity [92]. Indeed, acetaminophen, and more powerfully its metabolites NAPQI and hydroxyquinone are found to strongly inhibit MIF activity at IC50 levels of 10 mM, 40 μM and 0.7 μM, respectively [92]. Therapeutic steady-state serum concentration of acetaminophen is 100 μM [39]. However, acetaminophen is capable to block MIF *in vivo*, presumably because the metabolites of therapeutically given-acetaminophen can easily reach the MIF-inhibitory concentration [92]. Indeed, treatment of mice with therapeutically relevant doses of acetaminophen (300–600 mg/m^2) induced strong inhibition of liver MIF activity [92]. Moreover, NAPQI modulated MIF has been shown to strongly reduce its activity to inhibit glucocorticoid-suppression of TNFα or to trans-activate p44/p42 MAP Kinases, indicating that an important percentage of pro-

inflammatory MIF functions can be targeted via inhibition of its enzymatic activity [92]. Thus, we conclude that at clinically relevant concentrations of acetaminophen, suppression of ovarian cancer risk may be occurring dominantly via NAPQI blocking of glutathione and the MIF activity, in which the latter may subsequently block two roads to ovarian cancer simultaneously, – the ovarian inflammation and ovulation. Presumably the reproductive toxicity of acetaminophen may also link to its inhibition of MIF solely, or in addition to effects attributed to its sex-steroid resembling ring.

Cyclooxygenase-2 and cyclooxygenase-3 suppression by acetaminophen

Despite acetaminophen bears significant analgesic and antipyretic activity, it has mild anti-inflammatory activity, and it was first believed that it does not suppress prostaglandin synthesis profoundly in the periphery but in the brain with an IC50 value of 93 μM, which is seven times lower than for the spleen [39]. However, more recent studies indicated potential of acetaminophen to suppress peripheral prostaglandin synthesis. First acetaminophen efficacy to suppress COX-1 (aortic endothelial cells) and COX-2 (J774.2 murine macrophages) was compared. It was shown that acetaminophen had a significant block on COX-1; and reduced the activity of COX-2 at IC30 values of 2.7 μg/ml and 20 μg/ml, respectively [67]. BOTTING showed that COX-2 in cultured fibroblasts from COX-1 knockout mice is up-regulated by IL-1β and the resulting COX-2 activity is sensitive to inhibition with acetaminophen in concentrations as low as 1 μM [13]. Botting-group also showed a variant enzyme, which is up-regulated in J774.2 macrophage cell line upon 48 h incubation with diclofenac, and which is sensitive to acetaminophen at greater dosages than 60 μM yet not so sensitive to other NSAIDs with IC50 values of 10, 230 and 220 μM for diclofenac, flurbiprofen and tolfenamic acid, respectively [94]. Recently CHANDRASEKHARAN cloned a splicing variant of COX-1 from canine cerebral cortex, which is sensitive to inhibition with diclofenac, ibuprofen and acetaminophen at IC50 values of 0.008, 0.24 and 460 μM, respectively; and which they called as COX-3 [20]. It is clear that there are either further splicing variants, different genes or intracellular milieu-dependent conformation variants pertinent to cylooxygenase activity, since there are major differences between their sensitivity to acetaminophen and other NSAIDs. Moreover, there is a COX-2 activity, which is related with resolution of inflammation and synthesis of cyclopentenone prostaglandins [41]. It is obvious that an acetaminophen-target can not be this last enzyme to mediate slight anti-inflammation. On isolated enzymes, the necessary doses to inhibit cyclooxygenases by acetaminophen increase drastically; and only in the presence of glutathione peroxidase and glutathione, detectable inhibitions can be achieved with IC50 values of 33 and 980 μM for COX-1 and COX-2, respectively [77]. Studies on isolated enzymes also showed that oxidant micro-milieu reduces activity of acetaminophen to block prostaglandin synthesis, presumably because antioxidant effect of acetaminophen contributes to its inhibition on cyclooxygenases via blocking peroxidase function of these enzymes [77].

On the other hand, in a whole human blood assay acetaminophen was found to be a more effective inhibitor of COX-2 (in LPS stimulated blood, IC50 = 49 μM) than of COX-1 (in platelets IC50>100 μM) [91]. Parallel to these results, BOUTAUD also showed acetaminophen capable to inhibit IL-1β induced prostaglandin synthesis activity in human umbilical vein endothelial cells (HUVEC) by a low IC50 value of 4.3 μM, whereas an IC50 concentration of 1870 μM was necessary to do so in platelets (COX-1); and both of these inhibitory activities were sensitive to inhibition with exogenous peroxides [12]. These results are also very similar to observations of BOTTING [13] mentioned above. Moreover, despite MITCHELL described as COX-1 [67], the cyclooxygenase activity of bovine aortic endothelial cells showed a very close and intense sensitivity to inhibition by acetaminophen as Boutaud's group showed for HUVECs [12]. Thus, well in the range of its clinical concentration, acetaminophen activity to inhibit ovarian carcinogenesis may also relate with its potency to reduce COX-2 activity, which may be a growth-stimulating factor for both the tumor and its invading endothelia. It is time to investigate acetaminophen and NSAIDs as cheap and relatively non-toxic preventing agents against an insidious and highly fatal disease.

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