The inflammasome is a multimeric protein complex that resides in the cytoplasm [6]. An inflammasome has two primary roles (1) it facilitates activation of cysteine protease caspase-1 (2) it mediates proteolytic cleavage and release of pro-inflammatory cytokines IL-18 and IL-1β [5]. The activated form of cysteine protease caspase-1 initiates pyroptosis, an inflammatory form of programmed cell death [5]. Certain members of the NLR protein family and AIM2-like receptor family proteins form inflammasome complexes in response to endogenous danger signals (DAMPs), such as ATP that can be released as a result of tissue damage, and exogenous danger signals [5], PAMPs associated with fungi, bacteria and viruses [1]. Recognition of PAMPs and DAMPs by inflammasome components such as NLRP3 leads to activation of the inflammasome [5].

Many literature and studies have shown the diametric effects of the inflammasome in cancer. Some studies have shown the protective role of the inflammasome in inhibiting metastasis [1] [3], imparting resistance to carcinogens [8], while some studies found the opposite [2].

**The protective role of the inflammasome**

NLRP3 is a component of inflammasome and can recruit apoptosis-associated proteins like caspase-1 [2]. Zaki et al (2010) found that IL-18, a cytokine produced downstream of NLRP3 activation is important in protection against DSS-induced colitis-associated cancer (CAC). In a bone marrow chimera study by Zaki et al(2010), NLRP3-mediated secretion of IL-18 was also shown to protect against CAC. In the same study, injection of IL-18 was found to reduce the incidence of tumors in response to cancer-causing agents [13].

**The detrimental role of the inflammasome in cancer**

As noted, NLRP3 mediates the release of a cytokine called IL-18. Curiously, despite its protective role of inhibiting cancer progression, IL-18 was also shown to throw off the fine-tuning of the expression of a cytokine, called IL-22, by downregulating IL-22’s upstream regulator, IL-22BP [10]. Uncontrolled expression of IL-22 promotes tumor development [10].

While IL-18 induces NK cells’ tumoricidal activity, IL-1β, another cytokine whose secretion is mediated by NLRP3, suppresses NK cells via the NLRP3-IL-1β-IL-1R signaling pathway [3] [5]. IL-1R is the receptor for the IL-1 family, which includes IL-1β, whose presence was linked to many cancers through various mechanisms, such as inducing angiogenesis [3] and suppressing NK cells [5]. Moreover, Tu et al (2008) found in their study that mice engineered to express human IL-1β in the stomach experience an increased accumulation of myeloid-derived suppressor cells (MDSCs) to the stomach. MDSCs are a population of immature myeloid cells that suppresses T cell activation [3]. MDSCs were shown to predispose mice to gastric cancer [11]. The significance of IL-1-IL-1R signaling was further demonstrated by a study by Bunt et al (2007), where mice lacking IL-1 cytokine receptor IL-1R reduced MDSC accumulation and reduced primary and secondary mammary tumors. IL-1R contributes heavily to tumorigenesis in many cancers. For instance, IL-1β produced by MDSCs induces secretion of IL-17 by CD4 T cells[3]. IL-17 promotes angiogenesis and dampens the efficacy of chemotherapeutic agents [3]. Other than NLRP3 inflammasome, NLRC4 inflammasome also produces IL-1β. In a study by Kolb et al (2016), they found tumor microenvironment in obese patients recruit macrophages with activated NLRP4 that releases IL-1β, the cytokine then promotes disease progression by promoting adipocyte-oriented VEGF production, which promotes angiogenesis, thus worsening prognosis in these patients.

**Biomarker discovery**

The IL-1β-IL-1R signaling pathway is implicated in driving many models of cancer, making them attractive biomarkers to target for cancer therapy. Gemcitabine (Gem) and 5-fluorouracil (5-FU) are common chemotherapeutic agents that selectively deplete MDSCs [2]. MDSC depletion increase CD8 T cell tumor immunosuppression activity and increased survival of tumor-bearing mice [2]. However, Gem and 5FU also activate the NLRP3 inflammasome in MDSCs in vivo as a result of NLRP3 recognizing Gem and 5FU as danger signals, leading to IL-1β release by MDSCs [2]. IL-1β drives CD4 T cells to produce IL-17, a proangiogenic cytokine that promotes tumor progression. Therefore, IL-17 release limits the therapeutic effect of Gem and 5FU. In a study by Bruchard et al (2012), Anakinra, which is a recombinant soluble IL-1R antagonist, was found to enhance the antitumor efficacy of 5-fluorouracil (5FU) against EL4 thymoma in the mouse model. As a side note, Tu et al also found that administering IL-1Ra inhibits the development of gastric cancer and suppresses MDSCs mobilization. They administered IL-1Ra in combination with 5FU to show that IL-1Ra enhanced 5FU’s antitumor efficacy. Bruchard et al (2012) also showed that caspase-1 activation is necessary for IL-1β release. Indeed, in their study, both Nlrp3 and Casp1 (caspase-1 gene) double knockout mice treated with PBS(control) showed marginally better survival than wild-type mice. The survival advantage is more distinguished when the same mice groups were treated with 5FU post tumor injection, where 42% and 30% of Casp1-/- and Nlrp3-/- mice, respectively survived after 60 days, contrasting with the fact that all WT mice died within 30 days. The improvement in survival in Nlrp-/-5FU group and Casp-/- 5FU group were comparable to that observed in WT IL-1Ra 5FU treatment, suggesting that IL-1Ra has the equivalent anti-tumor effect to IL-1β deficiency. Interestingly, Bruchard et al’s study showed that Il1r1-/- mice (IL-1R deficient mice) treated with PBS does not seem to display reduced tumor size compared to WT mice treated with PBS, but they do show a significant reduction in tumor size with 5FU, this seems to suggest IL-1β exert its effect on tumor cells in an IL-1R independent manner. Anakinra has been approved for the treatment of active myeloma [13].

**Reference**

1. Allen, I., TeKippe, E., Woodford, R., Uronis, J., Holl, E., Rogers, A., Herfarth, H., Jobin, C. and Ting, J., 2010. The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer. *Journal of Experimental Medicine*, 207(5), pp.1045-1056.
2. Bauer, C., Düwell, P., Mayer, C., Lehr, H., Fitzgerald, K., Tschopp, J., Endres, S., Latz, E. and Schnurr, M., 2010. Colitis induced in mice with dextran sulfate sodium (DSS) is mediated by the NLRP3 inflammasome. *Zeitschrift für Gastroenterologie*, 48(10).
3. Bruchard, M., Mignot, G., Derangère, V., Chalmin, F., Chevriaux, A., Végran, F., Boireau, W., Simon, B., Ryffel, B., Connat, J., Kanellopoulos, J., Martin, F., Rébé, C., Apetoh, L. and Ghiringhelli, F., 2012. Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. *Nature Medicine*, 19(1), pp.57-64.
4. Bruchard, M., Mignot, G., Derangère, V., Chalmin, F., Chevriaux, A., Végran, F., Boireau, W., Simon, B., Ryffel, B., Connat, J., Kanellopoulos, J., Martin, F., Rébé, C., Apetoh, L. and Ghiringhelli, F., 2012. Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. *Nature Medicine*, 19(1), pp.57-64.
5. Guo, B., Fu, S., Zhang, J., Liu, B. and Li, Z., 2016. Targeting inflammasome/IL-1 pathways for cancer immunotherapy. *Scientific Reports*, 6(1).
6. Huber, S., Gagliani, N., Zenewicz, L., Huber, F., Bosurgi, L., Hu, B., Hedl, M., Zhang, W., O’Connor, W., Murphy, A., Valenzuela, D., Yancopoulos, G., Booth, C., Cho, J., Ouyang, W., Abraham, C. and Flavell, R., 2012. IL-22BP is regulated by the inflammasome and modulates tumorigenesis in the intestine. *Nature*, 491(7423), pp.259-263.
7. Karki, R., Man, S. and Kanneganti, T., 2017. Inflammasomes and Cancer. *Cancer Immunology Research*, 5(2), pp.94-99.
8. Kolb, R., Phan, L., Borcherding, N., Liu, Y., Yuan, F., Janowski, A., Xie, Q., Markan, K., Li, W., Potthoff, M., Fuentes-Mattei, E., Ellies, L., Knudson, C., Lee, M., Yeung, S., Cassel, S., Sutterwala, F. and Zhang, W., 2016. Obesity-associated NLRC4 inflammasome activation drives breast cancer progression. *Nature Communications*, 7(1).
9. Lust, J., Lacy, M., Zeldenrust, S., Dispenzieri, A., Gertz, M., Witzig, T., Kumar, S., Hayman, S., Russell, S., Buadi, F., Geyer, S., Campbell, M., Kyle, R., Rajkumar, S., Greipp, P., Kline, M., Xiong, Y., Moon-Tasson, L. and Donovan, K., 2009. Induction of a Chronic Disease State in Patients With Smoldering or Indolent Multiple Myeloma by Targeting Interleukin 1β-Induced Interleukin 6 Production and the Myeloma Proliferative Component. *Mayo Clinic Proceedings*, 84(2), pp.114-122.
10. Moossavi, M., Parsamanesh, N., Bahrami, A., Atkin, S. and Sahebkar, A., 2018. Role of the NLRP3 inflammasome in cancer. *Molecular Cancer*, 17(1).
11. Terlizzi, M., Casolaro, V., Pinto, A. and Sorrentino, R., 2014. Inflammasome: Cancer's friend or foe?. *Pharmacology & Therapeutics*, 143(1), pp.24-33.
12. Tu, S., Bhagat, G., Cui, G., Takaishi, S., Kurt-Jones, E., Rickman, B., Betz, K., Penz, M., Bjorkdhl, O., Fox, J. and Wang, T., 2011. Overexpression of Interleukin-1β Induces Gastric Inflammation and Cancer and Mobilizes Myeloid-Derived Suppressor Cells in Mice. *Cancer Cell*, 19(1), p.154.
13. Zaki, M., Vogel, P., Body-Malapel, M., Lamkanfi, M. and Kanneganti, T., 2010. IL-18 Production Downstream of the Nlrp3 Inflammasome Confers Protection against Colorectal Tumor Formation. *The Journal of Immunology*, 185(8), pp.4912-4920.