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REVIEW ARTICLE

Interleukin-6 (IL-6), Interleukin-8 (IL-8), and Tumor Necrosis Factor-Alpha (TNF-α): Their Role in the Development and Metastasis of Tumor Cells

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ABSTRACT

Cancer is a disease caused by uncontrolled and excessive cell division. The death caused by cancer is largely due to the cancer cell metastasis process. Cancer metastasis process is a consequence of molecules signaling pathways and interactions amongst cells in the body. Molecules involved and attributable to cancer metastasis are IL-6, IL-8, and TNF-α. This article aimed to describe the roles of IL-6, IL-8, and TNF-α in the process of various cancer cases.

Keywords*: cancer, IL-6, IL-8, TNF-alpha, metastasis*

ABSTRAK

Kanker merupakan suatu penyakit yang disebabkan oleh pembelahan sel yang berlebihan dan tidak terkendali (abnormal). Kematian akibat kanker sebagian besar disebabkan oleh metastasis sel kanker. Metastasis sel kanker diperantarai oleh berbagai sitokin, namun yang paling sering adalah IL-6, IL-8, dan TNF-α. Namun, belum diketahui secara jelas bagaimana peran berbagai sitokin tersebut dalam proses metastasis kanker. Review artikel ini adalah bertujuan untuk menguraikan bagaimana peran IL-6, IL-8, dan TNF-α pada metastasis sel kanker.

Kata Kunci: kanker, IL-6, IL-8, TNF-alpha, metastasis

INTRODUCTION

Around 9.6 million people died of cancer in 2018 throughout the world. In Indonesia, cancer prevalence has reached 1.4 ‰. The highest cancer prevalence is found in Special Region of Yogyakarta (4.1‰), followed by Central Java (2.1‰), Bali (2‰), Bengkulu, and DKI Jakarta at 1.9‰ respectively (KEMENKES, 2013; World Health Organization (WHO), 2018). Cancer (neoplasm) is the general term for a large group of diseases characterized by abnormal cell growth. The uncontrolled cancer cell/tissue growth, keep on growing and increasing and even spread to various tissues and lead to death (Liu, 2018). Most deaths in cancer is associated with metastasis mediated by numerous cytokines (Kasper et al., 2015).

Currently, the therapy used in treating cancer is divided into 2, namely local and systemic therapies. The local therapy includes surgery, radiation and photodynamic therapies. Meanwhile, the systemic therapy involves chemotherapy (including hormonal therapy) and biological therapy (immunotherapy) (Dicato and Cutsem, 2018; National Cancer Institute, 2018). Despite the many cancer therapies available, cancer patients developing metastasis is still found in a large number. Metastasis is a process of cancer/cancer cell spreading from the main organ to other organs through lymphatic and vascular pathways through various molecules inside our body. These molecules are often targeted in cancer medication through immunotherapy. An example is the interaction between programed cell death protein 1 receptor (PD-1) and its ligand (PD-L1), allowing apoptosis to occur in cancer cells (Gong et al., 2018). In addition to interaction between PD-1 and PD-L1, other molecules are also involved and plays a role in the development process of cancer cells, i.e. as a signal which induces the relocation (metastasis) of cancer cells to other organs. These molecules can take the form of cytokines, i.e. Interleukin 6 (IL-6), Interleukin 8 (IL-8) (Jayatilaka et al., 2017), and tumor necrosis factor-α (TNF-α) (Maolake et al., 2018).

This article review aimed at discovering the roles played by IL-6, IL-8, and TNF-α in inducing the development and metastasis of cancer cells for

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consideration of their uses for cancer and cancer metastasis medication therapy in the future.

CANCER AND METASTASIS

Cancer is a process or situation in which the cells in the body in a certain organ or tissue proliferate uncontrollably (Hanahan and Weinberg, 2011; Moses et al., 2018). Cancer occurs through a set of somatic changes in DNA. Most of these changes involve changes to the sequence of DNA chain (mutation). This mutation can take place as a result of random replication errors, exposure to carcinogen (radiation), or failed DNA repair process (Kasper et al., 2015).

The cells in a normal person will grow and divide (self-multiplying) and then will experience apoptosis to maintain a balance number of cells. However, in persons suffering from cancer, abnormality occurs in these processes, particularly in the ability to perform apoptosis, leading to continuous and uncontrolled cell growth (Hanahan and Weinberg, 2011; Medina-ramirez et al., 2011; Ichim and Tait, 2016). These cells with abnormality will then form a tumor. In general, tumor can be distinguished into two, namely solid tumor and nonsolid tumor. Solid tumor is the type of tumor frequently found in tissues or organs, and nonsolid tumor is the one found in non-solid cells or tissues such as in blood (Liu, 2018).

The mutation process from normal into tumor cells can be triggered by many factors, including chemicals (cigarette smoke, arsenic compound, and asbestos), physical agent (radiation and chronic trauma), virus infection (HBV, HPV, and EBV), immunology (AIDS and transplantation), endocrine (excessive production of endogenous and exogenous hormone), and hereditary (Liu, 2018). A small part of tumor cells in tissues capable of proliferating are known as cancer stem cell (CSC), suggested for the first time by Bonnet and Dick (Marusyk and Polyak, 2010; Clevers, 2011; Liu and Lathia, 2016). This CSC then proliferates rapidly to produce new tumor cells and this results in uncontrolled tumor tissue growth. CSC has the ability to change metabolism, allowing it to survive from various cancer therapy medicines. Additionally, CSC also has the ability to repair DNA damage very quickly and this also makes these tumor cells resistant to any medication which damage tumor cell DNA as its target (Skvortsov et al., 2014). Tumor tissue is known to have the ability to attract numerous non-neoplastic cells into the tumor cell environment to support the growth and development of the tumor cells and tissues themselves. Various substances and molecules are produced in the tumor microenvironment by these non-neoplastic cells including cytokine, and growth factor. These non-neoplastic cells can also form a matrix and form new blood vessels to supply nutrition and facilitate the disposal of wastes from the tumor tissues, despite its unknown mechanism (Yang, Pang and Moses, 2010; Hanahan and Coussens, 2012; Kidd et al., 2012).

The mutating primary tumor cells, cells in tissues, or the organ of origin can relocate through blood circulation and lymphatic vessels to other organs or tissues and then cause cancer in the tissues. It is this tumor which is known as metastatic cancer or secondary cancer. The new location for tumor cells (metastasis) is limited to certain tissues or organs, and this is usually different for each type of cancer. For example, breast cancer usually metastasizes to bones, brain, liver, and lungs, and in prostate cancer the metastasis occurs only in bones (Chaffer and Weinberg, 2011; Karaman et al., 2014; Su et al., 2016; Chaudhuri, Low and Lim, 2018). This has been explained through Stephen Paget's "seed and soil" hypothesis and James Ewing's "mechanical hypothesis." The "seed and soil" hypothesis suggests that tumor cells (seeds) grow and breed selectively in a conducive microenvironment (soil) for its growth (Langley and Fidler, 2011). Meanwhile, the mechanic hypothesis shows that the pattern of blood flow circulation determines a certain place for tumor cell's growth. In the circulation, circulating tumor cells (CTCs) will move following the blood circulation and then get caught in the narrow blood capillaries, then they will undergo extravasation to form micrometastasis in a certain (secondary) area such as bone, brain, liver, and lungs (Chaudhuri, Low and Lim, 2018).

The biological mechanism of a metastasis process is highly complex. Three important processes take place when tumor cells spread to tissues, namely tumor cell adhesion to basement membrane, local proteolysis in membrane, and cell movement through membrane and extracellular matrix (ECM). Under normal circumstance, if the cells are released from the extracellular matrix, it will experience a cell death process (anoikis), yet in the metastatic tumor cells, the anoikis process fails to occur, allowing the cells to keep on growing and developing (Kasper et al., 2015). Another equally important process in the metastasis process of cancer cells in epithelium is epithelial-mesenchymal transition (EMT). In EMT, cells lose their epithelial nature and changes into mesenchymal ones. Normally, this process usually occurs during the development process of an embrio, cells migrate to their respective places in the embrio. This process also occurs during wound healing, tissue regeneration, and fibrotic reaction (Lamouille,

Xu and Derynck, 2014). In a normal condition, when this process completes, the cells undergoing EMT will stop proliferating, yet the metastasized malignant tumor cells make use of EMT process as an important step in the metastasis process by maintaining the capacity to proliferate continuously/uncontrolled (Heerboth et al., 2015; Singh et al., 2017). The tumor cells successfully penetrating into the circulation, then migrate to find secondary place or tissue which support them to grow and develop. The metastasis process by making use of EMT process has begun before the tumor cells can be detected by histologic examination in primary tissues (Rhim et al., 2012). These cells can evade from the host immune cell detection and induce new blood growth. Tumor cells have the ability to survive and develop in a new environment (secondary tissue) and the host-tumor interaction significantly determines the final product of this metastasis process (Heerboth et al., 2015; Kasper et al., 2015; Moses et al., 2018).

ROLE OF IL-6 IN METASTASIS PROCESS OF CANCER CELLS

Interleukin 6 (IL-6) (previously referred to as interferon beta-2) is a cytokine produced by activated T and B cells, monocyte, fibroblast, and active macrophage cells. IL-6 is a pleiotropic cytokine which has many functions. IL-6 is pro-inflammatory, with an important effect on adaptive immunity, particularly after T and B cell activations. IL-6 induces the final step of B lymphocyte development in the peripheral into plasma cells(Yoshimoto and Yoshimoto, 2014; Hunter and Jones, 2015). IL-6 also plays a role in producing acute phase protein in liver cells, developing neurons, maturing megakaryocytes, activating osteoclast, proliferating keratinocyte, mesangial cells, and myeloma/plasmacytomas, as well as wound healing (Dembic, 2015).

IL-6 together with some cytokines and other factors are suspected to play a role in pathogenesis of postmenopausal osteoporosis, Castleman disease, multiple myeloma, and pituitary adenoma. IL-6 gene is also constitutively found active in a number of tumors such as cardiac myxoma, cervical and kidney cancer, prostate cancer, and bladder cancer (Taniguchi and Karin, 2014; Yoshimoto and Yoshimoto, 2014). High serum IL-6 concentration is correlated with the development of this disease. IL-6 at high concentration is also found in serum of patients with lungs and liver metastasis, indicating that this cytokine can also plays an important role in metastasis (Dembic, 2015).

Research by Jayatilaka (2017) shows that IL-6 together with IL-8 play a role in the cell migration process in tumor cells. IL-6 or IL-8 alone cannot induce this tumor cell migration, even at high concentration. This research also finds that the signaling path through IL-6/IL-8 is associated with and strengthened by cell proliferation and density, where the cells get more motile as the cell density increases. This is proven by an increase in Signal transducer and activator of transcription 3 (STAT3) two-fold more than in tumor cells with high density as compared to cells with low density (Jayatilaka et al., 2017). STAT3 is a transcription factor activated when there are stimuli from IL-6/IL-8. This transcription factor plays a role in the development process of cancer (Yu et al., 2014).

In addition, the research conducted by Hou et al., (2018) also shows that IL-6 is found to increase in 83.9% breast cancer tissue with negative estrogen (ER-) than with adjacent normal tissues. IL-6 triggers cancer cells to migrate by activating the Hippo kinase signaling which then causes phosphorylation and inactivation in the coactivator transcriptional factor of YES-associated protein (YAP), where the Hippo-YAP signaling has been known to cause proliferation and migration of breast cancer cells (Chen et al., 2012; Hou et al., 2018).

The study conducted by Razildo et al., (2018) also indicates the proinflammatory cytokine effect of IL6 in the development and migration of pancreatic cancer cells. In that research, it is found that IL-6 causes cancer metastasis process, through the activation of JAK2 and STAT3 which then will activate cell division cycle GTPase 42 (CDC42), resulting in the formation of pre-migratory filopodia. IL-6 signaling also activates pro-invasive GTPase signaling, which will then perform priming to the tumor cells to metastasize. CDC42 activation is needed in (IL-6-induced) cancer metastasis process since blocking CDC42 activity renders the cells insensitive to pro-invasive IL-6 effect (Razidlo, Burton and Mcniven, 2018).

Qin et al., (2018) found on their research on head and neck cancer (HNC) that IL-6 secreted by cancer-associated fibroblasts (CAFs) can trigger the induction of neoplastic Osteopontin (OPN). OPN is a protein similar to chemokin and plays a crucial role in proliferation and metastasis of various cancers. Thus, during the interaction between fibroblasts and cancer cells, increased neoplastic OPN induced by IL-6 stroma accelerate the growth, migration and invasion of cancer cells (Qin et al., 2018).

IL-6, either alone or with its interaction with another molecule (IL-8), can induce and trigger the migration of tumor cells in primary tumor organ to a secondary organ or tissue. IL-6 plays a role in many

ways and involves a complicated signaling process, depending on the type of cancer itself.

ROLE OF IL-8 IN METASTASIS PROCESS OF CANCER CELLS

IL-8 is the old name of chemokine CXCL1 (chemokin CXC group). CXCL1 is also known as: Growth Regulated Protein-α (GRO-α); Melanoma Growth Stimulatory Activity-α (MGSA-α); Macrophage Inflammatory Protein-2α (MIP-2α); mKC; NAP-3; GRO-1; and rCINC. CXCL1 serves to draw and activate neutrophils and basophils. CXCL1 is classified into the same group as CXCL2 and CXCL3. CXCL1 has 2 main receptors, namely CXCR1, CXCR2 receptors (Qin et al., 2018).

As mentioned earlier, IL-8 together with IL-6 can trigger migration of tumor cells to secondary organs or tissues by activating STAT3 transcription path (Jayatilaka et al., 2017). Another study also shows that IL-8 can trigger the migration of ovarian tumor cell in women to adipocyte cells in the omentum, despite the unknown mechanism yet (Nieman et al., 2011).

Another research indicating the role played by IL-8 in tumor cell migration is conducted by Jia (2018). In his research, it is shown that the level of IL-8 in cervical cancer tissues increases significantly than in normal uterine cervical tissue, and the efficiency of cell migration and proliferation given with exogenous IL-8 increases, compared to the one not added with IL-8 (Jia et al., 2018).

The role of IL-8 in tissue migration and invasion by tumor cells can happen through IL-8 signaling path activation which will then induce the activation of NFκB transcription factor, which then will increase the level of hypoxia inducible factor-1α (HIF-1α) significantly and this HIF-1α can induce the process of tumor cell migration (Feng et al., 2018). These evidences indicate that IL-8 can induce the process of tumor cell migration. The paths used by IL-8 in inducing the migration of tumor cells are highly varied, and it is possible for new paths used by IL-8 to induce the process tumor cell migration to be found.

ROLE OF TNF-α IN METASTASIS PROCESS OF CANCER CELLS

Tumor necrosis factor alpha (TNF-α) is a cytokine which belongs to necrosis factor superfamili (TNFSF) group with more than 20 members, including FasL and CD40L molecules. TNF-α is secreted/ produced by activated macrophage cells (Dembic, 2015). TNF-α is initially known as Cachexin. This is based on its ability to destroy tumor cells in a wide range in vitro and in experimented animal (Caminero, Comabella and Montalban, 2011). TNF-α is the main regulator in a complex interaction between inflammation and cancer. Interestingly, despite its ability to destroy tumor cells, TNF-a also plays an important role in tumor proliferation, migration, invasion and angiogenesis (Wu and Zhou, 2010).

TNF-α plays a role in the migration of tumor cells in many ways. One of them is by increasing the regulation of C-C chemokine receptor 7 (CCR7). CCR7 is a CCL21 chemokine receptor. CCR7 is expressed in various immune cells which migrate in lymphoid tissue. TNF-α existing in a tumor tissue induce the activation of CCR7 in tumor cells through the phosphorylation of extracellular signal-regulated kinases (ERK). Afterwards, the interaction between CCL21 and CCR7 causes the phosphorylation of protein kinase p38 which will then induce the migration of those tumor cells (Maolake et al., 2018).

Another study also shows the role of TNF-α in the migration process of tumor cells by activating tumor-associated calcium signal transduction protein-2 (TROP-2) through ERK1/2 signaling path. TROP-2 is a protein commonly found in intestinal tumor tissue. This protein can make tumor cells more aggressive and might increase the invasion and migration ability of these tumor cells, even though the mechanism underlying it remains unknown and still needs further research (Zhao and Zhang, 2018).

The research conducted by Ray (2017) also indicates the effect of TNF-α on tumor cells. In his research, TNF-α together with other pro inflammatory cytokine (IL-1β and IL-6) play the main role in the migration process of tumor cells. This pro inflammatory cytokine is formed as a result of the active MAPK-activated protein kinase 2 (MK2) signaling path, where this MK2 is the main contributor of inflammation process in colorectal cancer (CRC) (Ray et al., 2017).

CONCLUSION

Various complicated cell signaling mechanisms are involved in the migration process of tumor cells in primary organs to other (secondary) organs or tissues. Signaling paths are activated by numerous molecules, including cytokine IL-6, IL-8, and TNF-α. Many studies have proven the role of these three in inducing the migration process (metastasis) of tumor cells which results in severer journey of this disease. Nevertheless, further research is still needed on the working mechanism of these cytokines to allow these molecules to be targeted by cancer therapy or medication to prevent the cancer from metastasizing

and acting other organs which causes an increased severity of the cancer disease itself.

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REFERENCES

Caminero, A., Comabella, M. and Montalban, X. (2011) 'Tumor necrosis factor alpha (TNF- α), anti-TNF- α and demyelination revisited: An ongoing story', Journal of Neuroimmunology. Elsevier B.V., 234(1–2), pp. 1–6. doi: 10.1016/j.jneuroim.2011.03.004.

Chaffer, C. L. and Weinberg, R. A. (2011) 'A Perspective on Cancer', Science, 331, pp. 1559–1565.

Chaudhuri, P. K., Low, B. C. and Lim, C. T. (2018) 'Mechanobiology of Tumor Growth', Chemical Reviews. American Chemical Society, 118, pp. 6499–6515. doi: 10.1021/acs.chemrev.8b00042.

Chen, D. et al. (2012) 'LIFR is a breast cancer metastasis suppressor upstream of the Hippo-YAP pathway and a prognostic marker', Nature Medicine, 18(10), pp. 1511–1517. doi: 10.1038/nm.2940.

Clevers, H. (2011) 'Review the cancer stem cell: Premises , promises and challenges', Nature Medicine. Nature Publishing Group, 17(3), pp. 313–319. doi: 10.1038/nm.2304.

Dembic, Z. (2015) The Cytokines of the Immune System: The Role of Cytokines in Disease Related to Immune Response. USA: ELSIVIER.

Dicato, M. A. and Cutsem, E. Van (2018) Side Effects of Medical Cancer Therapy. 2nd edn. Switzerland: Springer International Publishing AG.

Feng, W. et al. (2018) 'HIF-1 α promotes the migration and invasion of hepatocellular carcinoma cells via the IL-8 – NF- κ B axis', Cellular & Molecular Biology Letters. Cellular & Molecular Biology Letters, 23(26), pp. 1–8. doi: 10.1186/s11658-018-0077-1.

Gong, J. et al. (2018) 'Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations', Journal for ImmunoTherapy of Cancer. Journal for ImmunoTherapy of Cancer, 6(1), pp. 1–18. doi: 10.1186/s40425-018-0316-z.

Hanahan, D. and Coussens, L. M. (2012) 'Accessories to the Crime: Functions of Cells Recruited to the Tumor Microenvironment', Cancer Cell. Elsevier Inc., 21(3), pp. 309–322. doi: 10.1016/j.ccr.2012.02.022.

Hanahan, D. and Weinberg, R. A. (2011) 'Review Hallmarks of Cancer: The Next Generation', Cell. Elsevier Inc., 144(5), pp. 646–674. doi: 10.1016/j.cell.2011.02.013.

Heerboth, S. et al. (2015) 'EMT and tumor metastasis', Clinical and Translational Medicine, 4(6), pp. 1–13. doi: 10.1186/s40169-015-0048-3.

Hou, L. et al. (2018) 'IL-6 Triggers the Migration and Invasion of Oestrogen Receptor Negative Breast Cancer Cells via Regulation of Hippo Pathways', Basic & clinical pharmacology & toxicology, (January). doi: 10.1111/bcpt.13042.

Hunter, C. A. and Jones, S. A. (2015) 'IL-6 as a keystone cytokine in health and disease', Nature Publishing Group. Nature Publishing Group, 16(5), pp. 448–457. doi: 10.1038/ni.3153.

Ichim, G. and Tait, S. W. G. (2016) 'A fate worse than death: apoptosis as an oncogenic process', Nature Review. Nature Publishing Group, 16(8), pp. 539–548. doi: 10.1038/nrc.2016.58.

Jayatilaka, H. et al. (2017) 'Synergistic IL-6 and IL-8 paracrine signalling pathway infers a strategy to inhibit tumour cell migration', Nature Communications. Nature Publishing Group, 8, pp. 1–12. doi: 10.1038/ncomms15584.

Jia, L. et al. (2018) 'IL - 8 is upregulated in cervical cancer tissues and is associated with the proliferation and migration of HeLa cervical cancer cells', Oncology Letters, 15, pp. 1350–1356. doi: 10.3892/ol.2017.7391.

Karaman, S. et al. (2014) 'Mechanisms of lymphatic metastasis Find the latest version: Review series Mechanisms of lymphatic metastasis', The Journal of Clinical Investigation, 124(3), pp. 922–928. doi: 10.1172/JCI71606.922.

Kasper, D. L. et al. (2015) Harrison's Principle of Internal Medicine 19th ed. Edited by D. L. Kasper et al. New York: Mc Graw Hill Education.

KEMENKES (2013) Riset Kesehatan Dasar 2013. Jakarta: Badan Penelitian Dan Pengembangan Kesehatan RI.

Kidd, S. et al. (2012) 'Origins of the Tumor Microenvironment: Quantitative Assessment of Adipose-Derived and Bone Marrow – Derived Stroma', PLoS ONE, 7(2). doi: 10.1371/journal.pone.0030563.

Lamouille, S., Xu, J. and Derynck, R. (2014) 'Molecular mechanisms of epithelial – mesenchymal transition', Nature Publishing Group. Nature Publishing Group, 15(3), pp. 178–196. doi: 10.1038/nrm3758.

Langley, R. R. and Fidler, I. J. (2011) 'The seed and soil hypothesis revisited — The role of tumor-stroma interactions in metastasis to different organs', International Journal of Cancer, 2535, pp. 2527–2535. doi: 10.1002/ijc.26031.

Liu, D. (2018) Tumors and Cancers: Head–Neck–Heart–Lung–Gut. Boca Raton: CRC Press, Taylor & Francis Group.

Liu, H. and Lathia, J. D. (2016) Cancer Stem Cells: Targeting the Roots of Cancer, Seeds of Metastasis, and Sources of Therapy Resistance. London: ELSIVIER.

Maolake, A. et al. (2018) 'Tumor necrosis factor- a induces prostate cancer cell migration in lymphatic metastasis through CCR7 upregulation', Cancer science, 109, pp. 1–8. doi: 10.1111/cas.13586.

Marusyk, A. and Polyak, K. (2010) 'Tumor heterogeneity: Causes and consequences', BBA - Reviews on Cancer. Elsevier B.V., 1805(1), pp. 105–117. doi: 10.1016/j.bbcan.2009.11.002.

Medina-ramirez, C. M. et al. (2011) 'Apoptosis Inhibitor ARC Promotes Breast Tumorigenesis , Metastasis , and Chemoresistance', Tumor and Stem Cell Biology, 16, pp. 7705–7715. doi: 10.1158/0008-5472.CAN-11-2192.Apoptosis.

Moses, C. et al. (2018) 'Hallmarks of cancer: The CRISPR generation', European Journal of Cancer. Elsevier Ltd, 93, pp. 10–18. doi: 10.1016/j.ejca.2018.01.002.

National Cancer Institute (2018) 'Types of Cancer Treatment'.

Nieman, K. M. et al. (2011) 'letterS Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth', Nature Medicine, 17(11), pp. 1498–1503. doi: 10.1038/nm.2492.

Qin, X. et al. (2018) 'Cancer-associated Fibroblast-derived IL-6 Promotes Head and Neck Cancer Progression via the Osteopontin-NF-kappa B Signaling Pathway', Theranostics, 8(4), pp. 921–940. doi: 10.7150/thno.22182.

Ray, A. L. et al. (2017) 'This article is protected by copyright. All rights reserved.', International Journal of Cancer, pp. 1–33.

Razidlo, G. L., Burton, K. M. and Mcniven, M. A. (2018) 'Interleukin-6 promotes pancreatic cancer cell migration by rapidly activating the small GTPase CDC42', JBC, (3). doi: 10.1074/jbc.RA118.003276.

Rhim, A. D. et al. (2012) 'EMT and Dissemination Precede Pancreatic Tumor Formation', Cell, 148(1–2), pp. 349–361. doi: 10.1016/j.cell.2011.11.025.

Singh, M. et al. (2017) 'EMT: mechanisms and therapeutic implications Mohini', Pharmacology and Therapeutics. Elsevier Inc. doi: 10.1016/j.pharmthera.2017.08.009.

Skvortsov, S. et al. (2014) 'Crosstalk between DNA repair and cancer stem cell (CSC) associated Intracellular pathways', Seminars in Cancer Biology. Elsevier Ltd. doi: 10.1016/j.semcancer.2014.06.002.

Su, S. et al. (2016) 'Cancer metastasis: mechanisms of inhibition by melatonin', Journal of pineal research, 62(1). doi: 10.1111/jpi.12370.

Taniguchi, K. and Karin, M. (2014) 'IL-6 and related cytokines as the critical lynchpins between inflammation and cancer', Seminars in Immunology. Elsevier Ltd, 26(1), pp. 54–74. doi: 10.1016/j.smim.2014.01.001.

World Health Organization (WHO) (2018) Cancer. Available at: www.who.int/cancer/en/.

Wu, Y. and Zhou, B. P. (2010) 'TNF- a / NF- k B / Snail pathway in cancer cell migration and invasion', British Journal of Cancer, 102, pp. 639–644. doi: 10.1038/sj.bjc.6605530.

Yang, L., Pang, Y. and Moses, H. L. (2010) 'TGF- b and immune cells: an important regulatory axis in the tumor microenvironment and progression', Trends in Immunology. Elsevier Ltd, 31(6), pp. 220–227. doi: 10.1016/j.it.2010.04.002.

Yoshimoto, T. and Yoshimoto, T. (2014) Cytokine Frontiers: Regulation of Immune Response in Health and Disease. Tokyo: Springer Japan. doi: 10.1007/978-4-431-54442-5.

Yu, H. et al. (2014) 'Revisiting STAT3 signalling in cancer: new and unexpected biological functions', Nature Publishing Group. Nature Publishing Group, 14(11), pp. 736–746. doi: 10.1038/nrc3818.

Zhao, P. and Zhang, Z. (2018) 'TNF- α promotes colon cancer cell migration and invasion by upregulating TROP-2', Oncology Letters, pp. 3820–3827. doi: 10.3892/ol.2018.7735.