Histol Histopathol (2019) 34: 125-136

http://www.hh.um.es

Histology and Histopathology

From Cell Biology to Tissue Engineering

Review

Interleukin-6: a molecule with complex biological impact in cancer

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Summary. Interleukin-6 is a multifaceted cytokine, usually reported as a pro-inflammatory molecule. However, certain anti-inflammatory activities were also attributed to IL-6. The levels of IL-6 in serum as well as in other biological fluids are elevated in an age-dependent manner. Notably, it is consistently reported also as a key feature of the senescence-associated secretory phenotype. In the elderly, this cytokine participates in the initiation of catabolism resulting in, e.g. sarcopenia. It can cross the blood-brain barrier, and so it is in causal association with, e.g. depression, bipolar disorder, schizophrenia, and anorexia. In the cancer patient, IL-6 is produced by cancer and stromal cells and actively participates in their crosstalk. IL-6 supports tumour growth and metastasising in terminal patients, and it significantly engages in cancer cachexia (including anorexia) and depression associated with malignancy. The pharmacological treatment impairing IL-6 signalling represents a potential mechanism of anti-tumour therapy targeting cancer growth, metastatic spread, metabolic deterioration and terminal cachexia in patients.

Key words: Cancer microenvironment, Cytokine, Interleukin-6, Cancer, Cachexia, Anorexia, Depression

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DOI: 10.14670/HH-18-033

Introduction

The incidence of cancer is increasing worldwide. This trend is naturally associated with the ageing of the population, more apparent in the developed countries. This increasing burden of cancer can be influenced by numerous factors of our civilisation including environmental pollution and unhealthy lifestyle. Nevertheless, reduction of gene-repair activity of our cells appears at the age of 50 years and higher, and it can further enhance the detrimental effect of the abovementioned harmful factors. Briefly, longevity represents an increased risk to develop a malignant disease (Smetana et al., 2016, 2018). Thus, according to scientifically-based prognosis, every second citizen of central Europe is at risk of developing a tumour at least once in his life. A More or less similar situation is expected in other parts of the world. This worrisome perspective requires urgent action to develop a new generation of antitumour therapy.

A tumour of any type is not formed exclusively by genetically altered cancer cells. In a closer view, it resembles a highly complicated ecosystem. Besides the cancer cells, various supporting populations are actively participating in the formation of this growing tumour mass. The list of involved cell population includes, but is not limited to, activated stromal fibroblasts, endothelial cells and numerous types of immune cells (Lacina et al., 2018). Once involved in tumour growth, the functionality of these genetically non-altered cellular populations diverges strikingly from the expected one. Thus, e.g. cancer-associated fibroblasts are not any more

innocent bystanders, and they are not equal to the normal tissue fibroblast (Szabo et al., 2013). These cells and their products such as interleukins represent a potential target for anticancer therapy (Gál et al., 2017). IL-6 is recognised as an essential agent in the context of cancer microenvironment. It can be produced by either cancer cells as well as by non-cancerous cells of the tumour ecosystem (Coward and Kulbe, 2012; Fisher et al., 2014; Lacina et al., 2015).

IL-6 and its receptor

IL-6 is a glycoprotein composed of 184 amino acids (MW 23,7 kDa). IL-6 is produced by many cell types of the immune system and also by non-immune cells including, e.g. muscle cells. IL-6 receptor (IL-6R) is also expressed by a great variety of cell types (Yamasaki et al., 1988). IL-6R is a transmembrane protein forming a complex with another transmembrane molecule, the glycoprotein gp130. Binding of IL-6 to IL-6R activates gp130 that consequently serves as a signal transducer (Fig. 1). IL-6 also binds to a soluble form of IL-6R (IL-6Rs). IL-6Rs is cleaved from its intramembrane domain by a membrane-bound protease, ADAM17 (Rose-John, 2013; Scheller et al., 2014). After shedding from the membrane, IL-6Rs interacts with IL-6 and forms complex with gp130. This complex later docks on the cell membrane. The signal transduction from gp130 via STAT (in-)dependent mechanism is thus initiated (Wolf et al., 2014; Schaper and Rose-John, 2015). IL-6 is generally considered to be a pro-inflammatory cytokine. Indeed, it is a potent inducer of the acute phase response. However, the IL-6 effect is more pleiotropic, and it also depends on the activity of ADAM17. The outcome of activation of the membrane-cleaved soluble IL-6Rs is pro-inflammatory. On the contrary, the membrane-bound IL-6R seems to be more linked to anti-inflammatory effects. IL-6R thus also appears to be pro-cancerogenic (Scheller et al., 2014). This receptor functional duality suggests the importance of ADAM17 and predisposes IL-6R as a target for potential therapeutic manipulation for the treatment of autoimmune disease and cancer (Moss and Minond, 2017).

Ageing

Numerous health problems accompany the course of ageing. Conditions such as visual and hearing deterioration, atrophy of the dermis, subcutaneous tissue, reduction of bone mass leading to fragility, sarcopenia, cardiovascular diseases, cognitive impairment, cancer and cachexia are common. The actual molecular mechanisms of these ageing-related morbidities are under extensive research (Ahmad, 2018). Surprisingly, IL-6 is present as a key player in virtually all the abovementioned pathologies. The "simple ageing effect" is here often combined and enhanced by the inflammatory mechanisms. This is not merely a coincidence. Therefore the concept of "inflammaging" was coined (Franceschi et al., 2007). Of note, the tissue environment including increased IL-6 level seems to be almost universally associated with the elderly (Puzianowska-Kuznicka et al., 2016; Lee et al., 2017). This phenomenon can be influenced by, e.g. ethnicity (Lima-Costa et al., 2015, 2017) and also by personal hormonal status (Campesi et al., 2016; Sebastiani et al., 2016). This increase of IL-6 predisposes old people for asthma and other respiratory disorders (Cho et al., 2015), increased risk of cardiovascular problems (Nadrowski et al., 2016) as well as osteoarthritis (Pearson et al., 2017). High serum level of IL-6 -strongly correlates with the functional impairment in aged individuals (Adriaensen et al., 2014) and predicts their hospitalisation and even mortality (Adriaensen et al., 2015; Minciullo et al., 2016). Interestingly, low socioeconomic status during childhood is linked to an increased level of IL-6 in the elderly (Lin et al., 2017). Conversely, IL-6 level is reduced in the elderly by memory-training programs (Pesce et al., 2017).

These data collectively indicate that IL-6 elevation is

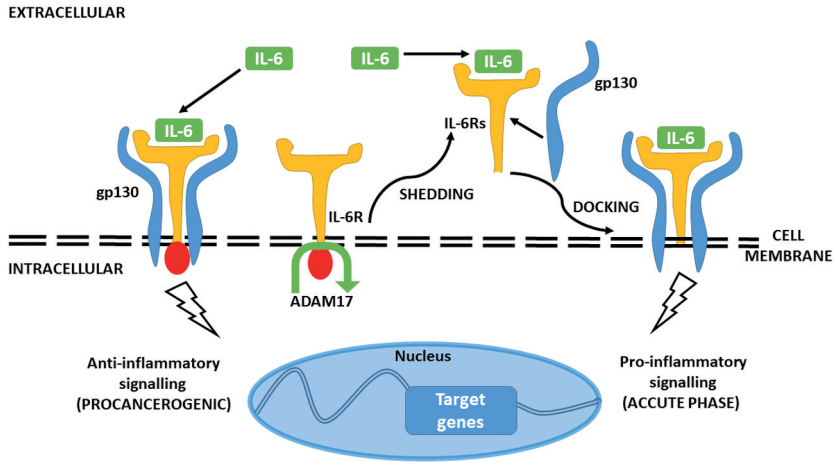

Fig. 1. IL-6R is a transmembrane protein forming a complex with the glycoprotein gp130. The signal transduction from gp130 via STAT (in-)dependent mechanism is thus initiated. IL-6Rs is cleaved from its intramembrane domain by a membrane-bound protease, ADAM17. IL-6 also binds to this soluble form (IL-6Rs). The outcome of activation of the membrane-cleaved soluble predominantly IL-6Rs is pro-inflammatory. The membrane-bound IL-6R seems to be more linked to anti-inflammatory effects.

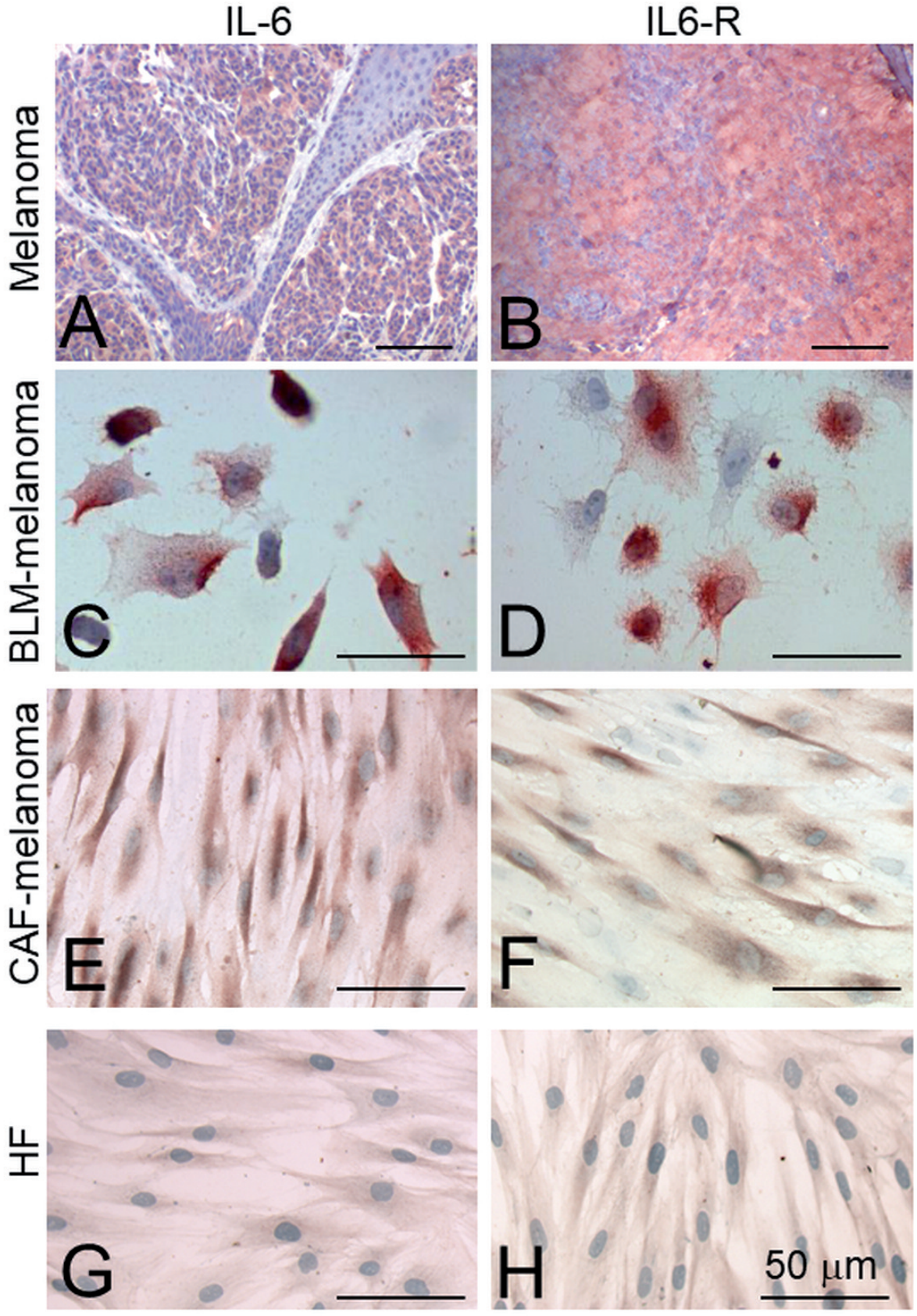

Fig. 2. Detection of IL-6 **(A, C, E, G)** and IL-6R **(B, D, F, H)**, in nodular type of malignant melanoma from human patient **(A, B)**, cultured human BLM melanoma cells **(C, D)**, human cancer-associated fibroblasts (CAF) isolated from melanoma **(E, F)** and normal human dermal fibroblasts (HF) **(G, H)**. Nuclei are counterstained by hematoxylin. Scale bars: 50 µm.

a component of the complex of mild pro-inflammatory milieu associated with ageing and that it can influence the general functional status in old individuals.

Mental health

Multidirectional interactions between the nervous and immune systems have been documented. The blood-brain barrier is permeable for certain pro-inflammatory cytokines including IL-6 (Na et al., 2014). This allows the direct participation of circulating cytokines such as IL-6 in mental disease. The level of IL-6 significantly increases in persons suffering from depression. Patients suffering from a severe inflammatory condition such as osteoarthritis with the significantly upregulated level of IL-6 also frequently exhibit depressive symptoms (Shimura et al., 2017).

The upregulated IL-6 in depressive patients may reflect the psychical trauma in childhood (Grosse et al., 2016) and also posttraumatic stress (Bob et al., 2010; de Oliveira et al., 2018). High IL-6 after delivery is associated with e.g. maternal depression during the six months post-partum (Liu et al., 2016). IL-6 also seems to have some relation to fatigue syndrome (Rich et al., 2017). A similar finding was observed in elderly patients with cognitive defects (Fan et al., 2016; Ali et al., 2018) and bipolar disorder patients (Grande et al., 2014; Luo et al., 2016). Elevated serum level of IL-6 was also observed in schizophrenia (Kunz et al., 2011; Strzelecki et al., 2018).

Murine models demonstrated that IL-6 influences hypothalamic serotonin turnover resulting in the development of anorexia (Dwarkasing et al., 2016). Very similar data were obtained from clinical material from anorexia in humans (Ostrowska et al., 2015).

These neuropsychiatric disorders demonstrating the influence of IL-6 on depression, bipolar disease and anorexia are very important for oncological research because depression and anorexia represent a severe complication of the malignant disease.

Elderly sarcopenia and cancer cachexia

In non-immune context, IL-6 also acts as an important myokine. It is released after muscle contraction and has multiple metabolic (systemic) effects, e.g. increases the breakdown of deposited fat from adipous tissue and also helps to improve peripheral insulin resistance. Surprisingly, the inflammatory factors including IL-6 seem to employed in the initiation and progression of sarcopenia in elderly (Bian et al., 2017). Moreover, these proinflammatory cytokines also lead synergistically to obesity, insulin resistance, mitochondrial dysfunction and support reactive oxygen radicals action to muscular tissue and sarcopenia initiation (Fan et al., 2016). IL-6 together with other factors, namely TNFα and IL-1, stimulate initiation of cancer cachexia (Narsale and Carson, 2014; Patel and Patel, 2017). STAT3 is an important component of IL-6 signalling cascade and influences lipolysis and browning of white adipocytes. STAT3 also impairs the function of hepatocytes, contributes to myofiber atrophy - the metabolic steps important for cancer cachexia (Zimmers et al., 2016). As mentioned in the paragraph focusing on the effect of IL-6 on the brain, the hypothalamus controls food intake. The described metabolic function of IL-6 harmonises with anorexia that is important for both the terminal stages of malignant disease and elders in terminal stages of life, where the level of IL-6 is also elevated.

Cancer

IL-6 concentration is significantly increased in serum and other biological fluids in patients suffering from multiple types of cancer (Sato et al., 2016) (Table. 1). The actual IL-6 level well correlates with some tumour stage and survival of cancer patients (Suh et al., 2013; Lippitz and Harris, 2016). This elevation of IL-6 level detectable in biological fluids indicates the role of IL-6 in tumour biology and also presumably use of IL-6

Table 1. Examples of human malignant tumors with elevated IL-6 in biological fluids.

Cancer	Reference
Ovary	Lane et al., 2011; Dobrzycka et al., 2013; Wouters et al., 2015
Prostate	Kuroda et al., 2007; Codony-Servant et al., 2013; Milicevic et al., 2014; Nguyen et al., 2014
Breast	Goswami et al., 2013; König et al., 2016; Noman et al., 2017; Wang and Yang, 2017
Liver	Wong et al., 2009; Kim et al., 2013; Sheng et al., 2015; Shao et al., 2017
Oral cavity, head and neck	Duffy et al., 2008; Brailo et al., 2012; Lofti et al., 2015; Zhang et al., 2017
Esophagus	Hardikar et al., 2014; Krzystek-Korpacka et al., 2008
Stomach	Ikeguchi et al., 2009; Lukaszewicz-Zajac et al., 2011; Necula et al., 2012
Colorectal	Knüpfer and Preiss, 2010; Li et al., 2014a,b; Shiga et al., 2016; Xu et al., 2016
Pancreas	Fujiwara et al., 2014; Miura et al., 2015; Yako et al., 2016; Kim et al., 2017a,b
Larynx	Hao et al., 2013; Nikakhlagh et al., 2015
Lung	Ujiie et al., 2012; Liao et al., 2014; Shang et al., 2017; Ding et al., 2018
Thyroid	Kobawala et al., 2016
Melanoma	Mouwad et al., 2002; Tas et al., 2005; Sinnya and De' Ambrosis, 2013
Bone sarcoma	Rutkowski et al., 2003; Kushlinski et al., 2014

as a biomarker.

IL-6 seems to participate in the maintenance of low-grade differentiation status of malignant cells in squamous and colorectal carcinoma (Kolář et al., 2012; Holmer et al., 2015). It enhances the epithelial-mesenchymal transition of cancer cells (Bharti et al., 2016). IL-6 supports the proliferation and/or migration and *in vitro* invasion of trophoblastic carcinoma cells (Jovanovic and Vicovac, 2009), melanoma cells (Jobe et al., 2016, 2018), prostate cancer cells (Santer et al., 2010) and head and neck cancer cells (Kanazawa et al., 2007). Of note, the IL-6 molecule is not produced only by cancer cells. IL-6 production by, e.g. cancer-associated fibroblasts, was clearly documented (Kolář et al., 2012; Jobe et al., 2016, 2018; Subramanian et al., 2016; Wang et al., 2017; Wu et al., 2017) (Fig. 2). Macrophages also represent another fundamental cell type participating in crosstalk between cancer cells and tumour microenvironment via IL-6 release (Wolfe et al., 2016).

Other simultaneously acting molecules can also antagonise this multilateral interaction between cellular populations of tumour stroma. This phenomenon can be exemplified by, e.g., activation of the estrogen receptor α in cancer-associated fibroblasts. Estrogen receptor activation consequently reduces production of IL-6 and CCL5. Such a decreased level of these molecules results in inhibition of invasiveness in prostate cancer cells (Yeh et al., 2016). This observation demonstrates the multifaceted nature of tumour microenvironment and complex equilibrium between its components.

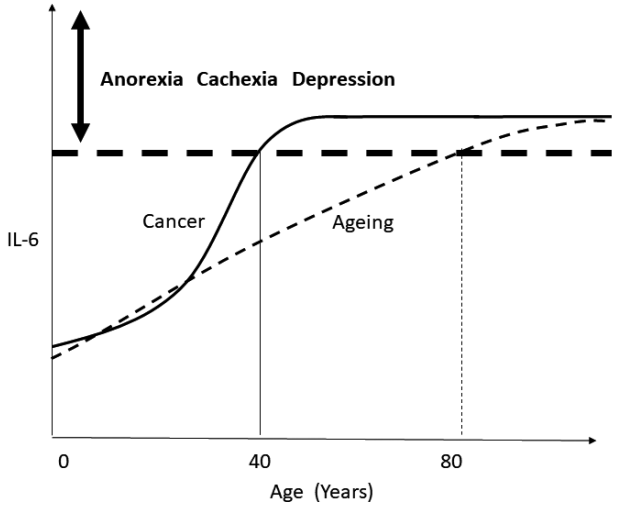

Fig. 3. Schematic correlation between ageing and the serum level of IL-6 (dashed line). When serum level of IL-6 is highly elevated above threshold (dashed bold line), the serious psychic and metabolic problems can occur. Malignant disease elevates production of IL-6 (continuous line) that can initiate fatal metabolic deterioration and anorexia in a cancer patient with accompanying depression in advanced disease.

The production of a set of bioactive molecules, including IL-6, seems to participate collectively in acquired resistance of BRAF mutated melanoma cells to Vemurafenib (Kodet et al., 2018). Downregulation of the IL-6 gene activity by miR-98 suppresed the metastatic behaviour of melanoma in an animal experiment (Li et al., 2014a,b). Similarly, p53-dependent expression of miR-34a suppresses the progression of colorectal cancer via inhibition of IL-6R/STAT3/mi-34a feedback (Rokavec et al., 2014).

Cancer stem cells are very resistant to anticancer therapy, and they are also crucial for a tumour metastasising. The stimulatory effect of IL-6 produced by endothelium on the migration of cancer stem cells can enhance the risk of metastatic spread of the disease (Kim et al., 2017a,b). Further, the increased level of IL-6 facilitates cancer cell metastasising to bone (Ara and DeClerck, 2010). High expression of IL-6 well predicts a poor response to chemoradiotherapy in oral squamous cell carcinoma and also in non-small cell lung cancer (Duan et al., 2015; Jinno et al., 2015). In IL-6 knockout mice model, the spontaneous immune response to cancer improves compared to wildtype and also immunotherapy is more efficient(Ohno et al., 2017).

The similar features of granulation tissue occurring during wound healing and tumour microenvironment were documented (Lacina et al., 2015; Gál et al., 2017). In this context, IL-6 is an essential factor for proper wound healing (Sugawara et al., 2001; Ebihara et al., 2011). IL-6 stimulates proliferation and migration in normal keratinocytes (reepithelization) and has similar effects also in biliary epithelial cells (Gallucci et al., 2004; Hernández-Quintero et al., 2006; Jiang et al., 2010). Based on regular clinical experience, the healing in patients who have diabetes is slow and frequently inefficient. It is not surprising that the IL-6/STAT3 axis dysregulation was observed in experimental animals models of diabetes (van de Vyver et al., 2016). These detailed observations of wound repair further suggest the role of IL-6 in cancer progression.

IL-6 seems to stimulate both the proliferation and invasiveness of cancer cells which are important for metastasising, the most severe complication of the malignant disease. However, this interleukin also significantly influences the metabolism in cancer patients by induction of cancer cachexia/wasting. This adverse effect is further intensified by the influence of IL-6 on the central nervous system where IL-6 is responsible for anorexia and depression of cancer patient. This effect of IL-6 signalisation is also typical for the advanced elderly. From this point of view, therapeutic inhibition of the IL-6/IL-6R/IL-6Rs could be beneficial for patients (Fig. 3).

Anti-IL-6/IL-6R therapy

Tumour-related interleukins represent a broad target field for anti-cancer therapy (Setrerrahmane and Xu, 2017). Relevant to the IL-6 signalling, either IL-6 or its

receptor represent a potential target for the therapeutic blockade. From the technological point of view, immobilisation of IL-6 neutralising antibodies to nanoparticles can improve removal of IL-6 from circulation (Lima et al., 2018). Although the anti-IL-6 therapy was primarily intended for the treatment of autoimmune diseases such as rheumatoid arthritis, its therapeutic anti-cancer potential seems to be promising (Scheller et al., 2014; Kim et al., 2015; Schaper and Rose-John, 2015). Principally, a panel of biologics with anti-IL-6 activity (Siltuximab, Elsilimomab, Sirukumab, Olokizumab, MAb 1339, Clazakizumab, PF-04236921, MEDI 5117), anti-IL-6R activity (Tocilizumab, Sarilumab, ALX-0061, NRI) are in clinical trials or already on the market. Other compounds alternatively influencing IL-6 signalisation (SANT-7, ERBF, ERBA) and drugs with anti-gp130 activity (B-R3, B-P4, MDL-A, SC144, Raloxifene, Bazedoxifene, LMT-28) have been also already developed. At least some of them were in various stages of clinical trials (Yao et al., 2014; Ranganath et al., 2015; Rossi et al., 2015; Heo et al., 2016).

Results of clinical studies in Castleman's disease, multiple myeloma, renal tumours, as well as prostate, lung, colorectal and ovarian cancer demonstrated some clinical response, and they are under discussion (Kampan et al., 2017). Tocilizumab can inhibit metastasising of lung tumour cells and breast cancer cells to the bone in animal experiments (Noda et al., 2012; Wakabayashi et al., 2018). The same antibody also minimises vascularisation of human squamous cell carcinoma in SCID mouse (Shinriki et al., 2009).

Experimental studies demonstrated that simultaneous targeting of IL-8 could further improve the results of anti-IL-6 therapy (Kolář et al., 2012; Smetana et al., 2012; Jobe et al., 2016; Jayatilaka et al., 2017; Wirtz and Jayatilaka, 2017). This simultaneous blockade can influence low differentiation status of cancer cells and their migration as demonstrated on cells of squamous cell carcinoma, malignant melanoma, breast carcinoma and glioblastoma. Because of this strong effect on cancer cell migration, the anti-IL-6 therapy (and namely in various combinations) fulfils the criteria of inclusion to the novel category of anti-cancer therapeutics: the migrastatics (Gandalovičová et al., 2017).

IL-6 and TNF-α also exhibited a synergistic effect in autoimmune diseases and simultaneous blocking of their activities seems to be a promising option in the therapy of these diseases (e.g. rheumatoid arthritis, Crohn's disease, ulcerative colitis etc.) (Drutskaya et al., 2017). TNF-α blockade positively influences resistance of melanoma cells to anti-PD-1 therapy (Bertrand et al., 2017). The role of TNF-α on cancer cachexia and depression was also established (Fan et al., 2017; Patel and Patel, 2017). From this point of view, the combination also affecting anti-IL-6 and anti-TNF-α can be beneficial for cancer patients.

Nonsteroid anti-inflammatory drugs (such as aspirin, ASA) administration reduces the risk of several types of cancer (Qiao et al., 2018), especially of colorectal cancer (Friis et al., 2009). It also brings prolonged survival in patients suffering from this malignancy or prostate cancer (Jacobs et al., 2014; Gray et al., 2018). ASA is known to elevate the risk of gastrointestinal bleeding, but its benefit for the patients as "anticancer" drug is higher (Tsoi et al., 2018). This positive effect of ASA is based on the blockade of IL-6-STAT3 signalisation (Kim et al., 2009) and disruption of NFκB-IL-6 signalisation (Saha et al., 2016). These activities result in a reduction of biogenesis of ribosomes (Brighenti et al., 2016) and promotion of apoptosis in cancer cells (Tian et al., 2011). However, ASA also reduces production of IL-6 by cancer cells (Sotiriou et al., 1999). The combination of anti-IL-6 with nonsteroid anti-inflammatory drugs such as ASA seems to be also suitable.

Conclusion

IL-6 oriented therapy or more likely in combination with other anti-inflammatory agents can be beneficial for cancer patients because it can efficiently focus several of the essential facets of malignant disease such as tumour growth, metastasising and metabolic problems such as cachexia and psychical disorders.

Acknowledgements. This study was supported by the Grant Agency of the Czech Republic (Project no. 16-05534S), Ministry of Health of the Czech Republic (projects 15-28933A and 16-29032A), the Charles University (project No. PROGRESS Q 28) and by the Ministry of Education, Youth and Sports of Czech Republic within the National Sustainability Program II (Project BIOCEV-FAR reg. no. LQ1604), and by the project BIOCEV (CZ.1.05/1.1.00/02.0109). The authors are also grateful for the support of the League Against Cancer, Prague.

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Accepted September 4, 2018