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Editorial overview: Cancer

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Francesco Di Virgilio received his MD at the University of Padova. He was Honorary Research Assistant at the University College (London) and Visiting Fellow Scientist at Columbia University, and is currently Professor of Clinical Pathology at the University of Ferrara. His main research interest is inflammation in its multifarious aspects and implications. This led to focus his interests on inflammation and cancer and on the role that purinergic signaling plays in this contexts.

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Paolo Pinton, received his PhD at the University of Padova and is currently Professor of General Pathology at the University of Ferrara. He obtained novel, unexpected information on the role of the oncogenes and oncosuppressors in modulating Ca^{2+} homeostasis and the importance of that for their mechanism of action. More recently, Dr. Pinton is studying the signaling occurring at the MAMs, mitochondria associated membranes and the molecular identity of the mitochondrial permeability transition pore.

The latest few years have witnessed an unprecedented acceleration in the accumulation of crucial information on basic aspects of cancer cell biology suitable of a rapid transfer to the patients' bed. Understanding of cancer cell energetics has kindled novel interest in role of intracellular messengers such as Ca^{2+}, and intracellular metabolic pathways such as glycolysis and mitochondrial oxidative phosphorylation [1]. An in-depth knowledge of cancer-stem cell properties and identification of specific factors expressed in these cells has taken off the lid of a Pandora vase of exceptionally important observations on the role of factors, such as transcriptional regulators, that are likely to become new targets for cancer therapy in the near future [2]. An in depth knowledge of the specific biochemical conditions within and around solid tumors (the tumor microenvironment, TME) has allowed to identify specific pathways that are overactivated and conducive to tumor growth and metastatic spreading [3]. On the basis of the identification of these pathways, novel effective anticancer drugs (or treatments) have been developed, and more importantly a novel 'ecology' of cancer saw the light [4].

Stefano Piccolo and co-workers highlight in this issue the properties of YAP and TAZ [5], two transcriptional regulators belonging to the size-controlling Hippo signaling pathway that have been the focus of recent hot interest by cancer students [2]. These molecules are endowed with the unique ability to both install cancer-stem cell features in tumor cells and be central mediators of mechanotrasduction. Cancer cells are known to be exposed to unusual mechanical stress forces transmitted via the stiffened extracellular matrix. Under these conditions, the cell cytoskeleton undergoes a complex reorganization governed by YAP/TAZ activity, which is eventually functional for tissue invasion and metastatic spreading. YAP/TAZ are at crossroad of multiple crucial intracellular signaling pathways, thus their targeting may offer several novel options for anti-cancer therapy. YAP and TAZ are essential for transducing the oncogenic activity of mutations that occur at multiple signaling pathways. This is the case for specific cancer-associated mutations in G-protein coupled receptors (GPCRs) and G proteins that promote uveal melanoma progression by activating YAP [6]. Indeed, deep sequencing studies showed a high rate of mutations in GPCRs and G proteins across a wide panel of human tumors [7].

Among GPCR-dependent intracellular messengers, Ca^{2+} has a leading role. A dysregulation in intracellular Ca^{2+} homeostasis in cancer cells was described as early as 1944, and has been an object of intense investigation eversince [8]. Paolo Pinton and collaborators highlight the multifarious roles of Ca^{2+} in malignant transformation [9]. Intracellular Ca^{2+} affects virtually all intracellular signaling pathways and organelle structure and physiology, as well as being a key determinant of cell death, whether necrotic, apoptotic or

autophagic [10]. Recent discoveries on the molecular nature of the mitochondrial Ca^{2+} import/efflux systems [11] as well as intracellular Ca^{2+} influx pathways [12] opened a new era of Ca^{2+} signaling in different physiopathological contexts. Intracellular Ca^{2+}-releasing channels have been variably implicated in oncogenesis and in the function of oncogenes and oncosuppressor genes, besides being themselves targets for the action of miRNAs suspected of a role in cancer.

The key role of the tumor microenvironment (TME) and its profound immunosuppressive features highlight the need for a deeper understanding of the biochemical properties of this privileged tissue interstitium. It was long known that the TME is eminently hypoxic, but it is a recent acquisition that this environment is also rich in nucleosides and nucleotides, and all these features are closely interrelated [13]. Francesco Di Virgilio and coworkers review current evidence supporting a central role for extracellular ATP in the modulation of tumor-host interaction [14]. Availability of novel molecular probes has shown that the TME contains large amounts of extracellular purines, ATP and adenosine, in contrast to the interstitium of healthy tissues where extracellular purines are virtually absent. Extracellular purines ligate specific receptors expressed on both the tumor and the host cells, thus producing a variety of effects that may promote, or inhibit tumor growth, depending on the given receptors involved.

The most common effect due to adenosine accumulation is immunosuppression mediated by A2A/A2B receptors expressed by host immune cells. Quite interestingly, hypoxia and adenosine accumulation have been shown to be strictly linked, prompting evaluation of combined treatments aimed at reducing both hypoxia and adenosine concentration ('co-adjuvant' treatments) [15]. Stephen Hatfield and Michail Sitkovsky discuss exciting new evidence supporting the feasibility of anti-cancer therapy based on the combined targeting of adenosine A2A receptor and HIF-1α [16]. Extracellular adenosine is a powerful immunosuppressant that in the TME hinders anti-tumor immunity and supports cancer progression [17]. On this basis, John Stagg and collaborators provide a comprehensive review of the effect of adenosine on tumor-infiltrating immune cells and of how these effects may be exploited to reinstate a proper anti cancer immune response [18].

With hindsight, accumulation of adenosine and ATP in the TME is not surprising since these purines also accumulate at inflammatory sites, and the TME is an eminently inflammatory microenvironment. Inflammation is one of the most important cancer-promoting conditions, and how inflammation generates a situation conducive to cancer is nowadays a very hot field of investigation [19]. A clear example of the predisposing role to cancer of chronic inflammation is offered by obesity. Weizhou Zhang and collaborators review here the links between obesity, inflammation and cancer [20]. Obesity affects over 600 million people worldwide, is associated to an increased risk of cancer likely mediated by the underlying inflammatory state typical of this metabolic disorder. Obesity is known to be associated with the release of a host of pro-inflammatory factors and cytokines, ranging from true pro-inflammatory cytokines to adipose tissue-released adipokines, from prostaglandins to growth factors.

The crucial role of the NLRP3 inflammasome in inflammation obviously raises the issue of this organelle in cancer. Quite interestingly, it is now clear that the NLRP3 protein is not merely confined to the cytoplasm, but is also secreted via a vesicular pathway. Healthy and cancer cells release into the blood stream large quantities of particulated material (e.g. exosomes and microvesicles) containing several bioactive factors and intracellular components among which cytokines, inflammasome constituents, surface markers and microRNAs [21]. Carracedo and Falcon-Perez and colleagues present solid evidence showing that in cancer patients circulating microvesicles bear the signature of the tumor, thus highlighting the exciting possibility of revealing presence of cancer by a simple blood analysis ('liquid biopsy') instead of the much more invasive 'tissue biopsy' [22].

These are exciting times in cancer studies: a deeper understanding of tumor cell biology and of the TME is providing novel tools for cancer therapy and diagnosis that will hopefully help win the fight against this disease.

Conflict of interest statement

Nothing .declared.

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