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New hope for the world cancer day

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Main text

The post-genomic era, marked by the completion of the Human Genome Project [1], has revolutionized oncological research by framing cancer as a genomic and molecular entity rather than merely a clinical one. In this context, the study of cancer genomes, along with advancements in transcriptomics, proteomics, and metabolomics, provides a comprehensive view of cancer biology, revealing unique tumor molecular signatures. The identification of these signatures opened the way for the precision medicine approaches, e.g., EGFR inhibitors, HER2 blockers. At the same time, in the last decade, tremendous progresses in the study of cell death mechanisms, cell metabolism, immune evasion, and the handling of big data is opening incredible advances in cancer research with subsequent innovative therapeutical target.

A comprehensive description of the advancement during le recent decade is well beyond the scope of this short editorial, but here we like to enlighten few points for reflection and discussion. On the occasion of World Cancer Day, we propose a fresh line of inquiry that might hold promise for offering new hope to cancer patients.

Interleukin-1α/β in inflammatory forms of programmed cell death and the immunosuppressive tumour microenvironment

Conventional chemotherapeutic agents primarily target the cell cycle mechanisms, with the majority inducing apoptosis across various cell types [2]. However, despite their efficacy, a significant number of tumour cells often survive, leading to patient relapse. To address this challenge, one promising approach is to enhance current treatment regimens by killing cancer cells in a way that also stimulates the immune system to provide sustained protection [3]. The advent of immune checkpoint inhibitors (ICIs) has already demonstrated a remarkable improvement in the prognosis of various cancers,

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highlighting the potential of harnessing the immune system to fight against cancer.

The various forms of programmed cell death (PCD) show differential capacities to stimulate adaptive immunity largely due to their distinct molecular and morphological features [2]. Among these are necrotic-like forms of PCD, such as necroptosis and pyroptosis, which are of particular interest. These processes are naturally immunogenic and can be triggered by pathogen infections or certain therapeutic interventions. When cells undergo necroptosis or pyroptosis, they release a plethora of signaling molecules known as damage-associated molecular patterns (DAMPs) [4]. DAMPs encompass preformed immune-stimulatory factors, inducible cytokines, such as IL-1 and IL-6, and chemokines. The combination of these molecules fosters the requisite adjuvanticity, thereby ensuring that antigen-presenting cells (APCs) not only engulf dead cells to present cancer epitopes but also become activated to promote $CD8^+$ T-cell cross-priming, a critical step in mounting an effective anti-tumour immune response.

However, the situation is not so straightforward. In some cases, inflammatory necrotic-like forms of PCD may fail to stimulate an adaptive immune response and instead promote tumour development by facilitating angiogenesis, cancer cell proliferation, and remodeling the tumour microenvironment (TME). Emerging evidence highlights the crucial role of IL-1 cytokines, particularly IL-1α and IL-1β, in shaping the TME and influencing tumour progression (Fig. 1). Recent work by Kay Hanggi et al. underscores the immunosuppressive properties of IL-1α in the TME [5]. Their findings reveal that the release of IL-1α during chemotherapy-induced necrotic cell death contributes to the recruitment of myeloid cells, the formation of an immunosuppressive TME, and resistance to therapy. In contrast, IL-1α-deficient tumours exhibited reduced growth, accompanied by a decrease in the proportion of macrophages and an increased infiltration of $CD8^+$ T cells with an activated and effector phenotype. The role of IL-1β, a major interleukin released during pyroptosis, in tumour progression remains controversial. In gastric, breast, and KRAS-mutant lung cancers, IL-1β suppresses the anti-tumour immune response by promoting the infiltration of immunosuppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [6]. These MDSCs, in turn, enhance tumour cell proliferation, migration, angiogenesis, and immune escape. However, therapeutic strategies targeting IL-1β, particularly in combination with ICIs, have shown promising results. Anti-IL-1β therapy can switch the immunosuppressive TME to an anti-tumour immune state, increasing $CD8^+$ T-cell infiltration while suppressing MDSCs and tumour-associated macrophages (TAMs) [7].

The recent observations from Kay Hanggi et al. [5] and a substantial number of publications on the pro-tumourigenic role of IL-1β, underline the complexity of cancer immunogenicity and raise critical questions about the interplay between IL-1 family cytokines and their influence on the TME. As members of the IL-1 family, do IL-1α and IL-1β act synergistically or antagonistically in shaping the TME? Furthermore, the influence of the type

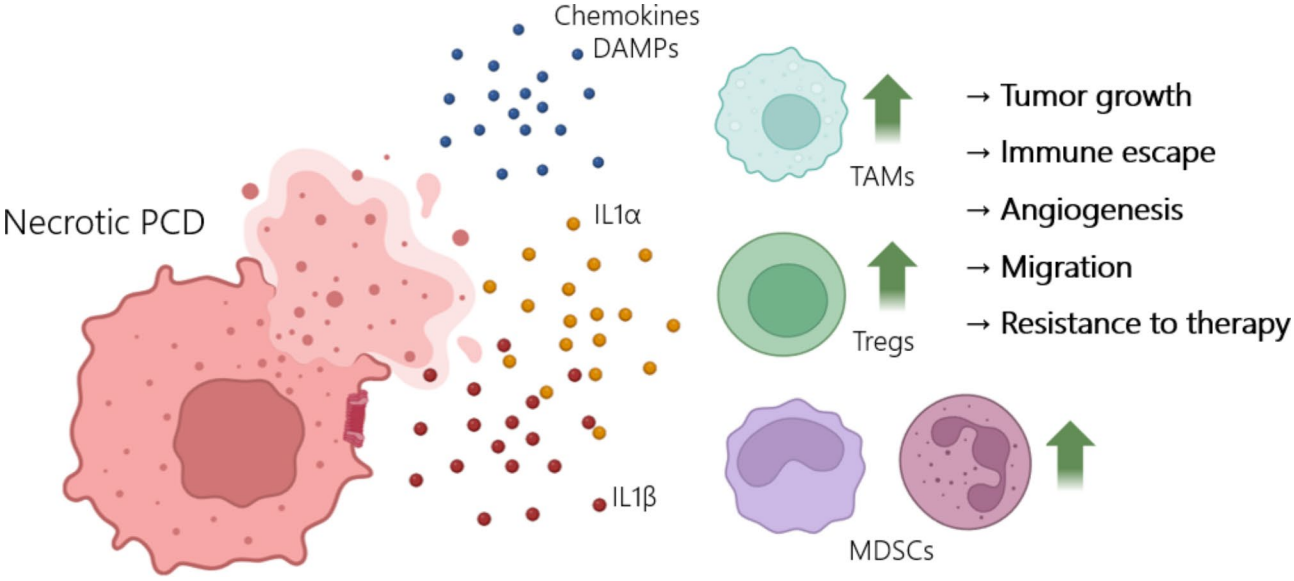

Fig. 1 Pro-tumourigenic role of IL1 in the generation of an immune-suppressive tumour microenvironment (TME)
IL-1 cytokines, particularly IL-1α and IL-1β, play a critical role in shaping the TME by promoting the recruitment and activation of immunosuppressive cells, such as tumour-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs). These cells contribute to tumour progression by facilitating angiogenesis, cancer cell proliferation, migration, and immune escape

of IL-1-producing cells, the patterns of expression, the type of PCD, and the timing of release on the composition of the TME is yet to be elucidated. Equally important is to understand how factors, such as disease type, stage, and therapeutic interventions, modulate the composition and ratio of DAMPs. It is imperative to determine which specific sets of DAMPs determine whether the TME becomes immunosuppressive or immunoactive. These questions are not merely academic in nature; they are of critical importance for the successful translation of ongoing clinical trials targeting members of the interleukin family into practical and effective strategies for cancer treatment.

In the context of the World Cancer Day, it is imperative to emphasize the significance of DAMPs-mediated crosstalk between the TME and PCD in the development of novel, effective therapeutic interventions aimed at eradicating cancer cells. A comprehensive understanding of the delicate equilibrium between immunogenic and immunosuppressive cell death processes, in conjunction with the functions of pivotal cytokines, such as IL-1α and IL-1β, is paramount for the design of next-generation anti-cancer therapies. By leveraging the immune system and targeting the TME, one can progress towards achieving durable remissions and, ultimately, cures for cancer.

AKR1B1 and the Warburg effect

Otto Warburg's pioneering research in the early 1920s revealed a crucial metabolic feature of cancer cells: their preference for aerobic glycolysis over oxidative respiration. In contrast to other metabolic processes studied at the time, cancer cells exhibit a tendency to rely on glycolytic pathways for energy production, even in the presence of oxygen, a phenomenon known as the Warburg Effect. It is important to note that cancer cells do not typically exhibit mutations in genes related to mitochondrial respiration, as such genetic alterations would be highly disruptive. Instead, cancer cells generate excess glycolytic byproducts, such as lactate, to manage reductive stress. Despite a century of investigation, the precise molecular mechanisms driving the Warburg Effect remain a subject of ongoing debate. Key questions persist regarding the interplay between glycolysis and oxidative phosphorylation, as well as the activation of alternative metabolic pathways in cancer cells. Recent studies continue to shed light on the dynamic landscape of cancer metabolism, underscoring the evolving nature of this critical field [8].

We recently found that fructose metabolism has emerged as a significant contributor to cancer cell proliferation [9], where cancer cells can convert glucose into fructose through a process called the AKR1B1-mediated polyol pathway. In this pathway, glucose is initially reduced to sorbitol using NADPH and the enzyme aldose reductase (AKR1B1). Subsequently, sorbitol is converted to fructose with the involvement of sorbitol dehydrogenase (SORD) and the conversion of NAD + to NADH. As illustrated in Fig. 2, this alternative pathway has been verified through in vitro metabolic tracing, demonstrating the significant production of 13 C-fructose. This alternative polyol pathway is likely to play a crucial role in meeting the heightened energy demands and building block requirements of cancer cells, bypassing key regulatory steps at the HK and PFK levels, as depicted in Fig. 2. Fructose can also be sourced exogenously. Notably, acute myeloid leukemia and pancreatic cancers exhibit elevated expression of GLUT5, which is encoded by the solute carrier family 2 member 5 (SLC2A5) gene, facilitating fructose uptake and lactolysis [10, 11].

However, a considerable amount of exogenous fructose from the normal diet is efficiently cleared by the intestine [12], underscoring the significance of the polyol pathway in meeting the fructose requirements of cancer cells in vivo. Cancer cells possess the ability to regulate the balance between endogenous and exogenous fructose sources [13]. Mechanistically, the polyol pathway provokes multifactorial effects, ranging from energetic breakdown and DNA damage, ultimately triggering the induction of the apoptosis pathway, as observed in lung cancer [14]. In addition, fructose can activate oncogenic mTORC1 signalling pathway in lung cancer cells, promote systemic inflammation, and trigger anti-cancer CD8 + T cell responses by stimulating leptin production in adipocytes [14–16]. Furthermore, fructose can serve as a signalling molecule to impair the polarization of M1-like macrophages and thus tumor growth [17]. Along similar lines, diminished mannose metabolism is a prominent feature of T cell dysfunction, and exhaustion, affecting cancer immunotherapy [18].

Metabolic adaptation is a hallmark of cancer cells, as tumours often exhibit altered nutrient use to sustain their uncontrolled growth and survival. For centuries, cancer metabolism research has centered on glucose, but now there is a growing evidence for the involvement of fructose metabolism. Advancements in our comprehension of fructose's role in cancer could lead to innovative therapeutic approaches that preferentially disrupt cancer metabolism and enhance patient survival [13]. Similarly, this research also paves the way for exploring new avenues in immunology. Lymphocytes have a remarkable ability to rapidly proliferate in a regulated manner, and the AKR1B1-mediated polyol pathways may play a role in regulating intracellular reductive stress and potentially T cell exhaustion.

Given that (i) the polyol pathway is highly relevant in diabetes, (ii) metformin has been associated with reduced cancer risk and progression, and (iii) cancer genome sequencing has uncovered mutations in genes involved in glucose uptake, investigating the regulation

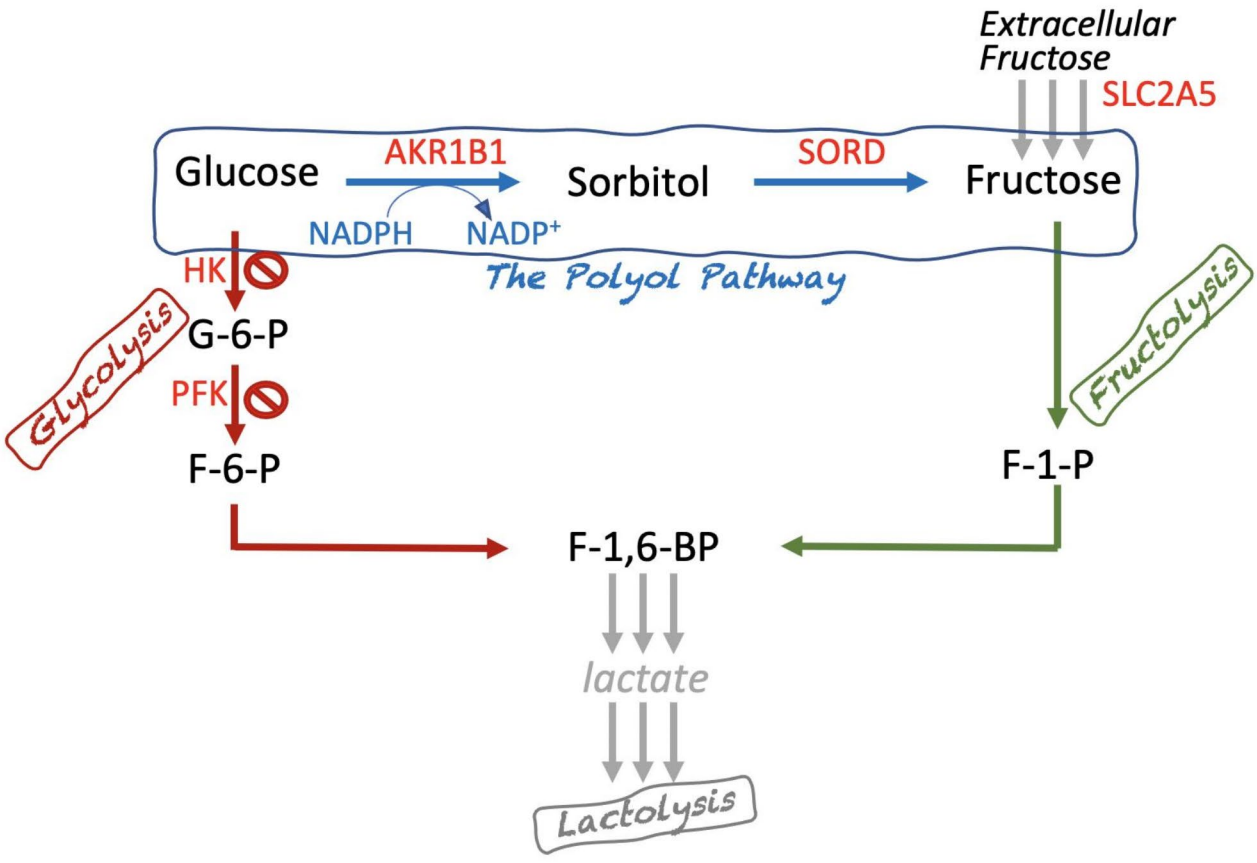

Fig. 2 The Polyol pathway, involving two subsequent reactions regulated by AKR1B1 and SORD can convert glucose into fructose. Alternatively, GLUT5 receptor, encoded by SLC2A5, allows the entry of fructose into the cell. Fructolysis is able to avoid two crucial regulatory steps: Hexokinase (HK) is inhibited by its product (G-6-P) while phosphofructokinase (PFK) is inhibited by the ATP steady state levels

of the AKR1B1-mediated polyol pathway could unveil unexpected connections in cancer biology.

Cancer complexity meets data-driven solutions

Cancer remains one of the most complex and heterogeneous diseases, presenting unique challenges for diagnosis, treatment, and prevention. To identify novel therapeutic approaches, the complex cell biological basis of cancer in patients needs to be deciphered and understood. Current technologies allow a deep analysis of cells and their molecular composition, and only when patient samples and matched corresponding normal tissue are analyzed together do the true cancer alterations emerge that allow the discovery of novel targets and associated therapeutics. Furthermore, this tissue must preserve biological reality without the significant noise and reactive effects that occur during the surgical removal of tumors before tissue collection.

A recent publication [19] demonstrated that the search for novel differentially expressed targets in cancer is highly affected by the time it takes to freeze tissue after surgical resection (the "cold ischemia time"). More than 2,000 potential targets are either not visible or incorrectly identified when tissue stays unfrozen for more than 20 min of ischemia time. These expression changes start to happen within 10 min of ischemia and mount up within minutes thereafter. Within 10–20 min post resection 25% of mRNA transcripts, 50% of proteins, and 95% of phosphoproteins have lost their original differential expression status, see Fig. 3.

This crucial finding underlines that cancer biorepositories, such as the database built by Hamburg-based biotech Indivumed, which have been at the forefront of ischemia time standards for 20 years. This database can transform how we understand and treat cancer, providing an indispensable resource for the advancement of precision medicine.

By studying different molecular layers of the tumour tissue (including DNA, RNA, protein, and phosphoprotein information), researchers can gain invaluable insights into the intricate nature of cancer subtypes and can identify novel targets and biomarkers. Linking molecular data with treatment outcomes is crucial to be

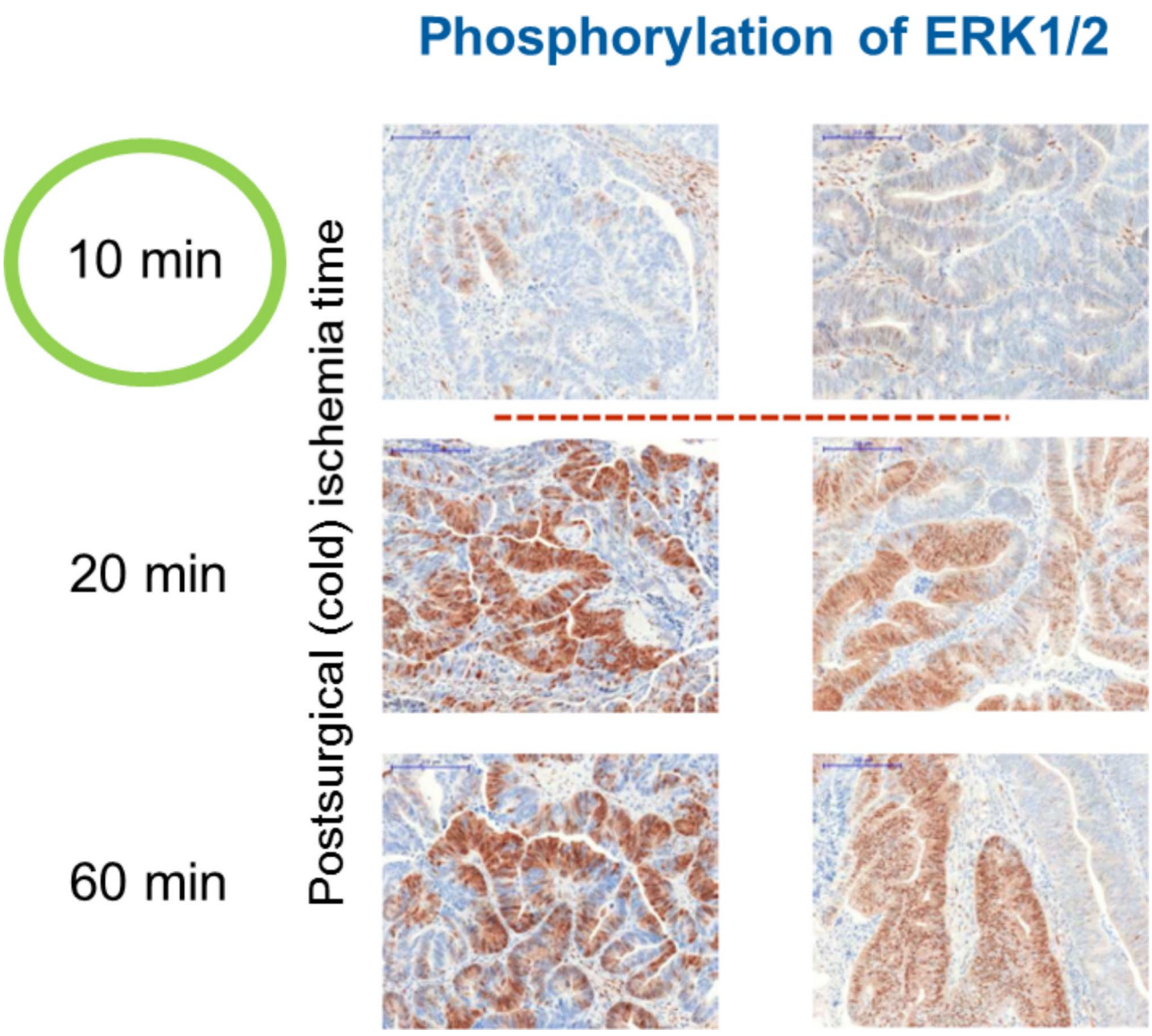

Fig. 3 Cold ischemia is a lack of blood flow to the tissue, and this is associated with increased signal of phosphorylated extracellular signal-regulated kinase (ERK)

able to identify patient-specific therapeutic targets, paving the way for individualized treatment strategies.

Precision medicine aims to tailor treatment to the individual characteristics of each patient, and high-quality biorepositories accelerate this paradigm by not only supporting the development of targeted therapies but also improving clinical trial design and predicting patient outcomes. Access to detailed molecular and clinical data enhances patient stratification, optimizing trial design and increasing the likelihood of success. Furthermore, machine learning algorithms applied to large-scale databases reveal patterns and correlations that can predict patient responses to therapies.

By enabling a deeper understanding of cancer's complexity and bridging the gap between research and clinical application, a database such as the database used by Indivumed, empowers scientists and clinicians to develop more effective, tailored treatments.

The molecular evolution of colorectal cancer

Colorectal cancer (CRC) is the third most diagnosed malignancy worldwide and a leading cause of cancer-related mortality [20], underscoring the urgent need for multidisciplinary strategies aimed at improving the current management of CRC patients. Recent breakthroughs in molecular oncology are unveiling new pathways for prevention, diagnosis, and personalized treatment.

An intricate interplay of genetic and epigenetic mechanisms regulates CRC occurrence and progression, including transcriptional plasticity and somatic chromatin

accessibility alterations as pivotal drivers of intratumoral heterogeneity [21]. CRC subtypes are not static entities, but dynamic landscapes influenced by spatial and temporal genomic changes [22, 23]. By identifying over 250 CRC putative driver genes, including novel targets in noncoding regions (e.g. ETV1, LEF1, NOTCH2, SRC, TFEB, DDR2), we can now redefine the molecular pathways associated with CRC development. Specifically, these molecular investigations allowed to categorize CRCs into distinct molecular subgroups, each with individual prognostic and therapeutic implications [24]. Advances in spatial transcriptomics and multi-omics investigations have further enriched our understanding of CRC's heterogeneity. Mapping consensus molecular subtypes (CMS) with single-cell resolution has uncovered TME interactions critical to treatment resistance and disease progression.

These insights have significant implications for immunotherapy, particularly in the context of anti-immune checkpoint therapies. For instance, CRC classified as CMS1 (MSI-H, immune-active) display a robust immune infiltration, with an abundance of T cells and a favorable response to ICIs such as those targeting the PD-1/PD-L1 and CTLA-4 pathways [25]. In contrast, CMS4 (mesenchymal subtype) CRCs are characterized by an immunosuppressive TME, rich in cancer-associated fibroblasts (CAFs) and MDSCs, which may contribute to resistance to ICIs.

The growing prevalence of molecular classifications, including CMS, based on the modulation of gene clusters, rather than individual molecules, has driven scientific research toward a transition from the traditional one biomarker–one treatment paradigm to a more comprehensive multi-marker approach.

This innovative vision becomes particularly important when identifying rare but clinically significant subgroups, such as those harbouring BRCA1/2 mutations or exhibiting unique mutational signatures like SBS93 [22, 23]. The identification of reliable targets, combined with the histological characterization of the tumor, can guide tailored interventions, aligning treatment plans with specific molecular characteristics. Targeted therapies, including cetuximab for RAS wild-type tumours and encorafenib for BRAF-mutant CRC, have shown considerable promise [26]. However, resistance to monotherapies remains a challenge, necessitating the exploration of innovative approaches such as combination regimens, bispecific antibodies, and oncolytic viruses.

Furthermore, the recognition of environmental factors that increase CRC risk, such as mycobiome alterations and pollutant bioaccumulation [27], highlights new opportunities for preventive measures. This underscores the potential of integrating lifestyle and microbiome-focused strategies into comprehensive cancer care. Advances in non-invasive diagnostic approaches, such as liquid biopsies and circulating tumor DNA (ctDNA) analysis, are revolutionizing CRC detection and monitoring. These technologies provide real-time insights into tumor dynamics, enabling the early identification of minimal residual disease (MRD) and therapeutic responses [28].

As we celebrate the World Cancer Day, it is fundamental to recognize the transformative impact of molecular classifications in CRC. These progresses reflect a broader shift in oncology, from a one-size-fits-all approach to a nuanced, patient-centered paradigm. By embracing this transition and addressing barriers to implementation, we can move closer to achieving the goals of Sustainable Development Goal 3 (SDG 3) thus ensuring healthy lives and promoting well-being for all.

In this era of rapid scientific progress, the World Cancer Day is not just a day of reflection but also a call to action to accelerate innovation, foster global collaboration, and ensure that every patient can benefit from the promise of personalized medicine.

Author contributions

GM, BZ and YS conceived the project, all authors wrote the manuscript; AVZ prepared Fig. 1; GM prepared Fig. 2. JB prepared Fig. 3. All of the Authors have approved this submitted version.

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Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

GM, YS, GSK, FN and BZ are members of the Editorial Board of Biology Direct. The authors declare no other conflict of interest.

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