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Table of Contents

Short communication

Hallmarks of Cancer; A Summarized Overview of Sustained Proliferative Signalling Component

Zainab Al Lawati[1], Alaa Al Lawati[2]

[1] MBBCh, MSc, ABEM, FPM, Ministry of Health (MOH), Muscat, Oman
[2] MBBS, Ministry of Health (MOH), Muscat, Oman

Abstract

Over the past fifty years, the field of cancer research has witnessed enormous growth and a wealth of knowledge gain, as it remains to be among the primary causes of death across the globe. As a result, significant advancement in cancer therapy has been achieved, particularly in the ones that target specific hallmarks in the process of tumor formation. These hallmarks are renowned as functional competences that enable malignant cells to subsist, grow and spread within the human body. Twenty–one years ago, six main traits were identified, to which two additions were made eleven years later. These are identified as self–sufficiency in growth signals, insensitivity to anti–growth signals, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, deregulating cellular energetics and avoiding immune destruction. Two supporting characteristics believed to empower the attainment of these hallmarks were also tagged, being instability and mutation of the gene and inflammation fostered by the malignant growth. This paper will highlight the main processes underpinning the self–sufficiency in growth signalling component. It will briefly discuss the process behind cell signaling and mechanisms by which tumors evade the immune system. Following that, it will delve into the therapeutic modality targeting this component and give some current illustrations of how therapies targeting this hallmark are being utilized.

KEYWORDS: Cancer hallmarks, cell signaling, sustained proliferative signaling, EGFR antagonists.

Introduction

Cancer is a multifaceted process that has been looked into from multiple aspects. It has been envisaged as an epigenetic disease, a systematic disease and also as a developmental disorder [1–5]. Hanahan and Weinberg's landmark article on the hallmarks of cancer in 2000 created a paradigm shift towards our understanding of the concepts underpinning cancer development. Their observations provided a framework for the biological capabilities that are essential for cells to grow within neoplastic diseases, which aid in organizing and understanding the capabilities of these diseases[1]. To begin with, six principles were flagged as the main components of this framework, and following the advancements in cancer research, two additional hallmarks were added as evolving principles, along with two enabling characteristics (Figure 1). The former comprises self–sufficiency in growth signals, insensitivity to growth inhibitory, or anti–growth, signals, evasion of programmed cell death, also referred to as apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, deregulating cellular energetics and avoiding immune destruction. The latter, on the other hand, encompasses genome instability and mutation as well as tumor promoting inflammation [1,6]. This report will review the steps involved in cell signaling, followed by the process by which cancer evades the immune system of the body. It will then delve into the therapeutics targeting the proliferative signaling component of cancer cell growth.

Discussion

Normal cell signaling

To begin with, the process of cell signaling comprises three components, being; reception, transduction and

Corresponding author: Dr. Zainab Al Lawati,
Contact No. +968 99201600,
Email address: dr.z.abdulla@gmail.com

Co–author contact information:
Dr. Alaa Al Lawati Contact number +968 92811990
Email address: alaa.a.1990@gmail.com

response. The first stage is very precise and entails binding of a specific ligand, or signal molecule, to a particular receptor on the cell membrane [7]. The second stage entails the signal transduction pathway, whereby a signal alteration, to a mode that can bring about specific response through messengers, protein kinases and the phosphorylation circuit [8]. The final step entails ensuing of gene expression regulation and generation of response (figure 1) [7, 8].

Evasion of the body's defense mechanisms

Under normal conditions, the body's regulatory mechanisms enable cellular proliferation, differentiation and demise to occur within a controlled fashion [10]. These processes remain well–regulated and together maintain cellular homeostasis [6]. Proliferation is activated when required then deactivated when no longer needed. At the same time, normal cells upon encountering stressors, such as deoxyribonucleic acid (DNA) damage, initiate apoptosis and subsequent demise in response to them [11]. Cellular division is ultimately regulated and reaches a ceasing point. With cancer cells, however, multiple reformed mechanisms alter the picture, enabling proliferative advantage to occur with both the presence and absence of stimuli. These mechanisms can be summarized into six main components. To begin with, growth signals peculiar to those cells become synthesized, like Transforming Growth Factor alpha (TGF–α), and Platelet–Derived Growth Factor (PDGF), creating an ongoing growth cycle [10]. Following

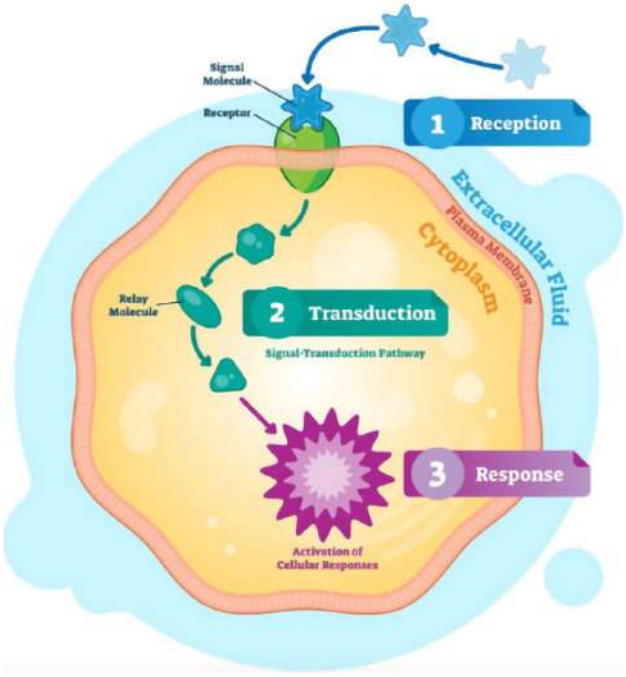

Figure 1: Outline of the steps involved in cell signaling. Those steps are: 1) reception – binding of signal molecule to receptor, 2) transduction – relay molecule triggering internal response within the cell & 3) response – activation of reaction within the cell [9].

that, receptor proteins become over–expressed, enabling an enhanced reaction to the external growth factors [10]. This step is critical, as its essential for the tumor to evolve and spread [11]. The over–expressed receptors then enable ligand–independent signaling to ensue, which allows division and growth to occur without signaling molecules [10]. The proliferative signals thereby become activated in response to the transformed intracellular circuits. These mutated oncogenes resemble normal growth signals [6]. Ultimately, the negative feedback loop that neutralizes the signal transmission pathway becomes disturbed, such as the defective oncogenic GTPase, creating a defective Rat Sarcoma Virus protein (RAS) [10]. Thereby, the damaged DNA generates ongoing cell division of the neoplastic cells (Figure 2).

The traits attained by tissues support them in overcoming defense mechanisms and allow their intrinsic capabilities to work. This enables them overcome the 'anticancer defense mechanism' encoded within the body and lose control over cellular proliferation [12]. This proliferative advantage is critical, and is believed to be the most vital trait as it enables those cells sustain continual growth. They thereby grow in size, spread to other sites and invade distant sites within the body [13]. The loss of regulation of the signaling pathway enables those cells to upregulate growth signals and downregulate the opposing signals [2]. The malignant cells also generate signaling molecules to which they are receptive, thereby generating ongoing stimulatory loop for cellular development [14]. An example of this is glioblastoma's generation of TGF–α and PDGF [14]. In the context of colorectal cancer, although RAS oncogenes do not appear to be the precursors or "gatekeepers" of disturbed cellular proliferation, they require only a single genetic event for them to be stimulated [15]. Studies show that these oncogenes appear to be present in more than 50% of human cancers [15]. In addition, the neighboring stromal extracellular matrix (ECM) also plays an important role in neoplasm propagation, where they undergo recruitment by the cancerous cells to generate and deliver growth stimulants to the microenvironment of the cancer itself [16, 17]. The study done by Schauer and colleagues in 2011 highlighted the events that follow abnormal fibroblast activation and generation of cancer–associated fibroblasts (CAF) that contribute to the malignant progression of ovarian cancer [16]. Another study done Bhowmick, Nelson & Moses in 2004 emphasized the importance of epithelial and ECM interaction, and the role of fibroblasts in paracrine signaling and propagation of certain cancers [18].

Moving onto somatic evolution, of which the role of it in cancer evolvement has long been looked into. It is well known that somatic mutations foresee circuits likely to activate the oncogenic pathway, and through potentiating

them, promote the oncogenic proliferation [2, 19]. In the context of tumor growth, serine–threonine protein kinase AKT (protein kinase B) activation and increased expression, via phosphoinositide 3–kinase (PI3–kinase) isoform mutation, is of major importance and is one of the most critical PI3K targets [20]. Mutations of a unit within this target are found in several types of cancer [20]. This process ensues enhanced activation of PI3–kinase signaling pathway. Another commonly referred to prototype is in the context of melanoma, where a significant proportion of cases demonstrate mutated B–Raf gene in the Mitogen–Activated Protein Kinase (MAPK) pathway [21]. It is worth noting that the relationship and effect of interaction between several growth factor generated pathways remains elusive [2]. Over the last few years, the theory of somatic mutation and its causality connection with cancer has been evaluated, in regards to whether it actually proceeds or follows the precise commencement of the malignant growth [22]. Back in 2013, Forsber, Absher and Dumanski' stated in their comprehensive report that "the vast majority, if not all, of aberrations that were observed in the cancer–affected cohort were also seen in cancer–free subjects, although at lower frequency" [23].

Another process vital for cellular stability is negative–feedback looping, interreference with which aids in the generation of sustained growth signaling [2]. An example of this evolves around the RAS oncoprotein. RAS genes play a vital role in cell signaling and mutations of this gene are the most commonly seen alterations in tumorigenesis [24]. This is a vital component in the negative–feedback mechanism that limits duration of the signaling process [2]. Upon becoming mutated, RAS proteins become obstinately active, which in turn impacts activity of RAS GTPase complex [24, 25].

Therapeutics targeting sustained growth signalling component

Multiple treatment modalities targeting specific mechanisms of cancer development have been studied. These encompass targeted cancer therapies like monoclonal antibodies, which are lab– manufactured human proteins [26]. Several types of those proteins are used in the management of carcinogenesis. Some monoclonal antibodies also deliver immunotherapy, a treatment genre that utilizes the patient's own immunity to oppose the malignant growth [27]. An example of treatment modality targeting sustained growth signaling hallmark is anti–Epidermal Growth Factor Receptor (EGFR) agents (figure 3). This solidifies the notion that the identified hallmarks and emerging traits are indeed crucial for the malignant transformation of the human cells (figure 3).

Epidermal growth factor receptor (EGFR) antagonists

EGFR or ErBB family, are receptor tyrosine kinases commonly vented in malignant growths [28]. Growth factors belonging to this family trigger malignant transformation in the majority of cancers of the epithelium. Those ligands, upon binding, stimulate autophosphorylation that results in growth of cancer cells [29]. EGFR antagonists, on the other hand, compete for the receptor binding to block the activation cascade. They are mono–target inhibitors that

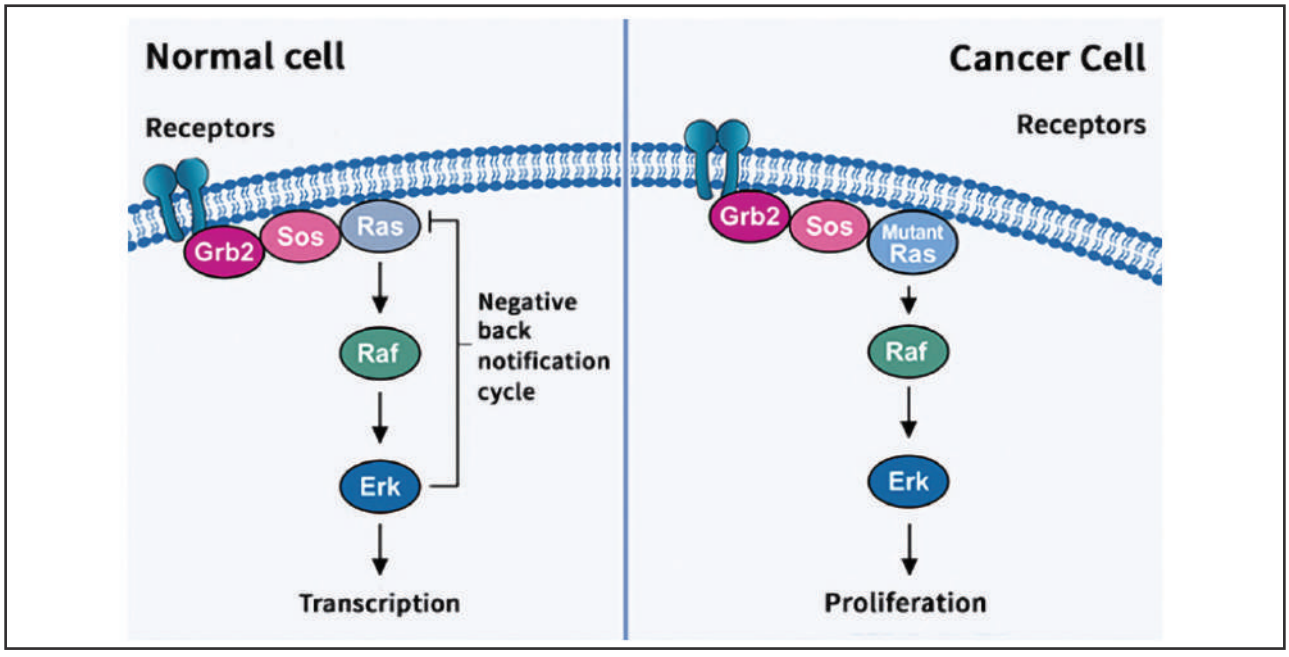

Figure 2: Outline of the events that proceed cell transcription and proliferation within normal (left) and mutagenic (right) cells. Following mutation of Ras protein, cellular division is altered. This generates uncontrollable cellular proliferation within the cancerous cells [10].

work on the growth signaling hallmark of cancer cycle, and they have been the foremost proteins to be used as target therapy against cancer [30]. With reduced EGFR within tumors, downstream signaling becomes repressed, thereby hindering progression and spread and leading to demise of the cancer cells [31].

Among the EGFR inhibitors in clinical use are small–molecule tyrosine kinase inhibitors (e.g., gefitinib) and monoclonal antibodies (e.g., cetuximab) [29,31]. Those agents are FDA–approved for treating cancers of the head and neck (squamous cell cancer), lungs (non–small–cell lung cancer – NSCLC), pancreas and colon [29]. Over the years, the invariable occurrence of resistance against first, second and third generation EGFR inhibitors has been a subject of concern, mechanisms of resistance of which entail activating mutation, Threonine–790–Methionine (T790M) and Cystein–797–Serine (C797S) mutations (figure 4) [32,33].

Emergence of fourth generation EGFR inhibitors, nonetheless, has been showing promise [34]. The pharmaceutical company 'Blueprint medicines' has been concentrating on evolving small molecules for treating EGFR triple mutant NSCLC. In their in vivo analysis of the antitumor activity of BLU–945, structure of which is yet to be revealed, results showed potent impedance of EGFR pathway by the drug assessed (Table 1) [35]. In another contemporary report, both in vitro and in vivo results on the combination of a fourth generation EGFR tyrosine kinase inhibitor (EA1045) and cetuximab revealed impressive responses with remarkable activity against models carrying the lung cancer xenograft [33].

Another member of this family that shares a similar mechanism of action, named MCLA (human anti–EGFR), is currently being trialed in a phase 1 study for determining the maximum tolerated dose, recommended phase 2 dose and it's antitumor activity against NSCLC, head and neck cancer and gastric cancer (NCT04868877) [36,37]. An additional ongoing trial, also focused on gastric cancer, is looking into the effectiveness of AZD8186 (inhibitor of kinase activity) in combination with paclitaxel (plant alkaloid chemotherapeutic agent) on this group of patients, primarily to identify the tolerated dose and recommended phase 2 dose (NCT04001569) [36,37].

Conclusion

Among the earliest breakthroughs in the field of cancer was Pott's detection in 1775 of the relationship between Squamous Cell Carcinoma & chimney soot [37,38]. This has since been trailed by a large mass of pioneering innovations in the field of tumor growth. Following an era

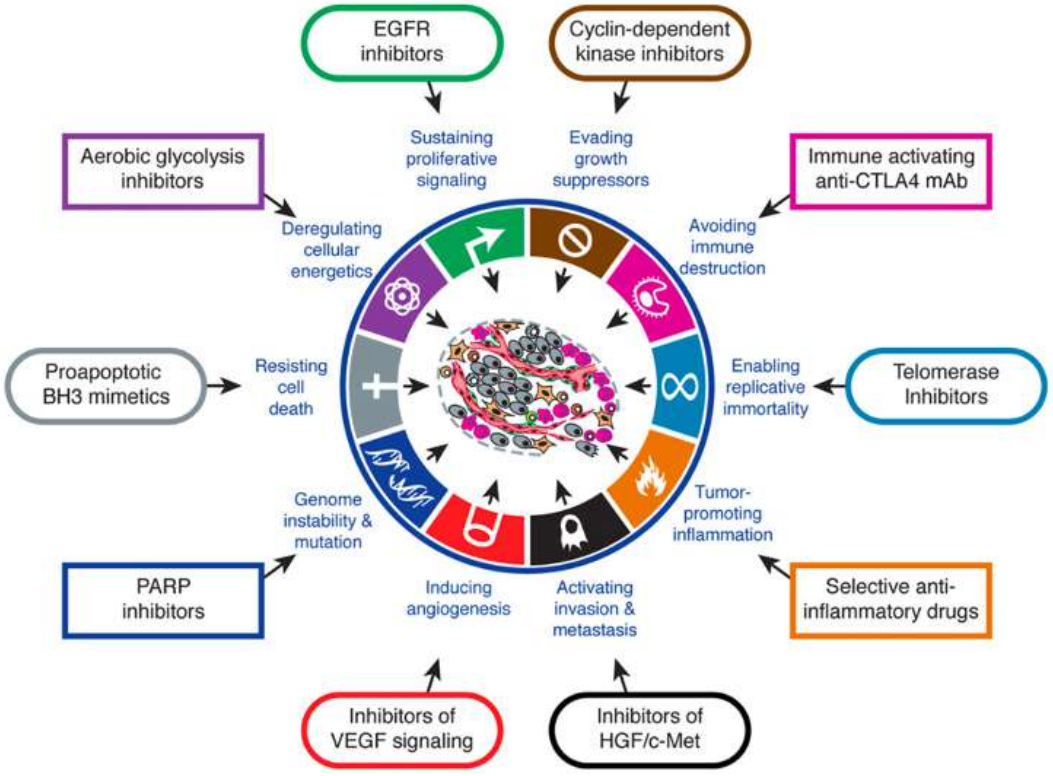

Figure 3: A summary of the eight cancer hallmarks and two enabling characteristics labelled by Hanahan & Weinberg, along with examples of treatment modalities targeting each component 2. (EGFR: Epidermal growth factor receptor, CTLA4: Cytotoxic T–lymphocyte–associated protein–4, HGF: Hepatocyte growth factor, VEGF: Vascular endothelial growth factor, PARP: poly ADP ribose polymerase, BH3: Bcl–homology domain 3)

of research into the pathogenesis of cancer, it can be noted that the armamentarium generated has aided in analysis of cancer genome and advancement of therapies, that identify and obscure the steps leading to cell seepage and cancer evolvement. Some lines of management have shown favorable results, and with gradual enhancement in our understanding of the molecular base of these conditions, preemptive approaches will be conceivable in the near future.

As the management of several tumors is going into a phase of "targeted therapy" against specific mutation–generating pathways, the successful understanding of the genetic anomalies is crucial for the evolvement of these stratagems. Nonetheless, as some patients show transient or no response to therapy, it is vital to delve further into the modes by which response can be improved. Unlike first, second and third generation EGFR inhibitors that the body develops resistance to, generating anti–EGFR that will withstand resistance will create a transforming shift in this ongoing battle against cancer. Another aspect that warrants further research is maintaining safety, where side–effect profile can be minimized without compromising efficacy profile. Whether the coming period will hold transformation of the hitherto known theories of tumorigenesis or the inauguration of new mechanisms of pathogenesis is yet to be determined.

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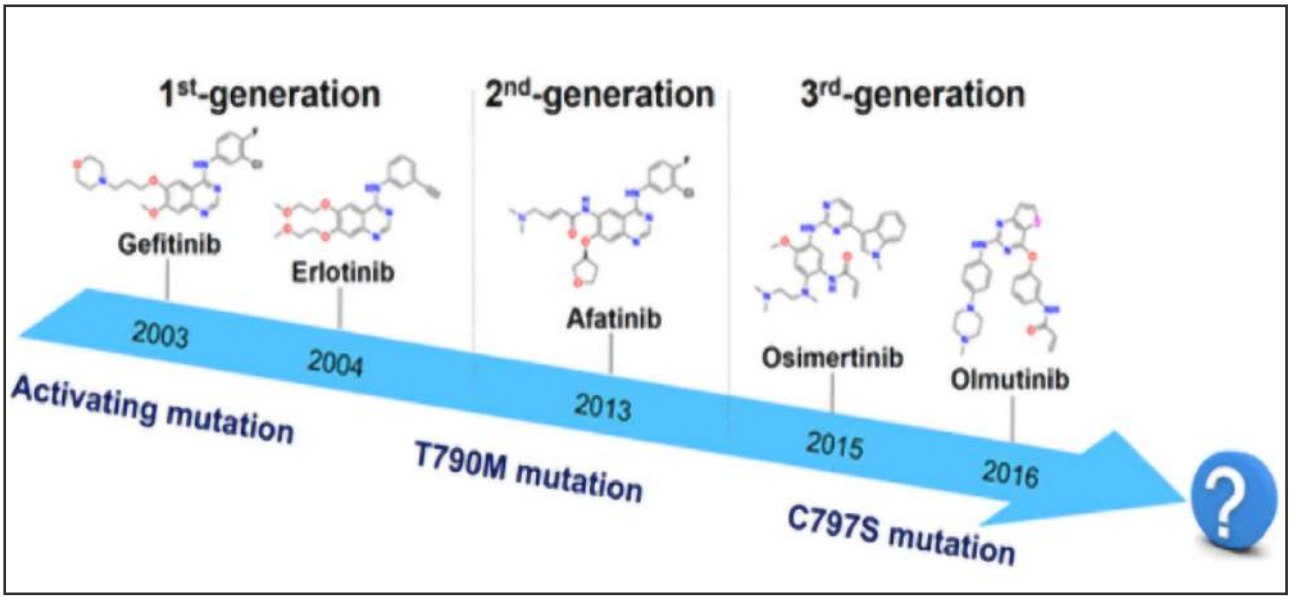

Figure 4: Outline of the first, second and third generation EGFR antagonists in use and the mutations emerging with each group. Examples of each cohort are raised, along with the year and mutation detected. Patients treated with first generation medications develop activating mutation, those treated with second generation medications show threonine (T) to methionine (M) mutation at position 790. Finally, patients treated with third generation antagonists express cystein (C) to serine (S) substitution in the EGFR domain [32].

	EGFR	EGFR mutations			Inhibition mode
	wt.	del_19 L858R	del_19/T790M L858R/T790M	del_19/T790M/C797S L858R/T790M/C797S	
Gefitinib (First Gen.)	Sensitive	Sensitive	Resistant	Resistant	Reversible
Afatinib (Second Gen.)	Sensitive	Sensitive	Sensitive	Resistant	Irreversible
Osimertinib (Third Gen.)	Resistant	Sensitive	Sensitive	Resistant	Irreversible
(Fourth Gen.)	Resistant	Sensitive	Sensitive	Sensitive	*Not irreversible*

Table 1 Summary of EGFR inhibitors. The table represents an example of each of the four generations of anti–EGFR agents, along with their response to wild–type EGFR, response to the most commonly identified EGFR mutation groups, along with their inhibition mode [28].

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