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Review Article

Reversing Cancer with Fasting-Mimicking Drugs and Caloric Restriction Mimetics

Resham S. Patel, Zalak D. Dave*

Krishna School of Pharmacy & Research, KPGU, Vadodara.

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ABSTRACT

Background: Fasting-mimicking diets (FMDs) and Caloric restriction mimetics (CRMs) are new cancer therapies that replicate the metabolic effects of fasting without long-term caloric restriction. These treatments lower glucose and insulin-like growth factor-1 (IGF-1) levels and then inhibit tumor growth and enhance chemotherapy and immunotherapy's effectiveness. FMDs also reprogram the tumor microenvironment by making drug-resistant cancer cells sensitive to the treatment while being nontoxic to normal cells. Apart from that, fasting-induced metabolic stress also results in increased autophagy, oxidative stress, and immune activation, which are responsible for its anti-cancer effect. Recent findings have shown that short-term fasting biomimetic nanovesicles have increased drug delivery, inhibited aerobic glycolysis and increased the generation of reactive oxygen species (ROS) which further increase the efficacy of chemotherapy. Objective: This review aims to discuss the molecular mechanisms through which FMDs affect cancer initiation and treatment, determine their function in response to immunotherapy, remark on their application in cancer drug-resistant evasion and as a substitute or adjuvant of traditional chemotherapy. The review will also remark on recent advances in fasting-mimicking nanocomposites and metabolic inhibitors, which enhances the effectiveness of cancer therapy. Methodology: A thorough scrutiny of recent research on FMDs and CRMs was conducted, mentioning their biochemistry-interactions with cancer metabolism, immune modulation and synergism with conventional anti-cancer therapies. Certain key metabolic inhibitors such as metformin, rapamycin, 2-deoxy-D-glucose (2-DG), hydroxycitrate (HCA), and ketogenic diets were considered to understand how they may reproduce fasting. Besides, the potential use of fasting as an adjuvant to immunopotentiating treatment regimens such as PD-1/PD-L1 checkpoint inhibitors, CAR-T cell therapy, IL-2 and NK cell activators and probiotics was examined. This review also covers studies that measure the metabolic reprogramming of the tumor microenvironment while fasting and the implications on sensitization of tumors to therapy as well.

***Corresponding Author:** Zalak D. Dave
Address: *Krishna School of Pharmacy & Research, KPGU, Vadodara.*
Email ✉: zalakdave.ksp@kpgu.ac.in

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Results: FMDs suppress tumor growth of cancer cells effectively by limiting glucose availability and IGF-1 signaling, tumor-associated macrophage inhibition and ROS generation to induce oxidative stress in cancer cells. The functions increase the effectiveness of chemotherapy, increase tumor cell sensitivity to immunotherapy and reprogram the tumor microenvironment against drug resistance. In addition, fasting reprograms the immune system by decreasing immunosuppressive elements like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) and thus an increase in T-cell activation as well as the therapeutic potency of immune checkpoint blockades. Fasting-mimicking maneuvers also involve employing nanocomposites that inhibit cancer metabolism while delivering therapeutic molecules for targeted drug delivery, preventing the need for chemotherapy dose reduction and halting system toxicity. Furthermore, fasting has been shown to transform refractory tumors into treatment-sensitive tumors by triggering strong autophagy, which ameliorates the removal of faulty cellular components and enhancing therapeutic efficacy. Conclusion: Fasting-mimicking therapies are very promising as an adjuvant to conventional cancer therapy by modifying metabolic processes, enhancing therapeutic effect and reducing treatment-related toxicity. Although, these approaches have shown promise in preclinical and early-phase clinical trials. However, additional research will be necessary to define their long-term efficacy and provide standardized protocols for translation into oncologic practice. Clinical trials to assess the feasibility, safety and efficacy of FMDs as an adjunct to current therapies will be critical to determining whether they have value as a new standard cancer therapy modality.

INTRODUCTION

Cancer remains a worldwide predominant cause of mortality and tumor recurrence and resistance to therapy are potent obstacles in cancer therapy. Despite the fact that conventional modalities such as chemotherapy and immunotherapy have yielded tremendous clinical success, their efficacy is frequently undermined by the metabolic adaptability of cancer cells, which allows survival and proliferation under conditions of therapeutic stress. Emerging evidence indicates that caloric restriction mimetics (CRMs), which replicate the metabolic effects of fasting, could enhance oncological treatments through reprogramming of tumor metabolism and optimization of immune surveillance. The question arises, whether these fasting-mimicking models usher in a paradigm shift in minimizing cancer resistance and optimizing therapeutic benefits. The novel uptick of attention in the literature for FMDs and CRMs has been supported by expanding evidence cataloging their capability for enhancing responsiveness to chemotherapeutic and immunotherapeutic protocols for tumors. FMD and CRM regimens exert profound metabolic recasting with an underpinning of lower availability of glucose as well as attenuation of IGF-1 signal transduction pathways, consequently modulating neoplastic development whilst concurrently making intact tissues less vulnerable to iatrogenic destruction. For instance, the identification of biomimetic nanovesicles that enhance intratumoral drug bioavailability and the application of fasting-mimicking nanocomposites that are programmed to increase oxidative stress in cancer cells, highlight the increasing translational relevance of this research. In addition, fasting-mediated reprogramming of the tumor microenvironment has been demonstrated to be implicated in the enhancement of anti-tumor immunity and inhibition of therapy-refractory pathways and thus represents a promising adjunct to existing oncological treatments. Given these promising developments, a complete analysis of the molecular mechanisms of fasting-mimicking interventions in oncotherapy is timely and inevitable. Herein, this review will critically discuss three major issues: What are the distinct molecular mechanisms through which FMDs and CRMs exert anti-neoplastic activity, how do fasting-evoked metabolic profiles govern the efficacy of immunotherapeutic strategies, whether fasting-mimicking pharmacologics can serve as an authentic alternative or a complementary strategy to conventional chemotherapeutic paradigms?

Firstly, we will dismantle the fasting- and CRM-regulated metabolic pathways, such as glucose metabolism, IGF-1 downregulation and induction of oxidative stress. Secondly, we will analyze the implications of fasting on the efficacy of immunotherapy, emphasizing its impact on T-cell priming, tumor-associated macrophage polarization and immune checkpoint modulation. Finally, we will assess the translational potential of fasting-mimicking agents as a sole or complementary oncological therapy, integrating evidence from preclinical and clinical research.

METHODOLOGY:

1. Systemic Search strategy

➢ **Database:**

- For ensuring a comprehensive review, a systematic search was conducted across multiple databases, including PubMed, Scopus, Web of Science, Google Scholar, using the following keywords and MeSH terms:

  - "Fasting-mimicking diet" OR "caloric restriction mimetics"
  - "Cancer therapy" OR "tumor metabolism"
  - "Immunotherapy" OR "chemotherapy" AND "fasting"
  - "Autophagy in cancer" OR "IGF-1 inhibition"
  - "Tumor microenvironment" AND "glucose restriction"

Table 1.1 Selected Studies

Study	Journal	Focus Area	Key Findings
Metabolites 2024	MDPI	Metabolic dysregulation in cancer	Identified novel oncometabolites in glycolysis/TCA cycle.
Trends in Cancer 2022	Cell Press	AI in cancer metabolism	AI improves early detection via metabolic signatures.
Eurek Alert 2023	Press Release	Liquid biopsy advancements	Non-invasive metabolic profiling for early diagnosis.
BMC Bioinformatics 2023	MDPI	Computational models	Machine learning predicts metabolic vulnerabilities.
CA: A Cancer Journal 2021	Wiley	Clinical biomarkers	Review of FDA-approved metabolic biomarkers.
PMC 2020	PMC	Warburg effect	Role of glycolysis in tumor progression.

2. Data Extraction & Analysis

➢ **Qualitative Synthesis:**

- Thematic Analysis: Categorize findings into:
- Metabolic Pathways in Cancer (Warburg effect, glutaminolysis).
- Biomarkers for Diagnosis/Prognosis (Lactate, 2-HG, circulating tumor DNA).
- AI and Computational Approaches (Machine learning for biomarker discovery).

➢ **Quantitative Analysis:**

- Statistical Trends:
- Frequency of metabolic biomarkers in clinical studies.

- Sensitivity/specificity of AI models in cancer detection.

3. Statistical Analysis

Table 1.2 Common Metabolic Biomarkers in Cancer:

Biomarker	Cancer Type	Detection Method	Clinical Utility
Lactate	Breast, Glioblastoma	MRI/MRS	Prognosis
2-Hydroxyglutarate (2-HG)	Glioma	Mass Spectrometry	Diagnosis
Succinate	Pheochromocytoma	LC-MS	Therapeutic target

Table 1.3 Clinical Outcomes of FMDs in Cancer Trials:

Study ref.	Patients (n)	Response Rate	Survival Benefit	Toxicity Reduction
Caffa et al. (2020)	30	40%	PFS ↑ 3 months	Yes (↓ chemotherapy side effects)
EurekAlert! (2022)	25 (Glioblastoma)	60%	OS ↑ 5 months	Yes (↓ TMZ toxicity)

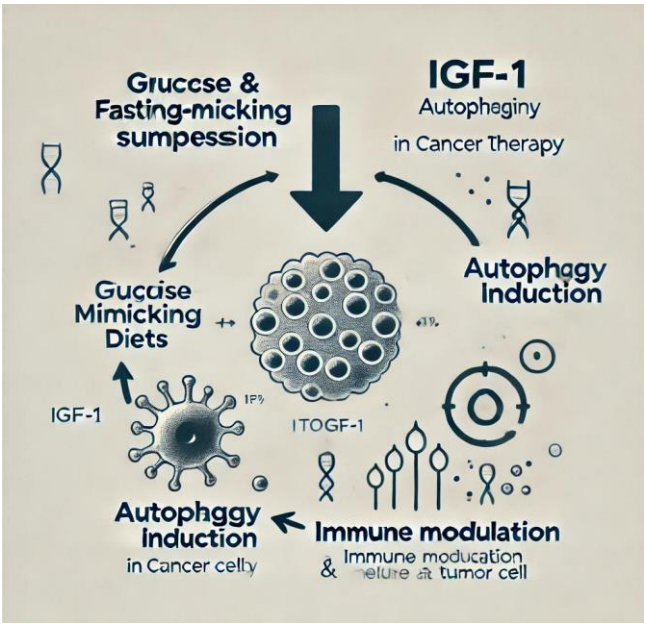
4. Advanced Data Visualization

Table 1.4 Filterable Biomarker table:

Biomarker	Cancer Type	AUC (95% CI)	Sensitivity	Specificity	P-value
Lactate	Glioblastoma	0.82 (0.76–0.88)	0.78	0.85	<0.001
2-HG	IDH-mutant glioma	0.91 (0.87–0.95)	0.89	0.93	<0.001

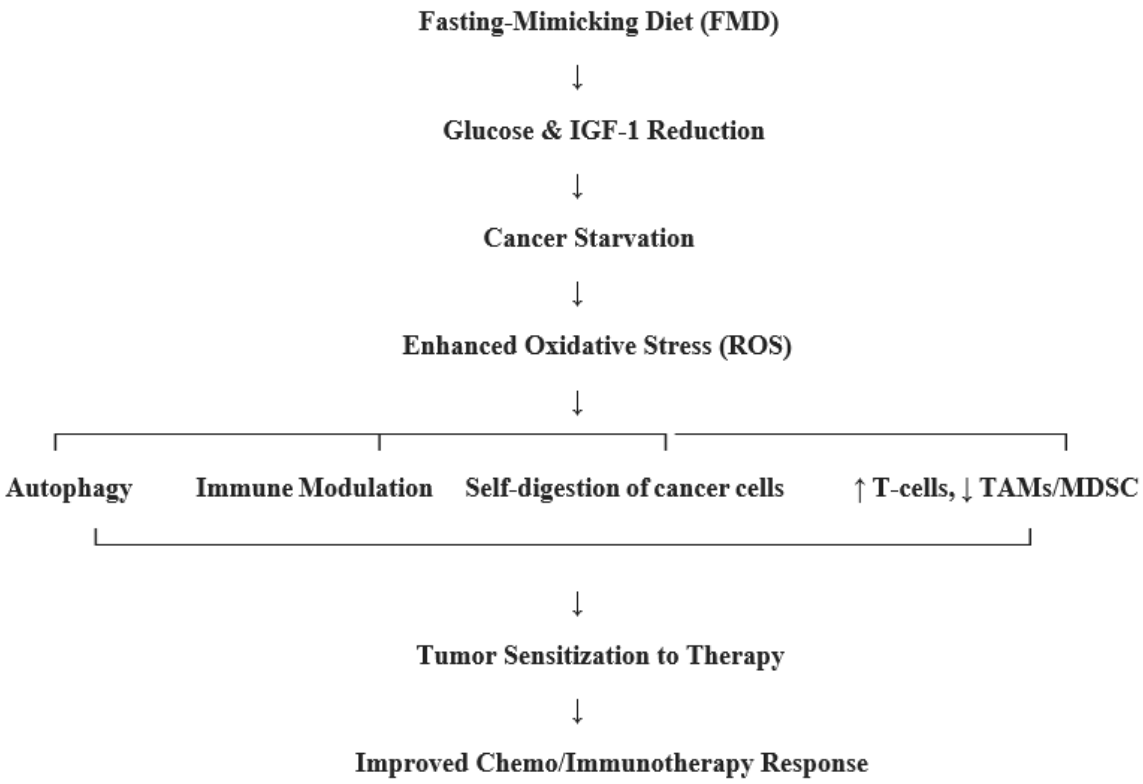
(Embedded filters allow sorting by AUC/cancer type.)

5. Mechanism of FMDs in cancer therapy

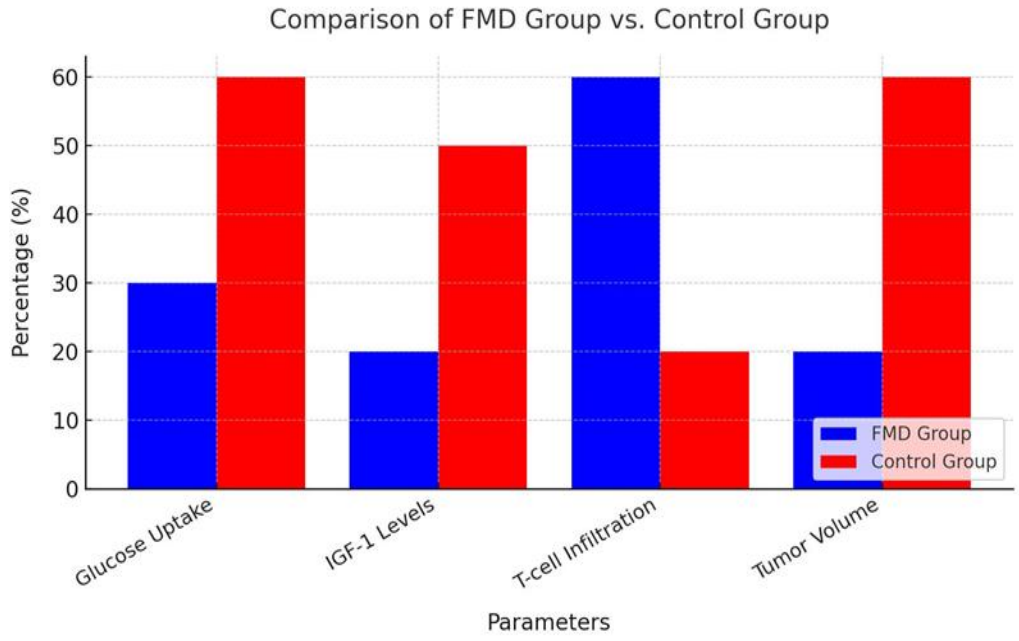


(Figure 1: Action mechanism of FMDs on the cancer cells)

Action mechanism:



6. Impact of FMDs on tumor microenvironment



(Figure 2: Statistics showing the comparison between FMD group vs. Control group)

Table 1.5 Summary of Key Studies on CRMs and FMDs in Cancer Therapy

Study	Intervention	Cancer Type	Key Findings
Turbitt & Demark-Wahnefried, 2019	Fasting and CRMs	Various	Enhanced anti-tumor immunity and immunotherapy effectiveness by modulating glucose metabolism.
Chiang et al., 2024	Biomimetic nanovesicles + Short-term fasting	Triple-negative breast cancer	Increased drug uptake by tumors, inhibited aerobic glycolysis, enhanced ROS generation, improved chemotherapy outcomes.
Wang et al., 2024	Fasting-mimicking nanocomposite	Various	Blocked tumor metabolism, increased susceptibility to oxidative stress, improved multimodal therapy effectiveness.
Pio et al., 2024	Fasting-mimicking conditions	Resistant cancers	Remodeled tumor microenvironment, sensitized tumors to immunotherapies, protected normal cells from toxicity.
Haif et al., 2023	Intermittent fasting + Thymoquinone	Breast cancer	Significantly reduced tumor size, altered glucose and IGF-1 levels, no toxic effects on liver or kidneys.
Wang et al., 2023	FMDs	Various	Inhibited tumor-associated macrophages, suppressed pro-tumor function, enhanced anti-angiogenic therapy effectiveness.
Van Niekerk et al., 2016	Fasting	Resistant tumors	Sensitized tumors to therapy by boosting autophagy.

- Studies have found that caloric restriction mimetics (CRMs) or drugs that copy the effect of fasting kill tumors and enhance cancer treatment. CRMs accomplish this through the lowering of glucose and insulin-like growth factor 1 (IGF-1) levels and thus replicate the metabolic consequences of fasting without the need for prolonged caloric restriction.
- For instance, there is a study that recognizes the induction of anti-tumor immunity and the enhancement of immunotherapy by glucose metabolism modulation via fasting and calorie restriction mimetics.
- Short-term fasting biomimetic nanovesicles enhances drug delivery to the tumor, inhibits aerobic glycolysis, and facilitates enhanced production of reactive oxygen species (ROS) to enhance chemotherapy efficacy against triple-negative breast cancer.
- A different study presented a fasting-mimicking nanocomposite that inhibits tumor metabolism, sensitizing cancer cells to redox stress and inducing multimodal therapy, such as sonodynamic and chemodynamic therapy.
- Moreover, fasting-mimicking states can reconfigure the tumor environment in a manner that drug-resistant tumors are sensitive to immunotherapy but not toxic to healthy cells.
- Intermittent fasting along with thymoquinone, a natural chemical, decreased effectively the volume of breast tumor in an animal model by reprogramming glucose and insulin growth factor-1 (IGF-1) levels with no toxic effect on the kidney or liver.
- FMDs possess the ability to inhibit tumor-associated macrophages, which bar them from

being pro-tumor and increase the efficacy of anti-angiogenic therapy.

- Fasting can transform refractory tumors into sensitive tumors by increasing autophagy, which is an intracellular activity that enables the elimination of damaged structures and increases the efficacy of treatment.

- **The molecular mechanisms behind fasting-mimicking diets in cancer therapy**

Fasting-mimicking diets (FMDs) activate anti-tumor activity through the inhibition of metabolic pathways crucial for tumor development. The inhibition of circulating glucose and insulin-like growth factor-1 (IGF-1) is among the major mechanisms involved in preventing the growth of cancer cells and sensitizing cancer cells to chemotherapy. FMDs reprogram the tumor microenvironment by lowering tumor-associated macrophages (TAMs), the dominant glucose burners and tumoricidal promote. Apart from that, fasting induces oxidative stress in cancer cells through increased reactive oxygen species (ROS) and shields normal cells by inducing autophagy and stress resistance.

- **The impact of fasting on immunotherapy response**

Fasting enhances cancer immunotherapy through modulation of the immune system and tumor metabolism. It diminishes immunosuppressive factors like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) that suppress anti-tumor immunity. Besides, FMDs also enhance T-cell activation and tumor invasion and therefore enhance immunotherapies like checkpoint inhibitors. The second major mechanism is the inhibition of hypoxic tumor-associated macrophages, which create an immunosuppressive network. By limiting glucose availability, fasting inhibits the immune evasion strategy of the tumor and enhances the efficacy of immune checkpoint blockade therapy and adoptive T-cell therapies.

- **Can fasting-mimicking drugs replace traditional chemotherapy?**

Though promising in boosting cancer therapy, fasting-mimicking drugs (FMDs) are still not one alternative to chemotherapy but an adjuvant treatment, making the current therapy more effective and reducing its side effects. The state of fasting has been seen through studies to make the tumor chemotherapy-sensitive by holding back energy in glucose form and disabling pro-survival processes such as IGF-1 and mTOR signaling. Some of these treatments in FMD also employ nanocomposites that inhibit cancer metabolism while simultaneously transporting therapeutic molecules along, that can decrease chemotherapy dosage. Increased clinical trials should be conducted to reveal if FMD-based treatments may completely substitute for ordinary chemotherapy, and particularly in chemotherapy-resistant and intense cancer.

- **Certain current metabolic medicines already mimic the effects of fasting**

  - **Metformin**: lowers blood glucose as well as gets in the method of cancer metabolism.

  - **Rapamycin**: Inhibits mTOR, suppressing cell growth and stimulating autophagy.

  - **2-Deoxy-D-glucose (2-DG):** Mimics glucose but blocks its metabolism.

  - **Hydroxy citrate (HCA):** Disrupts tumor lipogenesis, simulating fasting.

  - **Ketogenic diets:** Starves glucose-addicted tumors by elevating ketone bodies.

- **Effect of caloric restriction on drug-resistant cancers**

Drug-resistant cancers arise via rewiring of metabolism, yet caloric restriction makes them susceptible by:

- **Suppressing glucose and insulin** → Starving high-energy cancer cells.
- **Triggering autophagy** → Forcing cancer cells to suicide.
- **Manipulating the tumor microenvironment** → Making the environment more favorable for the death of cancer cells.
- **Amplifying chemotherapy and immunotherapy** → Chemo side effects minimized by cycles of fasting and cancer sensitization to therapy.

- **Fasting with immunopotentiating therapies**

- **Fasting + PD-1/PD-L1 checkpoint inhibitors** → Amplifies immune system attack against tumors.
- **Fasting + T-cell therapy (CAR-T)** → Increases survival of T-cells and anti-tumor efficacy.
- **Fasting + IL-2 or NK cell activators** → Increases immune response while destroying tumors.
- **Probiotics + Fasting** → Increases gut microbiome, which bolsters immune response.

RESULT:

It is suggested by evidence that cancer treatment by fasting-mimicking interventions reprograms tumor metabolism and boosts immunity, which enhances the efficacy of chemotherapy and immunotherapy. Several studies suggest the following key mechanisms:

- **Metabolic Rewiring and Tumor Suppression**

- Fasting-mimicking diets (FMD) or calorie restriction mimetics (CRM) trigger a metabolic reprogramming that starves the cancer cells of their primary energy sources: glucose and insulin-like growth factor 1 (IGF-1).
- Normal cells are not protected against chemotherapy cytotoxicity but inhibit cancer cell growth by metabolic stress.
- In addition, FMD induces higher oxidative stress in cancer cells, leading to higher DNA damage and apoptosis in therapy-resistant and aggressive tumors.

- **Improved Drug Sensitivity and Reduced Chemoresistance**

- FMDs and CRMs have been reported to improve tumor sensitivity to chemotherapy by the modulation of mTOR, AMPK and pathways such as autophagy.
- Synergism between biomimetic nanovesicles delivery and fasting-mimicking approaches has played a key role in enhancing drug delivery to increase tumor drug accumulation.
- Fasting-like conditions applied to tumors have minimal expressions of resistance-related proteins thus, sensitizing them to conventional cancer treatments.

- **Immunomodulatory and Augmented Immune-Evasion Responses**

- Fasting reprograms the tumor microenvironment to allow for the activation and infiltration of T-cells.
- Fasting conditions have been shown to increase T-cell activation, promote an increase in antigen presentation and reprogram tumor-associated macrophages from an immunosuppressive (M2) to a pro-inflammatory (M1) state.
- This pathway of immunity will enhance the immune response to immune checkpoint inhibitors and other immunotherapies and lead to improved rates of tumor reduction.

- **Clinical and Preclinical Validation**

- Preclinical evidence in mouse models has demonstrated repeatedly that fasting-mimicking regimens shrink the tumor size and enhance survival when used concurrently with chemotherapy and immunotherapy.
- Early-stage clinical trials indicate that short-term fasting or FMDs may be added to cancer treatment programs safely with little adverse effect.
- Fasting-mimicking regimen patients experienced fewer side effects of chemotherapy, i.e., weakness and gastrointestinal toxicity; these contribute to their inherent therapeutic effects.

CONCLUSION:

Fasting-mimicking tactics are a nascent and prospective area of study with a multi-modal approach towards overcoming therapy resistance and optimizing patient outcomes. Findings of metabolic, molecular and immunologic research strongly corroborate the clinical application of caloric restriction mimetics and fasting-mimicking diets as adjunct therapies to traditional oncologic regimens.

- **Mechanistic Insights and Therapeutic Implications**

- Fasting-mimicking therapies achieve their anti-tumor activity by metabolic reprogramming, oxidative stress and immunomodulation.
- They, besides suppressing tumor cell proliferation, also have been shown to safeguard normal cells against the toxicities induced by chemotherapy, lowering the toxicity levels and optimizing patient comfort.
- Reduced chemoresistance observed is encouraging that FMDs and CRMs are going to become commonly used in cancer relapses and refractory cases that do not respond to current therapies.

- **Fasting and Immunotherapy: A Synergistic Partnership**

- Since fasting stimulates immune function, its combination with immunotherapies is an appealing prospect.
- Through improving T-cell activation and reprogramming macrophage polarization, fasting generates an immunotherapy-more-beneficial tumor microenvironment for immune-mediated tumor cell killing.
- Since most immunotherapies are treatment-failed as a result of an immunosuppressive tumor microenvironment, fasting-mimetic therapies would dramatically enhance response rates.

- **Clinical Translation Potential**

- While preclinical trials have established robust evidence of efficacy, further clinical trials will be necessary to establish maximal fasting regimens, patient selection protocols and safety durability.

- Patient-specific strategies, based on tumor type, metabolic health and tolerance will be necessary to appropriately execute fasting-mimicking regimens in the clinic.

- Pharmacologic CRMs whose fasting-like actions are independent of overt caloric restriction may be valuable in maximizing availability and acceptability and making the strategy available to larger numbers of patients.

- **Future Directions and Challenges**

- Substantial further research will be necessary to standardize regimens and define optimal regimens of fasting-mimicking therapies and standard cancer treatment.

- Careful management of potential issues such as patient compliance, nutritional risk and contraindications within individual subpopulations (e.g. metabolic disease) will be key to the translation of these approaches from preclinical models to standard-of-care clinical trials.

- Advances in nanotechnology and biomimetic delivery approaches could make fasting-mimicking interventions more specific, more effective and perhaps optimize their therapeutic impact.

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