ImmunoTools *special* Award 2026

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Immune-Metabolic Biomarkers and Targeted Therapeutic Strategies for Early Diagnosis and Management of Obesity-Linked Colorectal Cancer

One of the most common cancers in the world, colorectal cancer (CRC) poses a serious threat to public health in Asian nations [1]. Obesity is a significant modifiable risk factor, and its rising prevalence has been closely linked to the increased incidence of colorectal cancer. Chronic low-grade inflammation, metabolic dysregulation, and altered immune responses are hallmarks of obesity-associated colorectal cancer (OB-CRC), contributing to tumor initiation, progression, and poor clinical outcomes. Despite advancements in screening methods such as colonoscopy and fecal occult blood tests, early detection and precise prognostic classification remain inadequate due to the lack of reliable, minimally invasive biomarkers. Therefore, identifying sensitive and specific immune-metabolic biomarkers is crucial for early diagnosis, prognostic assessment, and targeted therapy in OB-CRC [2].

This research aims to develop and evaluate novel immune-metabolic biomarkers and integrate these findings into targeted therapeutic strategies. Monocytes and their differentiated macrophages, particularly tumor-associated macrophages (TAMs), play a central role in obesity-driven inflammation and tumor progression. In obese individuals, hypertrophic adipose tissue secretes pro-inflammatory cytokines and chemokines, recruiting circulating monocytes that differentiate into TAMs within the tumor microenvironment [3]. These TAMs

promote tumor growth, angiogenesis, metastasis, and immune evasion, making them critical targets for both biomarker discovery and immunomodulatory interventions.

The study will recruit four groups: obese individuals with CRC, obese individuals without CRC, non-obese CRC patients, and healthy controls. Peripheral blood mononuclear cells (PBMCs) will be isolated and subjected to multiparametric flow cytometry to generate high-resolution functional profiles of monocyte subsets. Monocyte identification and classification will be performed using PerCP-conjugated anti-human CD14 in combination with FITC-conjugated anti-human CD16, enabling discrimination of classical, intermediate, and non-classical monocyte populations.

To further characterize monocyte functional states, additional surface markers will be employed. FITC-conjugated anti-human CD29 will assess adhesion and migratory potential, while FITC-conjugated anti-human CD47 will evaluate immune evasion signaling. Tumor interaction and metabolic reprogramming will be investigated using APC-conjugated anti-human CD147 (tumor invasion and matrix remodeling), APC-conjugated anti-human CD36 (lipid uptake and metabolic dysregulation), and APC-conjugated anti-human CD66ade (CEACAM1/3/5), which are implicated in tumor progression and immune modulation.

Immune activation and antigen-presenting capacity will be assessed using PE-conjugated anti-human CD11c, along with co-stimulatory molecules PE-conjugated anti-human CD80 and CD86, which are essential for T-cell activation. Immune checkpoint regulation and T-cell exhaustion will be evaluated using PE-conjugated anti-human PD1, while PE-conjugated anti-human CD25 will serve as a marker of T-cell activation and regulatory T-cell activity. Functional immune responses will be further characterized through intracellular staining of PE-conjugated anti-human IFN-γ, reflecting pro-inflammatory and anti-tumor immune activity.

To complement phenotypic and functional profiling, in vitro stimulation assays will be performed using recombinant human cytokines to model monocyte-to-macrophage differentiation and polarization. Pro-inflammatory (M1-like) polarization will be induced using IFN-γ and GM-CSF, whereas anti-inflammatory, pro-tumorigenic (M2-like) polarization will be achieved through M-CSF, IL-4, IL-10, IL-13, and TGF-β. Additionally, IL-6 will be utilized to mimic chronic inflammatory and metabolic signaling associated with obesity. These functional assays will enable the evaluation of monocyte plasticity and the identification of cytokine-driven immune-metabolic signatures relevant to OB-CRC.

Furthermore, signaling pathways critical to inflammation and tumor progression, including NF-κB, STAT3, and AKT, will be analyzed to establish mechanistic links between immune activation, metabolic dysregulation, and cancer development. The integration of phenotypic markers, cytokine profiles, and signaling pathway data will facilitate the construction of

predictive biomarker panels using advanced bioinformatics, multivariate modeling, and machine learning approaches. These panels will be validated for diagnostic accuracy and prognostic relevance, including associations with tumor stage, lymph node involvement, metastasis, and patient survival.

In addition to biomarker discovery, this study incorporates a therapeutic dimension. Identified immune-metabolic pathways will guide the development of targeted interventions, including cytokine modulation (e.g., targeting IL-6 and TNF-α), metabolic regulation (restoring leptin/adiponectin balance), immunomodulatory strategies (reprogramming TAMs from M2 to M1 phenotypes), and inhibition of key signaling pathways such as NF-κB, STAT3, and AKT. High-value biomarkers identified in this study may also serve as direct therapeutic targets, enabling precision medicine approaches and combination therapies.

By enabling cell-specific resolution of cytokine production and signaling activity within monocyte subsets, flow cytometry offers a significant advantage over traditional serum-based assays. This precise characterization is essential for understanding OB-CRC immunopathogenesis and identifying actionable therapeutic targets. The reproducibility and reliability of experimental findings will be ensured through the use of validated reagents and positive control antigens [4].

The anticipated outcomes of this study include:

1. Identification of novel immune-metabolic biomarker signatures for early detection of OB-CRC.
2. Development of improved prognostic tools for patient stratification based on disease progression.
3. Mechanistic insights into obesity-driven colorectal carcinogenesis, focusing on monocyte-mediated inflammation and metabolic dysregulation.
4. Establishment of targeted therapeutic strategies aimed at immune-metabolic pathways to improve clinical outcomes.

By integrating immunology, oncology, advanced flow cytometry, and translational therapeutics, this research addresses a critical gap in OB-CRC management. Focusing on monocyte subsets, their functional states, and metabolic influences will enable early diagnosis, accurate prognostication, and personalized treatment strategies, ultimately advancing scientific knowledge and clinical practice in this field.

References:

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ImmunoTools *special* AWARD

for **Vetriselvan Subramaniyan** and **Rajendra Solanki**

includes 20 reagents

FITC - conjugated anti-human CD16, CD29, CD47, CD147

PE - conjugated anti-human CD80, CD86, PD1, CD11c, CD25, IFN-γ

PerCP - conjugated anti-human CD14

APC - conjugated anti-human CD36, CD66ade (CEACAM1/3/5)

Recombinant human cytokines: IFN-γ, GM-CSF, M-CSF, IL-4, IL-10, IL-13, TGF-β, IL-6